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#### Flow driven vesicle unbinding under mechanosensitive adhesion

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Ligand receptor based adhesion is the primary mode of interaction of cellular blood constituents with the endothelium. These adhered entities also experience shear flow imposed by the blood which may lead to their detachment due to the viscous lift forces. Here, we have studied the role of the ligand-receptor bonds kinetics in the detachment of an adhered vesicle (a simplified cell model) under shear flow. Using boundary integral formulation we performed numerical simulation of a two dimensional vesicle under shear flow for different values of applied shear rates and time scale of bond kinetics. We observe that the vesicle demonstrates three steady state configurations - adhered, pinned and detached for fast enough ligand-receptor kinetics (akin to Lennard-Jones adhesion). However, for slow bond kinetics the pinned state is not observed. We present scaling laws for the critical shear rates corresponding to the transitions among these three states. These results can help identifying the processes of cell adhesion/detachment in the blood stream, prevalent features during the immune response and cancer metastasis.

#### I. INTRODUCTION

Cell adhesion is one of the fundamental processes in the biological systems required during embryonic development,<sup>1</sup> physiological functions such as immune response,<sup>2</sup> as well as in disease conditions.<sup>2,3</sup> The cellcell adhesion as well as adhesion of cells with extracellular matrix is primarily driven by the direct interaction between receptors and their respective ligands, which are present on the two adhering surfaces.<sup>4</sup> In several contexts, cells under adhesion may also be exposed to stresses due to blood flow, as happens to cells adhering to the endothelium. The cell deformation under flow plays an essential role in the process by which cells detach from the surface.<sup>5</sup> The prevalence of this process has led to experimental as well as theoretical studies regarding the detachment (also known as unbinding) of adhered cells under flow conditions. $^{6-9}$ 

In one of the early works, the unbinding of a vesicle adhered to a flat substrate with Lennard-Jones adhesion was studied theoretically to discover three different steady state configurations- adhered, pinned and detached.<sup>6</sup> More recently, there has been an upsurge of interest in the research activity towards the study of the dynamics of capsules (a biomimetic system) adhered to a substrate by ligand-receptor interactions.<sup>7,8,10–12</sup>

The kinetic rates and the availability of ligand and receptor molecules on two adhering surfaces<sup>13</sup> play an essential role in cell response to an external flow. Even though the effect of ligand and receptor availability, in the form of adhesion strength, has been extensively studied, the role of bond kinetics on the cell detachment under flow has not been explored yet. The rate of bond kinetics ranges from  $10^{-4}$ /s for integrins<sup>14</sup> to 10/s for selectins and fibronectins<sup>15,16</sup> and constitutes a crucial factor from the biological point of view, and its precise function still calls for further considerations.

In this paper, we have attempted to dig further into this matter by studying the dynamics of a two dimensional vesicle adhered to rigid substrate having different rates of bond kinetics. We characterize the bond formed between a receptor and corresponding ligand by its potential energy and a characteristic timescale of the reaction kinetics. This turns Lennard-Jones type adhesion to be a special case of the ligand-receptor interaction corresponding to the limit where the characteristic timescale of the bond becomes irrelevant. This limit corresponds to the situation where the bond formation/dissociation is very fast as compared to cell deformation. We will also account for the slip-catch natures of the bonds, which correspond to two opposing behaviors where the bond stretching results in their faster (slip bond) and slower (catch bonds) dissociation, respectively.<sup>17</sup> In the following section we describe the basic model of a vesicle adhered to a flat substrate followed by results on the effect of bond kinetics on vesicle unbinding under shear flow.

#### II. MODEL

#### A. Vesicle

We consider a two-dimensional vesicle under shear flow in a channel of width W (Fig. 1). The vesicle is characterized by an enclosed fluid (viscosity  $\eta_{in}$ ) with an impermeable and incompressible membrane of length L and enclosed area  $A_0$  immersed in another fluid of viscosity  $\eta_{out}$ . We define the reduced area of the vesicle to be  $\nu = (A_0/\pi) / (L/2\pi)^2$  which describes the deviation of

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FIG. 1. (A) Schematic of vesicle adhered to the channel wall under shear flow. The enlarged version of the region in the dashed box is shown in (B) for slip and catch bonds. (B) Schematic showing ligand-receptor interactions for different bond strains (top panels) and qualitative dependence of  $k^-$  on bond length l (lower panels) for slip and catch bonds.

the vesicle from a circular shape for which  $\nu = 1$ . The excess perimeter from a circle allows for the deformation of vesicle under flow. Besides incompressibility the membrane resists bending and its energy is given by<sup>18</sup>

$$E = \frac{\kappa}{2} \oint c^2 ds + \oint \zeta dr_m \tag{1}$$

where  $\kappa$  is the bending rigidity of the membrane, c is the local membrane curvature,  $r_m$  is the curvilinear coordinate along the membrane and  $\zeta$  is a tension-like term to fulfill the local membrane incompressibility condition. The vesicle is initially placed close to one of the channel walls (located at y = -W/2) to facilitate its adhesion. The applied plane shear flow is given by  $u_x^0 = \dot{\gamma} (y + W/2)$ .

In the biological contexts (as described in the introduction) for cells in the blood stream, such as the immune cells and circulating metastatic cancer cells, the flow velocity and the cell sizes are quite small.<sup>19</sup> This leads to small Reynolds number (approximately  $10^{-4}-10^{-2}$ ) and we can describe the flow inside and outside of the vesicle in the Stokes limit (vanishing inertia) by

$$-\nabla p + \eta_i \nabla^2 \mathbf{u} = 0, \nabla \cdot \mathbf{u} = 0 \tag{2}$$

where p is the fluid pressure, **u** is the fluid velocity field and  $\eta_i = \eta_{in}(\text{or } \eta_{out})$  for the fluid inside (or outside) the vesicle. Due to the linearity of the Stokes equations we can utilize the boundary integral method<sup>20</sup> for the numerical simulation of vesicle dynamics under shear flow. The boundary integral method requires information about the forces on the membrane due to its bending, incompressibility and its adhesive interaction with the wall (see next section). In this formalism the velocity of a point on the membrane can be written by

$$\mathbf{u}(\mathbf{r}) = \frac{2}{1+\lambda} \mathbf{u}^{0}(\mathbf{r}) + \frac{1}{2\pi(1+\lambda)\eta_{out}} \int_{\text{mem}} \mathbb{G}^{2w}(\mathbf{r}_{0}, \mathbf{r}) \cdot \mathbf{f}(\mathbf{r}_{0}) dr_{m} + \frac{1-\lambda}{2\pi(1+\lambda)} \int_{\text{mem}} \mathbf{n}(\mathbf{r}_{0}) \cdot \mathbb{T}^{2w}(\mathbf{r}_{0}, \mathbf{r}) \cdot \mathbf{u}(\mathbf{r}_{0}) dr_{m}$$
(3)

where  $\mathbb{G}^{2w}$  and  $\mathbb{T}^{2w}$  are the Green's functions satisfying the no-slip boundary condition at the walls,  $\lambda = \eta_{in}/\eta_{out}$ is the viscosity ratio,  $\mathbf{u}^0$  is the externally imposed velocity field and  $\mathbf{f} = \mathbf{f}_{\kappa} + \mathbf{f}_{LR}$  is the total force acting on the vesicle with contributions from membrane bending and incompressibility as

$$\mathbf{f}_{\kappa} = \kappa \left( \frac{d^2 c}{ds^2} + \frac{1}{2}c^3 \right) \mathbf{n} - \zeta c \mathbf{n} + \frac{d\zeta}{ds} \mathbf{t}$$
(4)

and the force due to the stretching of ligand-receptor bonds  $\mathbf{f}_{LR}$  (to be described in the next section). In the equation above  $\mathbf{n}$  and  $\mathbf{t}$  are the unit normal and tangent

vectors on the vesicle membrane. For more details about the numerical implementation of the method readers are referred to.  $^{21}\,$ 

#### B. Ligand-receptor adhesion

The adhesion between the vesicle membrane and the channel wall is mediated by bonds between the ligand and receptor molecules (each of which is present either on the vesicle membrane or the channel wall). The formation and dissociation of the bonds are considered to be stochastic chemical process described by the respective rates  $k_0^+$  and  $k_0^-$  for an unstrained bond. We follow the bond kinetics described by Dembo et al.<sup>22</sup> for the mechanosensitive adhesion, and write the expression for these rates in the presence of any bond strain as

$$k^{+} = k_{0}^{+} \exp\left(-U_{b}/k_{B}T\right) \tag{5}$$

$$k^{-} = k_{0}^{-} \exp\left(+U_{b}/k_{B}T\right).$$
(6)

where  $U_b = k_b \left( l - l_b \right)^2 / 2$  is the free energy of the bond with  $k_b$  spring constant and  $(l - l_b)$  the bond deformation, with  $l_b$  the equilibrium length of the ligand-receptor bond. This dependence on the bond free energy implies a higher rate of bond dissociation for a stretched bond. This is a classical intuitive case which is a characteristic of the so-called 'slip' bond.<sup>22</sup> Besides slip bond, there has been evidence in literature<sup>23</sup> that some ligand-receptor bonds may have an intermediate state between perfectly bound and dissociated states which has higher stability. In other words these bonds can strengthen under stretching (due, for example, to the action of shear stress), and therefore their dissociation becomes less probable as compared to their unstretched state. This kind of bond is called 'catch bond'. It has to be noted that the catch nature of a bond persists until a given stretch level beyond which the dissociation rate increases with the stretching level. A reasonable way to take into account the catch nature of the bond is to set

$$k^{-} = k_{0}^{-} \left[ (1 - \chi) \exp\left(U_{b}/k_{B}T\right) + \chi \exp(-\tilde{U}_{b}/k_{B}T) \right]$$
(7)

where  $\tilde{U}_b = \tilde{k}_b(l-l_b)^2/2$  is the free energy in the intermediate state (second blue bond shown in Fig. 1B) of the ligand-receptor bond with spring constant  $\tilde{k}_b$  (not necessarily equal to  $k_b$ ). The parameter  $\chi$  captures the deviation of the bond characteristic from that of slip bond. For a slip bond we have  $\chi = 0$  and for for  $\chi = 1$  the bond demonstrates a purely catch nature.

Let us denote the density of the bonds as  $P(\mathbf{r}_m, \mathbf{r}_w, t)$ at time t, where  $\mathbf{r}_m$  and  $\mathbf{r}_w$  are two points on the vesicle membrane and channel wall, respectively. The governing equation for P is given by

$$\frac{\partial P}{\partial t} + v_r \frac{\partial P}{\partial x} = [LR]k^+(\mathbf{r}_m, \mathbf{r}_w) - k^-(\mathbf{r}_m, \mathbf{r}_w)P \qquad (8)$$

where [LR] is the product of the ligand and receptor densities on the two surfaces,  $v_r$  is the velocity of the membrane relative to wall and the dependencies of Pare not shown in the arguments of P for brevity. The two terms on the right hand side of the above equation capture the rate of bond formation and dissociation, respectively. Here, we have also assumed sufficiently high densities of ligand and receptors on the two surfaces such that formation of the bonds does not influence the availability of the free ligands and receptors. For moderate or small densities, this equation can be modified appropriately.<sup>24</sup> For high ligand and receptor densities, it can be seen that in the absence of any relative motion between two surfaces, the equilibrium bond density  $P_{eq} = [LR]k^+/k^- \sim [LR]k^+_0/k^-_0$  is proportional to [LR].

The coupling between the ligand-receptor adhesion dynamics and the fluid flow is via the forces due to stretched bonds between vesicle membrane and the wall  $\mathbf{f}_{\text{LR}}$  as mentioned in equation (3). The force acting at a point on the membrane due to the ligand-receptor bonds is given by

$$\mathbf{f}_{\mathrm{LR}}(\mathbf{r}_m, t) = \int_{\mathrm{wall}} P(\mathbf{r}_m, \mathbf{r}_w, t) f_b\left(\mathbf{r}_w, \mathbf{r}_m\right) \frac{\mathbf{r}_w - \mathbf{r}_m}{l} dr_w$$
(9)

which is the integral of the forces due to all bonds formed between the membrane point and the wall.

#### C. Dimensionless numbers

We describe the results in the following using two dimensionless numbers. The Capillary number

$$C_{\kappa} = \frac{\eta_{out} \dot{\gamma} R_0^3}{\kappa} \equiv \dot{\gamma} \tau_c \tag{10}$$

is defined as the ratio of the typical relaxation time of the vesicle shape  $(\tau_c)$  and the time scale of applied shear. It can also be seen as a measure of the strength of the flow relative to the bending energy of the vesicle membrane.

The second dimensionless number

$$C_b = \frac{\kappa}{\eta_{out} k_0^- R_0^3} \equiv \frac{1}{k_0^- \tau_c} \tag{11}$$

describes the ratio of the characteristic time scales of the bond kinetics and the vesicle shape deformation. Therefore, large (small)  $C_b$  corresponds to the slow (fast) bond formation and dissociation compared to the time scale of cell deformation. We have studied the response of a vesicle for a wide range of  $C_{\kappa}$  and  $C_b$  to capture different adhesion regimes of the vesicle under shear flow. In order to analyze the effect of the nature of the ligand-receptor bond (slip vs catch) we have also varied the parameter  $\chi$ between 0 (purely slip bond) to 0.7 (catch bond for small bond stretch).

There are several other dimensionless quantities in the systems which we have kept fixed for the results presented in this paper. We have set the viscosity contrast  $\lambda = \eta_{in}/\eta_{out} = 1$ , the degree of confinement  $C_n = 2R_0/W = 0.1$  and the reduced area of the vesicle  $\nu = 0.8$ . For individual ligand-receptor bond we have fixed the equilibrium bond length  $l_b = 0.14R_0$  and the bond stiffness follows  $k_b l_b^2/\kappa = 1$  and  $k_b = 100k_BT$ . In order to study the effect of the adhesion kinetics we vary  $C_b$  while keeping  $[LR]R_0^2k_0^+/k_0^- = 2 \times 10^4$  fixed. In the results shown below, the velocities have been non-dimensionalized by  $R_0/\tau_c$ .

#### III. RESULTS

In order to characterize the effect of mechanosensitive nature of vesicle adhesion we first describe the dynamics of vesicle with a Lennard-Jones adhesion.<sup>6</sup> With a small enough characteristic time of the bond kinetics (that is  $k_0^- \to \infty$ ), Lennard-Jones adhesion presents a limiting case of the mechanosensitive adhesion considered in this paper.

First, we recall the main results of<sup>6</sup> here. The application of shear flow results in a viscous lift force on the vesicle due to its asymmetric shape caused by the flow (an asymmetry is necessary in order to break the time reversal symmetry present in the Stokes equations). For very small values of  $C_{\kappa}$  (due, for example, to a small enough shear rate) the vesicle remains strongly adhered to the channel wall. An increase in the applied shear rate results in the vesicle unbinding in two steps (Fig. 2). At a first critical  $C_{\kappa 1}$  the configuration of vesicle changes from adhered to a pinned one where the length of the adhesion zone is practically zero. At a second higher  $C_{\kappa 2}$ the vesicle gets completely detached from the wall.



FIG. 2. Schematics of three vesicle states- adhered, pinned and detached under shear flow for  $k_0^- \to \infty$ . For vesicle shapes with Lennard-Jones adhesion please refer to this<sup>6</sup> paper.

This two staged detachment process has been shown to be arising out of the interplay between three forces- hydrodynamic lift force, membrane bending force and adhesion. After the first transition at  $C_{\kappa} > C_{\kappa 1}$ , the lift force overcomes the adhesion in the front end of the adhered vesicle, giving rise to pinned configuration of vesicle. In the pinned state the vesicle shape does not depend on the adhesion strength or the bending rigidity. This can be explained in the following manner. In the pinned vesicle configuration, the contact length between vesicle and wall is very small. This results in vesicle shape and tilt quite similar to those of a vesicle in an unbound flow where the vesicle shape is known to be dependent only on its reduced volume  $\nu$ ,<sup>25</sup> and does not depend on the shear rate or the adhesion strength. However, the effect of the shear rate and bond kinetics is visible in the translational and tank-treading velocities of the vesicle (see Fig. 5B-C).

The second transition, arising at  $C_{\kappa} > C_{\kappa 2}$ , ensues following lift forces overcoming total adhesion at the pinned length of contact. Therefore, for Lennard-Jones adhesion the two critical values of the capillary number can be uniquely determined as a function of adhesion potential and vesicle characteristics. In the following we systematically study the effect of the mechanosensitive nature of the adhesion bonds on the two critical capillary numbers,  $C_{\kappa 1}$  and  $C_{\kappa 2}$ .

#### A. Vesicle configurations and dynamics under mechanosensitive adhesion



FIG. 3. Phase diagram showing the steady state configurations of the vesicle for different  $C_{\kappa}$  and  $C_b$  with slip bonds based adhesion.

Figure 3 shows the steady state configurations of a vesicle forming slip bonds ( $\chi = 0$ ) with the channel wall for different values of capillary number and bond kinetics timescale. We observe that for mechanosensitive slip bonds, the two stages (adhered to pinned, then pinned to detached) of detachment are not always present for all values of  $C_b$ . For small  $C_b$ , that is akin to Lennard-Jones type adhesion, the two stages are recovered but for large  $C_b$  the adhered vesicle detaches from the substrate in a single step. Further, we also see that the two critical values of the capillary number,  $C_{\kappa 1}$  and  $C_{\kappa 2}$  depend on the timescale of bond kinetics. For small  $C_b$ , the first critical capillary number  $C_{\kappa 1}$  increases with  $C_b$ , whereas for large  $C_b$  it shows opposite behavior. On the other hand,  $C_{\kappa 2}$ , for whichever value of  $C_b$ , decreases monotonically with  $C_b$ .

Figure 4 shows the vesicle configurations for different degrees of 'catch' nature of the ligand-receptor bonds

 $(\chi = 0.1, 0.25 \text{ and } 0.7)$ . Qualitatively, the vesicle response with catch bonds is similar to that with the slip bonds (Fig. 3). However, the critical value of  $C_b$ , beyond which pinned configuration is not observed, gets smaller with an increase in the 'catch' nature of bonds (increasing  $\chi$ ). Further, for any given value of  $C_b$  the values of  $C_{\kappa 1}$  and  $C_{\kappa 2}$  also increase with  $\chi$ . In addition to its effect on the critical shear rates the catch nature of the bonds also affects the vesicle shapes in the adhered steady states (Fig. 5A). With increasing  $\chi$  the fore-aft asymmetry in the vesicle shape gets smaller. As explained in the next section this results in a decrease in the lift force with increasing  $\chi$ .

We also characterized the vesicle dynamics in the adhered and pinned states and its dependence on  $C_b$  and  $\chi$ . As shown in Fig. 5B, the vesicle demonstrates tank treading motion in both adhered and pinned states. Within adhered or pinned regimes the tank treading velocity  $v_{\tau\tau}$  is proportional to the applied shear rate. At the transition between adhered and pinned states, however, the tank treading velocity demonstrates a considerable jump. This sudden change in the tank treading motion can be attributed to the change in the vesicle orientation as it transitions from adhered to the pinned state. Further, an increase in  $C_b$  results in smaller jump in  $v_{\scriptscriptstyle TT}$  due to increasing contribution of the bond kinetics in the vesicle motion. Similarly, with increasing  $\chi$ also the jump in  $v_{\tau\tau}$  gets reduced since for higher  $\chi$  the bond dissociation slows down which results in bond kinetics timescale dominating over shear rate (Fig. 5C). In the following we explore the mechanisms for the  $C_b$ dependent vesicle unbinding under shear flow.

#### B. Adhered to pinned transition

Figures. 3 and 4 show that for  $C_b \ll 1$  the vesicle first changes its configuration from adhered state to pinned state with an increase in shear rate,  $C_{\kappa}$ . As mentioned previously, there are primarily three forces acting on the vesicle- bending force which depends only on the shape of the vesicle (see Eq. (1)), lift force which is due to the foreaft asymmetry of the vesicle as well as the surrounding flow pattern, and the force due to the mechanosensitive ligand-receptor bonds.

The hydrodynamic lift force  $F_L$ , defined as the integral of the pressure forces at the vesicle membrane, is sensitive to the vesicle shape, this is why we have to inspect the shape for different  $C_b$  in order to estimate the dependence of the lift force on bond kinetics. As shown in Fig. 6A, for  $C_b \ll 1$  and a fixed value of  $C_{\kappa} < C_{\kappa 1}$ , the vesicle shapes weakly depend on  $C_b$ . Therefore, for the first transition the bending force does not contribute to the increase in  $C_{\kappa 1}$  upon increasing  $C_b$ . For a complete characterization of the variation of the lift force with  $C_b$ , we focus on the fluid flow in the region between the vesicle and the channel wall and estimate the pressure.<sup>6</sup> Due to its small thickness, the flow in this region can be approximated using lubrication approximation. In this limit we can safely neglect  $\partial p/\partial y$  and the flow field can be described by

$$\frac{\partial^2 u_x}{\partial y^2} = \frac{1}{\eta} \frac{dp}{dx}, \frac{\partial u_x}{\partial x} = -\frac{\partial u_y}{\partial y}.$$
 (12)

Following the approach of, $^{6}$  it can be shown that the pressure in the lubrication region scales as

$$p(x) \sim u_s \tag{13}$$

where  $u_s = (v_0 + v_{TT})/2$  is the average flow velocity in the lubrication region in the reference frame co-moving with the vesicle, and may be referred to as the slip velocity. Here  $v_0$  and  $v_{TT}$  are the translational and tank-treading velocities of the vesicle, respectively. Figures 6B and 6C show the slip velocity and lift force  $F_L$ , respectively, as a function of  $C_b$  corresponding to the adhered regime. Expectedly, the slip velocity decreases to zero as  $C_b$  is increased from 0 to  $C_b \gg 1$ . For small  $C_b$  the leading order behavior of the decrease in the average velocity of the fluid flow with  $C_b$  can be written as

$$u_s = u_s^0 - \alpha_1 C_b + \mathcal{O}(C_b^2) \tag{14}$$

where  $u_s^0$  is the velocity for  $C_b = 0$  (fast kinetics, corresponding to a Lennard-Jones potential) and  $\alpha_1 > 0$  is a coefficient which depends on other non-dimensional numbers described previously and has been estimated numerically (see inset in Fig. 6B). This decrease in the average flow velocity can be attributed to the ligand-receptor bond based friction, which corresponds to the force component acting parallel to the bounding wall

$$f_b^x(\mathbf{r}_m, t) = \int f_b(\mathbf{r}_m, \mathbf{r}_w) P(\mathbf{r}_m, \mathbf{r}_w, t) \cos\theta dr_w \quad (15)$$

where  $f_b$  is the force along the bond formed between the points  $\mathbf{r}_m$  and  $\mathbf{r}_w$  and  $\theta$  is the angle between the bond and the channel wall. For  $C_b = 0$  the bond kinetics is extremely fast as compared to other time scales of the systems. This results in  $P(\mathbf{r}_m, \mathbf{r}_w, t) \approx P_{eq}(\mathbf{r}_m, \mathbf{r}_w)$  which is a symmetric function along the channel wall, that is  $P(\mathbf{r}_m, \mathbf{r}_w, t) = P(\mathbf{r}_m, -\mathbf{r}_w, t)$ . The symmetric nature of bond distribution leads to  $f_b^x = 0$  for  $C_b = 0$ . With increasing  $C_b$ , however, the distribution of P does not remain symmetric and the friction component of the forces in the bond increases.

Further, we can also estimate the strength of the adhesion for given  $C_b$  from the number of total bonds between the vesicle and the channel wall, that is

$$W_b = \int \int P(\mathbf{r}_m, \mathbf{r}_w, t) \, dr_w dr_m. \tag{16}$$

As mentioned previously, for  $C_b \ll C_{\kappa}$ , the bond probability density is practically the same as at equilibrium  $P_{eq}$ . From equation (16) this results in  $W_b \sim [LR]k_0^+/k_0^$ in the case of fast bond kinetics. However, for  $C_b \approx C_{\kappa}$ 



FIG. 4. Steady state vesicle configurations for (A)  $\chi = 0.1$ , (B) 0.25 and (C) 0.7. For comparison, dashed lines are showing boundaries of three states for  $\chi = 0$  (vesicle with slip bond adhesion).



FIG. 5. Adhered vesicle dynamics under shear flow. (A) Steady state shapes of the adhered vesicle ( $C_{\kappa} = 3.8$ ) as a function of  $\chi$ . The dashed curve for  $\chi = 0$  (slip bonds) is shown for comparison. Vesicle tank treading velocity under (B) slip and (C) catch (with  $C_b = 10^{-2}$ ) bond adhesion.

and  $C_b > C_{\kappa}$  the bonds do not dispose of sufficient time to form, resulting in a smaller value of  $W_b$ . Figure 6C shows the changes in the adhesion strength as a function of  $C_b$  as obtained from the numerical simulations of the vesicle under shear flow for different  $C_b$ . It can be seen that for  $C_b \ll 1$ , the adhesion strength weakly depends on  $C_b$ . This observation, combined with Eq. (14), shows that the increase in  $C_{\kappa 1}$ , which corresponds to the critical shear rate for the adhered to pinned transition, is primarily due to the decline of lift force (Fig. 6). The linear decrease in the lift force (Eq. (14)) results in the linear increase in  $C_{\kappa 1}$  with  $C_b$  for small  $C_b$  as

$$C_{\kappa 1} = C_{\kappa 1}^0 + \tilde{\alpha}_1 C_b \tag{17}$$

which agrees with the numerical simulations (Fig. 7). Here  $C_{\kappa_1}^0$  is the critical shear rate for  $C_b = 0$  and the coefficient  $\tilde{\alpha}_1$  depends on other dimensionless numbers and has been estimated by fitting equation (17) to the numerical data (Fig. 7).



FIG. 6. Vesicle under shear flow with slip bond based adhesion. (A) Steady state vesicle shapes for  $C_{\kappa} = 3.8$  (Adhered regime). The three shapes shown here coincide with each other. (B) Average flow velocity  $u_s = (v_0 + v_{TT})/2$  in the lubrication region between the vesicle and channel wall. Inset shows the change in  $u_s$  scales linearly with  $C_b$ . (C) Average adhesion strength and lift force in the adhered state as a function of  $C_b$ .



FIG. 7. Dependence of  $C_{\kappa 1}$  and  $C_{\kappa 2}$  on  $C_b$  as per Eqs. (17) and (20), respectively, for  $C_b \ll 1$ .

#### C. Vesicle detachment from pinned state

In the pinned state an increase in  $C_{\kappa}$  results in vesicle detachment. This transition is also observed for the Lennard-Jones adhesion (see Fig. 2). However, for  $C_b > 0$  the critical shear rate for this transition,  $C_{\kappa 2}$ , exhibits a decrease with  $C_b$  (Fig. 3).

Similar to the adhered state, in the pinned state also the shape of the vesicle does not depend on  $C_b$  significantly. Therefore, here too we need to look at the dependence of adhesion strength and the lift force on  $C_b$ . Following similar steps as in the previous section, we calculated the adhesion strength  $W_b$  (Eq. (16)) and the average flow velocity  $u_s$  in the lubrication region. Figure 8 shows the estimation of these two quantities from numerical simulations as a function of  $C_b$ . We can write the leading order dependence of slip velocity and adhesion strength on  $C_b$  as

$$u_s = u_s^0 - \alpha_2 C_b + \mathcal{O}(C_b^2) \tag{18}$$

$$W_b = W_b^0 - \beta_2 C_b + \mathcal{O}(C_b^2),$$
(19)

resulting in a decrease in the lift force (via a decrease in  $u_s$ ) as well as the adhesion strength with increasing  $C_b$ . Here the coefficients  $\alpha_2 > 0$  and  $\beta_2 > 0$  are determined numerically as shown in Fig. 8.



FIG. 8. Change in the average velocity in the lubrication region  $u_s$  and the adhesion strength  $W_b$  with increasing  $C_b$  in the pinned configuration of vesicle  $(C_{\kappa} = 4.9)$ .

As shown in,<sup>6</sup> the vesicle detachment from the pinned state takes place when the lift force equals the total adhesion force. In case of ligand-receptor adhesion for large  $C_b$  the lower rate of bond formation as compared to the rate of shape change of vesicle results in the reduction of adhesion strength (bonds do not have ample time to form) which prevents the pinned configuration of the vesicle. Since, lift force is proportional to the slip velocity (Eq. (13)), equation (18) shows that the lift force also decreases linearly with increasing  $C_b$  for  $C_b \ll 1$ . Therefore, the lift force exceeds the adhesion at the second critical shear rate

$$C_{\kappa 2} = C_{\kappa 2}^0 + \left(\tilde{\alpha}_2 - \tilde{\beta}_2\right) C_b, \qquad (20)$$

where  $C_{\kappa 2}^0$  is the critical shear rate for  $C_b = 0$  and fitting Eq. (20) to the numerical data shows that two coefficients follow  $\tilde{\alpha}_2 < \tilde{\beta}_2$  (see Fig. 7) and may depend on other dimensionless numbers such as viscosity contrast, excess area etc. In the above equations, for  $C_b < 1$ , the adhesion term dominates that of the lift force giving rise to overall decrease in  $C_{\kappa 2}$  with  $C_b$ . The comparison between the analytical and numerical results shows a very good agreement in the small  $C_b$  regime (Fig. 7) where the approximation leading to the analytical expressions is expected to make sense.

#### D. Vesicle detachment from adhered state

As shown in Fig. 3, for  $C_b \approx 1$  and  $C_b > 1$ , the vesicle does not exhibit the pinned configuration as a steady state and an increase in the shear rate results in its detachment directly from the adhered state. Given the nature of the dependence of  $C_{\kappa 1}$  and  $C_{\kappa 2}$  on  $C_b$  (see Eqs. (17) and (20)), showing an increase and a decrease with  $C_b$ , respectively, it is expected that for  $C_b$  beyond the critical value

$$C_b^0 = \frac{C_{\kappa 2}^0 - C_{\kappa 1}^0}{\tilde{\alpha}_1 + \tilde{\beta}_2 - \tilde{\alpha}_2}$$
(21)

the pinned state is not anymore possible. This is due to the fact that for  $C_b < C_b^0$  the shear rate for the adhered to pinned transition is smaller than that for the vesicle detachment from that pinned state. For  $C_b > C_b^0$ , however, we get  $C_{\kappa 1} > C_{\kappa 2}$  and the adhesion force required for the pinned vesicle configuration is weak due to excessive breakage of the bonds.

A further result is that for  $C_b \geq 1$ , the critical shear rate for the vesicle detachment decreases with increasing  $C_b$ . In order to gain insight into this behavior we analyzed the  $C_b$ -dependence of the vesicle-wall force (ligandreceptor force), which can be decomposed into a tangential part (which we may call friction force), and a normal one (referred to as adhesion force)

$$F_{b}^{x}(t) = \int \int f_{b}(\mathbf{r}_{m}, \mathbf{r}_{w}) P(\mathbf{r}_{m}, \mathbf{r}_{w}, t) \cos \theta dr_{w} dr_{m}$$
(22)

$$F_{b}^{y}(t) = \int \int f_{b}(\mathbf{r}_{m}, \mathbf{r}_{w}) P(\mathbf{r}_{m}, \mathbf{r}_{w}, t) \sin \theta dr_{w} dr_{m},$$
(23)

Figure 9A shows that for  $C_b \geq 1$  the two components of the ligand-receptor force become comparable to each other. Therefore, for these values of  $C_b$  the friction force along the contact surface also starts to influence the vesicle dynamics leading to a decrease in the critical shear rate for its detachment. In fact, for  $C_b \gg 1$ , the application of shear flow results in the bond based forces to have a larger component along the contacting surface  $(|F_b^x| > |F_b^y|)$  before vesicle detachment. In other words the friction force due to the bonds exceeds the adhesion force for  $C_b \gg 1$ . This can be explained by the fact that due to slower bond kinetics for  $C_b \gg 1$ , the application of flow results in a vesicle movement along the wall causing an alignment of the bonds along the channel wall. This also results in bond stretching which leads to high magnitude of friction force,  $F_b^x$ . Further, we also observe that for  $C_b \gg 1$  the average velocity field in the lubrication region  $u_s = (v_0 + v_{TT})/2 \sim C_b^{-1}$  (Fig. 9B). This highlights the fact that for large  $C_b$  the lift force becomes negligible as compared to other forces. Therefore, for  $C_b \gg 1$ , the vesicle detachment is not due to the lift force but due to the drag force experienced by the vesicle along the wall. The drag force experienced by the vesicle results in the detachment of bonds. Since for  $C_b \gg 1$  the formation of new bonds is very slow, all the bonds eventually break. This detached vesicle is then forced away from the wall by the lift force, albeit small, it plays role since the two other forces cancel each other. For large enough  $C_b$ , the translational velocity of the vesicle is almost negligible and the drag force experienced by the vesicle along the channel is expected to be proportional to the applied shear rate, that is  $F_d \sim C_{\kappa}$ . Consequently, the vesicle detachment happens when  $F_d > |F_b^x|$  that is when the drag force exceeds the force exerted by the bonds along the channel wall.

For  $C_b \gg 1$ , the vesicle translation velocity is primarily governed by the time scale of bond kinetics  $C_b$ . This results in the typical stretch in the bond to be proportional to  $C_b$ . By considering the typical number of bonds in the steady state regime to be proportional to  $1/C_b$  for  $C_b \gg 1$ we get  $|F_b^x| \sim C_b \times 1/C_b = 1$  We obtain the critical value of shear rate for vesicle detachment  $C_{\kappa 1}$  by comparing the drag force and the friction force arising from bonds, yielding  $C_{\kappa 1} \sim const$ . for  $C_b \gg 1$ . This means that the critical shear rate  $C_{\kappa 1}$  for  $C_b \gg 1$  attains a plateau (see Fig. 7). This shows that for  $C_b > 1$  the critical shear rate for the vesicle detachment decreases with  $C_b$  but not indefinitely. For  $C_b \gg 1$ , the drag force driven detachment results in critical shear rate to be independent of  $C_b$ .

All the results described till now pertain to the case of the slip-bond regime. We will now turn our attention to the analysis of the catch-bond regime.

#### E. Effect of the catch nature of bonds

The vesicle detachment dynamics with catch bonds ex-



FIG. 9. (A) The components to total forces applied by the bonds in the vesicle for  $C_{\kappa} = 3.8$  (Adhered regime). (B) Vesicle translational velocity  $v_0$  as a function of  $C_b$ . Inset shows the  $u_s \sim C_b^{-1}$  scaling for  $C_b \gg 1$ .

hibit the same three phases, albeit, with relatively higher values of  $C_{\kappa 1}$  and  $C_{\kappa 2}$ . Additionally, it also shows a lower value of critical  $C_b$  beyond which pinned configuration is not observed (Fig. 4).

Due to their higher stability (or lower  $k^-$ ) the fraction of stretched bonds is higher (the exact value depends on  $\chi$ ) for catch bonds. This makes the overall bond dissociation slower for the catch bonds resulting in the higher values of  $C_{\kappa 1}$  and  $C_{\kappa 2}$  for a given  $C_b$ .

The steady state vesicle shapes in the adhered regime with catch bonds do not show any significant dependence on  $C_b$  for  $C_b \ll 1$  (Fig. 10A). Therefore, similar to the analysis performed for the slip bonds, we focus on characterizing the dependence of lift force on  $C_b$ . The average flow velocity in the lubrication region  $u_s$  is smaller for the vesicle with catch bond adhesion than with slip bonds (Fig. 10B). However, it still decreases linearly with  $C_b$  for  $C_b \ll 1$ . Therefore, for catch bonds the result  $u_s = u_s^0 - \alpha_1^{\text{catch}} C_b$  still holds, with  $\alpha_1^{\text{catch}} > \alpha_1$ (see Eq. (14)) since the slip velocity is smaller in case of catch bonds relative to that with slip bonds. Another feature is that the average adhesion density  $W_b$  is relatively higher for catch bonds as compared to the slip bonds for the same  $C_{\kappa}$  (Fig. 10C). The combined effect of the decrease in the lift force and increase in the adhesion force results in an ampler increase of  $C_{\kappa 1}$  with  $C_b$ for  $\chi > 0$ . The behavior of  $C_{\kappa 2}$  with  $C_b$  shows a more pronounced decreases with catch bonds. Therefore, the two corresponding curves meet at a value of  $C_b$  which is smaller for catch bonds ( $\chi \neq 0$ ) than for slip bonds  $(\chi = 0).$ 

#### IV. DISCUSSION AND CONCLUSIONS

Here we have studied the shear flow driven detachment of a vesicle adhered to a flat rigid substrate by the ligand-receptor bonds. In particular, we have focused on the effect of the time scale of the bond kinetics and bond stability under stretch (slip vs catch nature) on the vesicle dynamics. We performed numerical simulations for different values of  $C_b = 1/(k_0^- \tau_c)$  and have extracted scaling laws for the critical shear rates for the extreme values of  $C_b$ .

For increasing shear rates, we have demonstrated two pathways for the detachment of an adhered vesicle depending on  $C_b$  – first, from adhered state via the pinned configuration and second, without the intermediate pinned state (Fig. 3). These two detachment paths also have varying contributions of different forces. For small  $C_b$  the detachment via pinned state is primarily driven by the lift force generated by the asymmetric shape of the vesicle. On the other hand, for large  $C_b$ , owing to very small bond kinetic rates it is the drag force in the flow direction which drives the vesicle detachment directly from the adhered state. Therefore, this mechanism of detachment can also be extended to nearly spherical vesicles, capsules or even the rigid particles for which the lift force is almost zero, due to the weak shape asymmetry.

The ligand-receptor adhesion plays a central role in several biological contexts, especially in the functioning of immune cells which form slip and catch bonds with the endothelium,<sup>2</sup> cancer metastasis where circulating tumor cells adhere to the blood vessel walls (and possibly transmigrate in the tissues and organs beneath) with the help of slip and catch bonds,<sup>26,27</sup> and adhesion of activated platelets surrounding any wound.<sup>28,29</sup> The blood flow exerts in turns hydrodynamic stress which may lower (slip bonds) or strengthen the adhesion (catch bond). Therefore, the density of the ligands and receptors notwithstanding, the involvement of different ligandreceptor pairs in these examples gives rise to a diverse range of cell response under flow.<sup>8,11</sup> The typical val-



FIG. 10. Vesicle under shear flow with catch bond based adhesion. (A) Steady state vesicle shapes for for  $C_{\kappa} = 3.8$  (Adhered regime). (B) Average flow velocity  $u_s$  in the lubrication region for different  $\chi$ . (C) Average adhesion strength as a function of  $C_b$  for different  $\chi$ .

ues of the time scale of bond kinetics  $(1/k_0^-)$  range from  $10^{-1}s^{15,16}$  to  $10^4s.^{14}$  For a cell of size  $1 - 10\mu m$ , bending stiffness  $\approx 10^{-19}$ N-m,<sup>30</sup> and the viscosity of the surrounding fluid to be  $\eta = 10^{-3}$ Pa-s (similar to that of water) these values correspond to  $C_b = 10$  to  $10^6$ . This demonstrates that cells and substrates with ligand receptor pairs with high  $C_b$ , such as fibronectin-aIIb $\beta 3$ ,<sup>16</sup> GPIba-vWFA1<sup>15</sup> may not demonstrate the pinned configuration under shear flow. Similarly, many cells also have integrins,<sup>31</sup> CD44,<sup>26</sup> P-selectins<sup>32</sup> or cadherins<sup>33</sup> receptors on their surfaces which have a catch characteristics with their respective ligands. For similar values of bond kinetics time scale, we can see that the pinned configuration is not possible for these cells too. A systematic experimental investigation with different ligand-receptor pairs is required to validate the present predictions.

It needs to be noted here that the results shown in this paper are for two dimensions. In three dimensions (3D) we expect that the qualitative features of the vesicle detachment will hold albeit with different values of critical shear rates. A possible source of deviation in vesicle behavior in 3D is when the vesicle is highly deflated (low values of  $\nu$ ). For low values of  $\nu$  the exact vesicle shape and its orientation relative to the flow direction can also influence the detachment dynamics. Furthermore, here we have only considered the bending stiffness of the membrane. In a more general set-up in 3D for real cells, the cytoskeleton can also give rise to elastic contributions to the cell mechanics which may reflect in the relaxation time scale of the cell  $(\tau_c)$  and possibly some other steady state configurations, including flipping,  $^{11,12}$  crawling<sup>12</sup> and rolling,  $^{7,8,10-12}$  may take place. The combined effect of the cytoskeleton elasticity and bond kinetics on the unbinding dynamics of cells under flow requires a separate systematic analysis. However, from the mechanisms shown in this paper some speculations about the effect of cell elasticity can be made. We can see that the elastic nature can lead to reduced tank-treading motion owing to the preferred stress-free configuration. Therefore, the cells with elastic cytoskeleton may experience higher drag (similar to the behavior under high  $C_b$ ) and we expect to see even smaller region of pinned configuration in  $C_b - C_\kappa$  space. Further, the qualitative differences in the form of stable steady state configurations (adhered, pinned and detached) as well as the quantitative scaling laws for the extreme values of  $C_b$  can be utilized in the experiments to validate the results shown in this paper.

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