Surface deformation and shear flow in ligand mediated cell adhesion

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Received: 22 April 2015 / Revised: 22 January 2016 / Published online: 10 March 2016
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Abstract We present a unified, multiscale model to study the attachment/detachment dynamics of two deforming, charged, near spherical cells, coated with binding ligands and subject to a slow, homogeneous shear flow in a viscous, ionic fluid medium. The binding ligands on the surface of the cells experience both attractive and repulsive forces in an ionic medium and exhibit finite resistance to rotation via bond tilting. The microscale drag forces and couples describing the fluid flow inside the small separation gap between the cells, are calculated using a combination of methods in lubrication theory and previously published numerical results. For a selected range of material and fluid parameters, a hysteretic transition of the sticking probability curves (i.e., the function $g^*$) between the adhesion phase (when $g^* > 0.5$) and the fragmentation phase (when $g^* < 0.5$) is attributed to a nonlinear relation between the total nanoscale binding forces and the separation gap between the cells. We show that adhesion is favoured in highly ionic fluids, increased deformability of the cells, elastic binders and a higher fluid shear rate (until a critical threshold value of shear rate is reached). Within a selected range of critical shear rates, the continuation of the limit points (i.e., the turning points where the slope of $g^*$ changes sign) predict a bistable region, indicating an abrupt switching between the adhesion and the fragmentation regimes. Although, bistability in the adhesion-fragmentation phase diagram of two deformable,
charged cells immersed in an ionic aqueous environment has been identified by some in vitro experiments, but until now, has not been quantified theoretically.

**Keywords** Adhesion · Bistability · Binding kinetics · Micro hydrodynamics · Surface deformation · Sticking probability

**Mathematics Subject Classification** 92C05

1 Introduction

The adhesion and fragmentation of cells in suspension is an ubiquitous and biologically significant process. Examples include binding of bacterial clusters to medical implants or host cell surfaces during infection (Zhu 2000), cancer cell metastasis (Moss and Anderson 2000), coalescence of medical gels with functionalized particles or micro-bubbles for targeted drug delivery (Jadhav et al. 2007) and the adherence of platelets and monocytes to atherosclerotic plaques (Forest et al. 2006). Cell adhesion is commonly mediated by specific ligand interactions, e.g., the ligand-mediated surface adhesion is an important case in the experimental studies of the P-selectin/PSGL-1 catch bond interactions of leukocytes (a roughly spherical particle) with and without fluid flow (Marshall et al. 2003). The adhesive properties of biological surfaces connected by multiple independent tethers have inspired the development of novel adhesives mimicking the remarkable properties of beetle and gecko feet (Varenberg and Gorb 2007). Several other applications as well as in vivo and in silico studies of cell adhesion are listed in (Lauffenburger and Linderman 1993; Springer 1995; Hammer and Tirrell 1996; Jones et al. 1996; Zhu 2000). However, the models and the experiments listed in these references fail to capture, with a single unified theory, the several interrelated physical features associated with the adhesion process. Therefore the motivation of this article is to develop a unified theory and approach that can capture these coupled effects.

The theoretical modelling of surface adhesion in a fluid-borne environment presents significant challenges. The adhesive forces are composed of numerous physical processes including ligand-receptor binding kinetics (Dembo et al. 1988), surface deformation and the related mechanical stresses due to the elastic forces on the cell membrane (Hodges and Jensen 2002), excluded volume effects and paramagnetism (Forest et al. 2006), short range interactions (Sircar and Bortz 2013), and flow past the surrounding surfaces (Reboux et al. 2008), all of which determines the fate of the binding surfaces. Consequently, many detailed kinetic models have successfully, yet independently, described these physical features imperative in the adhesion-fragmentation processes. Korn and Schwarz (2006) and more recently Mani et al. (2012) studied the cellular adhesion between the ligand coated wall and a rigid sphere moving in a shear flow. A similar model by Bihr et al. (2012) described the membrane adhesion via Langevin simulations. However, a link between the nanoscale and the microscale description connecting the above mentioned physical details is still missing in these models, which we address in this article.
Multiscale models provide a powerful route to explore possible connections between microscopic physiological observations, such as the minimum shear threshold for surface adhesion (Hammer and Tirrell 1996) and the nanoscale mechanochemical effects operating within individual intermolecular bonds (Dembo et al. 1988). Corezzi et al. (2012) reported research in this direction, but their numerical studies were done with chemically inert particles. Other examples of recent work includes developing probabilistic extensions of the Smoluchowski’s multiplicative aggregation kernel in one (Odriozola et al. 2007) and two dimensions (Moncho-Jordá et al. 2001) and with kernels containing one scaling parameter to be fit to data. Jia et al. (2006) developed a method for predicting critical coagulant concentration via deriving a kernel incorporating surface charge density and potential as a function of the electrolyte. Gilbert et al. (2007) investigated and validated the forces and potentials for nanoparticles, whereas Bäbler and Morbidelli (2007) studied aggregation and fragmentation, but only driven by diffusion and shear flow. In summary, each of these research efforts focused on the adhesion and fragmentation using separate theories that we unify in this article.

The aim of this article is to develop and investigate a unified, multiscale model (within the nano-micro spatial organization) for a ligand mediated deformable cell-cell adhesion dynamics in slow, viscous, shear flow conditions. This unique study considers several competing physical processes influencing simultaneous transition between the adhesion-fragmentation regimes, namely, binding-unbinding of the ligands, surface deformation, fluid flow and interaction between the charged surface and the liquid medium. In particular, we quantify the existence of the bistable phase in the adhesion-fragmentation phase diagram of two, deforming, charged cells immersed in an ionic fluid (addressed in Sect. 3). In the next section, we present the details of the comprehensive model, including the bond mechanics (Sect. 2.1), the interaction of charged surface in a fluid medium (Sect. 2.2), nanoscale binding forces on the cell surface (Sect. 2.3), microscale drag forces and couple arising due to the flow-hydrodynamics inside and outside the narrow gap between the cell surface (Sect. 2.4) and the calculation of the adhesion area of deformed cells in slow, viscous shear flow (Sect. 2.6). The nanoscale forces and the entire system of non-dimensionalized equations are listed in Sect. 2.5 and coupled with the microscale hydrodynamics in Sect. 2.7. Section 3 highlights the simulation results of the binder kinetics at steady state and the bifurcation analysis in a select range of material and fluid parameters. We conclude with a brief discussion of the implication of these results and the focus of our future direction (Sect. 4).

2 Mathematical model: binder kinetics, surface deformation and hydrodynamics

This section derives the evolution equation governing the dynamics of the binding ligands, attached on the charged surface of the cells and immersed in an electrolytic solvent subject to slow shear flow. We model a cell as a thin sphere with extensible membrane subject to tension but having negligible bending stiffness, surrounding a fluid interior of fixed volume per unit length. The viscosity of the cell’s interior is assumed to be low enough that it behaves as if it were inviscid. The effects of gravity,
non-specific forces acting on the cell, as well as the roughness of the cell surface are neglected. Further, we assume that subject to a finite tilting, the ligands are fixed on the cell surface. The spherical cells adhere through well-defined disc-like patches covered with binding ligands (Fig. 1). Due to their relatively large micron-size scale, the binding kinetics of these cells are significantly different from the core-shell nano-crystal interactions, which are applicable at much smaller scales (Duval et al. 2008). The next few subsections detail aspects of this model.

### 2.1 Binder kinetics

Figure 1 illustrates the motion of two deformed spheres, with an identical size of (undeformed) radius $R$. The spheres are moving in a fluid undergoing planar shear flow. To simplify the visualisation of the dynamics, consider a moving frame, $(R_m)$, with origin $O_m$, fixed on the surface of the sphere $S_2$ at a point equidistant from the edge of the separation gap. The unit vectors for this frame of reference are $e_x$, $e_y$ and $e_z$. For a given spatial point $x = (x, y, z)$ in this moving frame, the velocity of the fluid is $G z e_x$, where $G$ is the shear rate. The total relative velocity (of sphere $S_1$ with respect to sphere $S_2$) in this frame is $V(G, x) = U_x e_x + U_z e_z$, where $U_x$ and $U_z$ are, respectively, shearing flow (along the plane perpendicular to the line joining the centres), and the velocity of the squeezing motion of the spheres (along the line joining the centres). Let $D(x)$ be the distance between the two spheres. Define $A_{Tot} g(x, t) dA$ as the number of bonds that are attached between the surfaces $dA$ at time $t$ where $A_{Tot}$ is the total number of binding ligands. In established research on colloids, the function $g$ is synonymous with the term sticking probability (Somasundaran et al. 2005). The total number of bonds formed is $\int_{A_c} A_{Tot} g(x, t) dA$, where $A_c$ is the area of adhesion. The adhesion of the two cells occur inside a circular patch of area $A_c = \pi R_c^2$, where $R_c$ is the radius of the patch (Sect. 2.6 details the derivation of this area).
Allowing highly stretched bonds to be readily broken by thermal energy fluctuations, the forward and the reverse reaction rates for the ligand binding are then written as Boltzmann distributions. The kinetics are also influenced by the surface potential of the two charged surfaces. Further, we account for the ligand tilting by a finite angle $\alpha_0$ with respect to the vertical direction. This tilt is again expressed as a Boltzmann distribution, $\mathcal{D}(\alpha_0)$, such that a bond may form between the two spheres for a given angle $\alpha_0 \in (-\frac{\pi}{2}, \frac{\pi}{2})$. With these degrees of freedom, the bond attachment/detachment rates are

$$
K_{\text{on}}(x) = K_{\text{on,eq}} \exp \left[ \frac{-\lambda_s(L(x) - l_0)^2 + W(D(x))}{2k_B T} \right] \mathcal{D}(\alpha_0),
$$

$$
K_{\text{off}}(x) = K_{\text{off,eq}} \exp \left[ \frac{(\lambda_0 - \lambda_s)(L(x) - l_0)^2 + W(D(x))}{2k_B T} \right],
$$

where $k_B$ is the Boltzmann constant, $T$ is the temperature, $l_0$ is the mean rest length of the binders, $\lambda_0$ is the binder stiffness coefficient, and $\lambda_s$ is the spring constant of the transition state used to distinguish catch ($\lambda_0 < \lambda_s$) from slip ($\lambda_0 > \lambda_s$) bonds (Dembo et al. 1988). $W(D)$ is the total surface potential described in §2.2. In further description of the model and without loss of generalisation, we denote $D(x) \equiv D$. As depicted in Fig. 1, $L = \sqrt{D^2 + |x|^2}$ is the length of a bond in a stretched configuration. The energy associated with a bond tilted from its vertical position is $(1/2)\kappa_{\theta} \alpha_0^2$, ($\kappa_{\theta}$ being the torsion constant) and (Reboux et al. 2008)

$$
\mathcal{D}(\alpha_0) = \exp \left( -\frac{\lambda_{\theta} \alpha_0^2}{2k_B T} \right) \frac{1}{D_0}, \quad \alpha_0 = \tan^{-1} \frac{x}{D},
$$

where $D_0 = \int_{-\pi/2}^{\pi/2} \exp \left[ -\frac{\lambda_{\theta} \alpha_0^2}{2k_B T} \right] d\alpha_0$ is the normalization constant for all possible tilt orientations along the flow-direction. In the limit of small binding affinity and abundant ligands on the binding surface (i.e., $A_{\text{Tot}} K_{\text{on,eq}} / K_{\text{off,eq}} \ll 1$), the bond ligand density evolves in accordance with the PDE (Dembo et al. 1988; Hodges and Jensen 2002; Reboux et al. 2008)

$$
\frac{dg}{dt} = A_{\text{Tot}} K_{\text{on}} - K_{\text{off}} g, \quad g = 0 \quad \text{for} \ x \geq R_c,
$$

where the material derivative $\frac{dg}{dt} = \frac{\partial g}{\partial t} + \mathbf{V} \cdot \nabla g$.

### 2.2 Long range interactions

Derjaguin, Landau, Verwey and Overbeek theory is utilized to describe the interaction between the charged cell surfaces as well as due to the ions dispersed in the fluid medium, via a surface potential $W(D)$ (Eq. (1)). Only the effects of Coulombic repulsion and Van der Waals attraction are incorporated. Other interactions including hydration effects, hydrophobic attraction, short range steric repulsion and polymer
bridging (Gregory 2006), which are absent in the length scales of our interest are neglected in the present study. For two charged, identically sized, spheres, the potential due to the Coulombic forces in the gap of separation \( D \) is

\[
W_C(D) = 2\pi \varepsilon_0 \varepsilon \psi_0^2 R e^{-\delta D},
\]

where \( \delta \) is the Debye length, \( \varepsilon_0 \) and \( \varepsilon \) are the dielectric constant of vacuum and the medium, respectively, and \( \psi_0 \) is the average Zeta potential or the electric potential of the diffuse cloud of charged counterions. The potential due to the Van der Waal forces for these spherical cells in the regime of close contact is

\[
W_{VW}(D) = -\frac{A R}{12 D} \text{ for } D \ll R,
\]

where \( A \) is the Hamaker constant measuring the van der Waal ‘two-body’ pair-wise interaction for ‘large’ spherical objects.

### 2.3 Nanoscale forces: bond mechanics

Consider one individual bond formed between the points \( O_m \) on sphere \( S_2 \) [which is also the origin of the frame \((R_m)\)] and \( P \) on sphere \( S_1 \) (Fig. 1). The instantaneous force it exerts on the two spheres has three components: an extensional force related to bond stretching given by the Hooke’s law, \( f_E = \lambda (L - l_0) e_L \); a force due to surface-charges, \( f_C = \nabla W(D) e_z \); and a torsional force proportional to the angle formed by the bond with the vertical, \( f_T = (\lambda \theta e_T^0) e_{L\perp} \), where \( e_L = -(x e_x + D e_z) / L \) and \( e_{L\perp} = (-D e_x + x e_z) / L \) are the unit vectors in the direction tangential and perpendicular to the bond as shown in Fig. 1, respectively. The operator, \( \nabla \), in the expression of the force due to surface charges, \( f_C \), denotes the derivative with respect to \( D \). The total nanoscale force, due to each component, arising from all such bonds inside the adhesion area is (Reboux et al. 2008)

\[
F_i(x, t) = A_{Tot} \int_{A_r} g(x, t) f_i(x, t) dA(x, t), \quad i \in \{E, C, T\}.
\]

### 2.4 Microscale forces: flow hydrodynamics

In this section, we outline the derivation of the different components of the hydrodynamic force arising out of the flow past the surrounding cells. First, we present the hydrodynamic force resisting the relative motion of two deformable cells moving along their lines of centres (i.e., along the direction \( e_z \), Fig. 1) as well as the force and couple associated with the transverse translation of these drops along the direction of the flow (i.e., along the direction \( e_x \)), in the Stokes regime. Haber et al. (1973) considered a very general problem of two viscous drops with unequal sizes, velocities and viscosities, translating along their lines of centres in birefringent coordinates. The drops are in close proximity (\( D \ll 1 \), Fig. 1) so that the drag force is derived via
lubrication theory. For the case of two identical drops moving toward each other with equal speed, Haber’s solution for the drag force reduces to (Kim and Karrila 2005)

\[ F^*_z = \frac{F_z}{6\pi\mu RU_z} = \frac{2}{3} \sinh \beta \sum_{n=1}^{\infty} C_n K^0_n(\beta) + \lambda K^1_n(\beta) Q^0_n(\beta) + \lambda Q^1_n(\beta) e_z, \]  

(7)

where the functions

\[ K^0_n(\beta) = 2 \left[ (2n+1) \sinh 2\beta + 2 \cosh 2\beta - 2e^{-(2n+1)\beta} \right], \]
\[ K^1_n(\beta) = (2n+1)^2 \cosh 2\beta - 2(2n+1) \sinh 2\beta - (2n+3)(2n-1) + 4e^{-(2n+1)\beta}, \]
\[ Q^0_n(\beta) = 4 \sinh(n - \frac{1}{2})\beta \sinh(n + \frac{3}{2})\beta, \]
\[ Q^1_n(\beta) = 2 \sinh(2n+1)\beta - (2n+1) \sinh 2\beta, \]
\[ C_n = \frac{n(n+1)}{(2n-1)(2n+3)}. \]  

(8)

The starred quantity in Eq. (7) is the non-dimensional counterpart of the force \( F_z \). The product \( (\lambda\mu) \) is the viscosity of the fluid inside the drop (\( \mu \) being the viscosity of the fluid outside the drop). Parameter \( \beta \) is related to the distance between the centres of the cell by \( 2D_c + D = 2R \cosh \beta \) (Fig. 1). The scalar \( U_z = \|U_z\| \) (where \( \| \cdot \| \) denotes the magnitude of a vector). For inviscid cells, we set \( \lambda = 0 \) in Eq. (7) and, following Cox and Brenner (1967), break the summation into an “inner sum” \( \sum_{n=1}^{N} \) and an “outer sum” \( \sum_{n=N+1}^{\infty} \) (with the breakpoint \( N \) determined by requiring \( \beta N \sim 1 \)) and simplify the expression for large \( N \) to obtain the drag force on either cell,

\[ F^*_z = \frac{F_z}{6\pi\mu RU_z} = \left[ \frac{1}{3} \ln \left( \frac{R}{D} \right) + \frac{2}{3}(\gamma + \ln 2) \right] e_z, \]  

(9)

where \( \gamma = 0.57722 \) is Euler’s constant. The flow in between the inviscid cells, along the plane perpendicular to the line joining the centers of the cell, is not dominated by the gap region and thus lubrication theory does not apply (Davis et al. 1989). However, in a slow shear flow regime, we use the leading order results obtained by Davis and Zinchenko (2009) for the forces and the couples:

\[ F^*_s = \frac{F_s}{6\pi\mu RU_x} = 1.15e_x, \quad T^*_s = \frac{T_s}{8\pi\mu R^2 U_x} = 1.1e_y, \]  

(10)

where \( U_x = \|U_x\| \). By principle of linear super-position, the total forces and the torque on the two moving cells in slow shear flow conditions are the sum of the contributions from Eqs (9,10); \( \mathbf{F} = \mathbf{F}_z + \mathbf{F}_s \), and \( \mathbf{T} = \mathbf{T}_s \).
2.5 Non-dimensionalized system

We non-dimensionalize the length scales with respect to the undisturbed radius of the cell, $R$, and introduce the following dimensionless variables denoted by stars

\[ x = Rx^* \quad D = RD^* \quad L = RL^* \quad R_c = RR_c^* \]

\[ K_{on} = K_{on}^* K_{on,eq}, \quad K_{off} = K_{off}^* K_{off,eq}, \quad g = g^* K_{eq}, \]

\[ t = t^*/G, \quad U_{x,z} = U_{x,z}^* R K_{off,eq}, \quad \text{and} \quad V^* = U_x^* + U_z^*. \]

where $K_{eq} = A_{Tot} K_{on, eq} / K_{off, eq}$. Two time-scales are introduced, one associated with the fluid shear rate (i.e., $t_1 = G^{-1}$) and the other with the rate constant of the unbinding reaction (i.e., $t_2 = K_{off,eq}$). This is done to neglect the lower order terms in the non-dimensional form of equations (in the limit of slow time-scales), as shown in §2.7. Further, we introduce the following non-dimensional parameters,

\[ r = \frac{\lambda_0 l_0^2}{k_B T}, \quad \lambda_\theta^* = \frac{\lambda_\theta}{k_B T}, \quad \lambda_s^* = \frac{\lambda_s}{\lambda_0}, \quad \varepsilon = \frac{l_0}{R}. \]

The non-dimensional form of the reaction rates, Eq. (1), bond-density evolution, Eq. (3), and the boundary conditions are

\[ K_{on}^* = \exp \left[ -\lambda_s^* \frac{r}{2\varepsilon^2} (L^* - \varepsilon)^2 - \frac{\lambda_\theta^*}{2} \alpha_0^2 + W^*(D) \right] / P_0, \]

\[ K_{off}^* = \exp \left[ (1 - \lambda_s^*) \frac{r}{2\varepsilon^2} (L^* - \varepsilon)^2 + W^*(D) \right], \]

\[ \frac{G}{K_{off,eq}} \frac{\partial g^*}{\partial t^*} + V^* \cdot \nabla^* * g^* = K_{on}^* - K_{off}^* g^*, \]

\[ g^* = 0 \quad |x^*| \geq R_c^*. \]

where $W^*(D) = W(D)/(2k_B T)$. Similarly, the non-dimensional form of the nanoscale forces arising from all bonds are

\[ F_E^*(U_x, U_z, D) = -\int_{A_c^*} g^* \left( 1 - 1/L^* \right) \left[ x^* e_x + D^* e_z \right] dA^*, \]

\[ F_C^*(U_x, U_z, D) = -(1/l_0 r) e_z \int_{A_c^*} g^* \left[ \pi \varepsilon_0 \varepsilon_0^2 \psi_0^2 \frac{2R_1 R_2}{R_1 + R_2} \left( e^{-\kappa D} - \frac{A}{24D^2} \right) \right] dA^*, \]

\[ F_T^*(U_x, U_z, D) = (\kappa_\theta^*/r) \int_{A_c^*} \left( g^* / L^* \right) \alpha_0 \left[ -D^* e_x + x^* e_z \right] dA^*, \]

where $F_E^*$, $F_C^*$ and $F_T^*$ are the non-dimensional forces due to extension, surface charges and torsion, respectively, and $F_i^* = F_i / (A_{Tot} K_{eq} k_0 R^3)$. 

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2.6 Adhesion area: $A_c$

We determine the radius of the adhesion area by splitting the computational domain into two distinct regions: an inner region (which is the gap between the two cells) and an outer region, outside the gap (in the horizontal sense). We define the variables $(P, C)$ as the corresponding variables in the outer region. The variables are scaled with $c_{\text{ref}} = \tau$ for surface tension and $p_{\text{ref}} = \tau/R$ for pressure, respectively, and the non-dimensional counterparts are denoted with starred quantities (i.e., $p^*, P^*, c^*, C^*$). For a small, non-dimensional separation gap, $D^*$, between the two cell surfaces; a perturbation expansion of the variables of the form, $q^* = q^{*0} + D^* q^{*1} + O(D^*2)$, is used. The membrane curvature is denoted by $Q$ (and the non-dimensional curvature denoted by $Q^* = Q/R$). Inside the inner region, the cells deform under the action of the adhesive forces and the shear flow. For static cell configurations, Jensen found that the stress balance on one of the cell surface in the inner region (Fig. 1), at the leading order in $D^*$, is (Hodges and Jensen 2002)

$$M K_{\text{on}}^* (f_E^* + f_C^* + f_T^*) + p^{*0} e_z = Q^* c^{*0} e_z - c_x^{*1} e_x,$$

(16)

where $M = \lambda_0 A_{\text{Tot}} K_{\text{on,eq}} R^2 \varepsilon/\tau$ (the uniform tension of the undisturbed cell) is a dimensionless parameter related to the strength of the cell surface; that is, reducing $M$ corresponds to making the cell less deformable and vice-versa. $f_i^* = f_i / (\lambda_0 l_0)$. For slow shear rates ($G \leq 5 \text{s}^{-1}$), the stress balance at the next order of approximation in the inner region, is

$$p^{*1} e_z = Q^* c^{*1} e_z - c_x^{*1} e_x + \sigma e_x,$$

(17)

where $\sigma = \mu GR/\tau$. The superscripts, 0 and 1, denote variables at the leading order and the next order approximation, respectively, and the variable $c_x^{*1}$ denote derivative of the surface tension in the moving frame. The cell membrane is flat (with $Q = 0$) along the majority of the inner region, except at the edge of the gap where it connects with the outer region (point K, Fig. 1). In the outer region, the leading order and the next order of approximation in the stress balance on the cell surface is

$$P^{*0} e_R = Q^* C^{*0} e_R - C^{*0}_\theta e_\theta,$$

(18)

$$P^{*1} e_R = Q^* C^{*1} e_R - C^{*1}_\theta e_\theta + \sigma e_x,$$

(19)

where $e_R$ and $e_\theta$ are the unit vectors along the directions normal and tangential to the cell surface, and the variables $C^{*0}_\theta$ and $C^{*1}_\theta$ denote the derivative of the surface tension along a tangent to the surface at leading order and first order, respectively.

For an undisturbed cell (satisfying stress balance (16)), Hodges and Jensen (2002) found an asymptotic expression for the patch radius in the limit of a small separation gap, with no sharp corners and with a uniform tension and curvature in the outer region of the cell. In the slow shear rate regime, we account for the first order correction to the surface tension and the net pressure (Eqs (17, 19)), then match the solution in the inner and the outer region with matching conditions at the juncture (i.e., at point K, Fig. 1), via the method of matched asymptotic expansion. Hodges and Jensen (2002)
provided a detailed analysis for static cell shapes. The expression of the patch radius for slow shear rates, is

\[ R_c = R \left| \sqrt{1 - \left[ 1 - \frac{\varepsilon \, \lambda \, \mu}{r} \left( 1 + \frac{\lambda_0^*}{r} \right) \right]^2 - \sigma - W^*(D) \right|, \]

(20)

For neutral cells in static equilibrium \((G = \lambda_0^* = W^*(D) = 0)\), the expression of the patch radius derived by Hodges and Jensen (2002) [relation 2.10] is recovered from (20).

2.7 Nano-micro coupling

Under the assumption that the bonds are formed and broken at a rate sufficiently rapid for them to remain in equilibrium, i.e., \(G/K_{off,eq} \ll 1\), the unsteady binding effects (i.e., the time-dependent term in Eq. (14)) are neglected and the evolution equation for the sticking probability is solved at steady-state

\[ V^* \cdot \nabla^* g^* = K_{on}^* - K_{off}^* g^*. \]

(21)

The coupling between the microscale and the nanoscale description is obtained via the global force balance on the spheres in the horizontal and vertical directions, and the torque balance about the center of mass of the spheres. Assembling the forces and couples from the fluid hydrodynamics, Eqs (9, 10), and the total forces due to bond-extension, surface charges and bond-torsion, arising from all bonds (Eq. (6)), we obtain

\[
\begin{align*}
(F^*_E + F^*_C + F^*_T) \cdot e_z + F^*_z &= 0, \\
(F^*_E + F^*_C + F^*_T) \cdot e_x + F^*_x &= 0, \\
\frac{R}{2} (F^*_E + F^*_C + F^*_T) \cdot e_x + T^*_s &= 0,
\end{align*}
\]

(22)

where the factor \(R/2\) denotes the effective radius of a system of two spheres of equal radius. \(F^*_z, F^*_x, T^*_s\) are the scalar values of the forces and couples outlined in Eqs. (9, 10). The nano-micro force balance is utilized to solve for the unknowns, the translational speeds \(U_x, U_z\) and the separation gap between the spheres \(D\). The solution procedure is outlined as follows. Using Eq. (15), we first numerically determine the nanoscale forces \(F^*_E, F^*_C, F^*_T\) as functions of \(U_x, U_z\) and \(D\) for a fixed sample of parameter values (i.e., \(G, \delta, \lambda_0, \lambda, \mu\)). We expect that this nonlinear system has multiple solutions in the selected range of parameter space. For each point on a fine grid in the \((U_x, U_z, D)\)-space, numerical integration is performed with finite differences via the subroutine d03raf in the NAG library to solve for the system of PDEs (21, 22) and via the subroutines e01baf, e01bdf for spline interpolation and spline integration for the integral Eq. (15), respectively. Solutions are presented below using 100 × 100 × 100 grid points over a domain of volume \(\pi R_c^2 R^* (= \pi)\). The resulting
data set is then fitted by 3D spline interpolates, allowing us to implement $F_E^*, F_C^*$ and $F_T^*$ as smooth functions of $U_x$, $U_z$ and $D$ and for a fixed set of material and fluid parameters. The numerical results are compared with previously published asymptotic results, in the limit $U_x \ll 1$ and $U_x \gg 1$ (Reboux 2008) and (within 1 % numerical error in the $l_\infty$ norm of the difference in the two solutions) found to be in excellent agreement. The next section qualitatively describes these numerical results and the resulting biophysical implications.

3 Binder kinetics at steady state

Table 1 lists the parameters used in our numerical calculations. The parameter values are chosen so that they closely replicate the adhesion-fragmentation of neutrophils in slow viscous shear flow conditions. For example, the p-selectine molecule extends about 40 nm from the endothelial cell membrane, so when combined with its ligand PSGL-1 it is reasonable to take $l_0 \approx 100$ nm as an estimate of the length of the unstressed bond (Shao et al. 1998). Typically, neutrophils have a size of $R \approx 4 \mu m$ which gives the length ratio $\varepsilon \approx 0.025$ (Eq. (12)). Shao et al. (1998) measured variations of up to three orders of magnitude in vivo in measuring the values of the microvillus stiffness, $\lambda_0$, as well as the membrane tension of an undisturbed cell. Direct measurements of the parameters, $A_{Tot}$, $K_{on,eq}$ and $K_{off,eq}$ are scarce, although values in several thousands have been used in previous models (Hammer and Tirrell 1996). Since we do not wish to study the effects of finite rotation of the ligands (Reboux et al. 2008) or the effect of catch-versus-slip bonds (Dembo et al. 1988), the corresponding parameters related to these material properties are fixed at $\lambda_*^{\theta} = 1.0$ and $\lambda_*^{s} = 0.5$, respectively. The dielectric constant in vacuum is $\varepsilon_0 = 8.854 \times 10^{-12} Fm^{-1}$, whereas the permittivity of water at temperature 25°C is $\varepsilon = 78.5$ (not to be confused with $\varepsilon$ which is a length ratio, Eq. (12)). The dissolved salt (furnishing the ions in the fluid) is assumed to be a 1-1 electrolyte with a zeta potential of $\psi_0 = 25$ mV (corresponding to the surface potential studies by Gregory (2006) [Chap. 3]). We assume that the solute concentration in the fluid only effects the Debye length, $\delta$. The Boltzmann factor is taken as $k_BT = 4 \times 10^{-21} J$.

As a preliminary step, the model was validated by estimating the net hydrodynamic speed, $V = \|U_x + U_z\|$, of two noninteracting, nearly rigid spheres as a function of the shear rate, $G$. For this purpose, spherical capsules with a membrane stiffness coefficient of nearly rigid spheres, $\mathcal{M} = 0.01$, and high ligand stiffness, $\lambda_0 = 10^{-2} Nm^{-1}$, was used. Simulations indicate that the hydrodynamic velocity increases linearly with the shear rate from 0.5 $\mu m/s$ at 0.25 $s^{-1}$ to 2 $\mu m/s$ at 1.0 $s^{-1}$ (Fig. 2). These values are in excellent agreement (with $< 0.1 \%$ difference in $l_\infty$-norm) with the velocity calculated by O’Neill and Majumdar (1970) for the motion of two hard spheres of the same size and at the same separation distance in a linear shear field.

Next, we explored the flow/binding kinematics of the deforming spheres in a uniform shear flow. Figure 3a depicts the steady-state solution in the sticking probability-shear flow phase space ($g^*, G$) at a distance $x^* = 0.5$ from the origin of the moving frame, and for variable surface deformabilities, $\mathcal{M}$. An adhesion phase is defined when the majority of the binders (inside the adhesion area, $A_C$) are hooked with each other, i.e., $g^* > 0.5$; otherwise the spheres are in the fragmentation phase.
Table 1 Parameters common to all numerical results and used in studies of the system of Eqs. (13, 15, 21, 22)

| Parameter | Value | Units | Source |
|-----------|-------|-------|--------|
| $A_{\text{Tot}}$ | $10^9$ | m$^{-2}$ | (Hammer and Tirrell 1996) |
| $K_{\text{on, eq}}$ | $10^2$ | s$^{-1}$ | (Hammer and Tirrell 1996) |
| $K_{\text{off, eq}}$ | $10^{14}$ | s$^{-1}$ | (Hammer and Tirrell 1996) |
| $\lambda_0$ | $10^{-5} - 10^{-2}$ | N m$^{-1}$ | (Mani et al. 2012) |
| $\mu$ | $10^{-3}$ | N s m$^{-2}$ | (Reboux et al. 2008) |
| $G$ | 1 – 5 | s$^{-1}$ | (Reboux et al. 2008) |
| $l_0$ | $10^{-7}$ | m | (Shao et al. 1998) |
| $R$ | $4 \times 10^{-6}$ | m | (Shao et al. 1998) |
| $\tau$ | $2.5 \times 10^{-5} - 2.5 \times 10^{-3}$ | N m$^{-1}$ | (Shao et al. 1998) |

A third, bistable phase in which the spheres exhibit a stable steady-state adhesion and fragmentation (e.g., inside the shear rate range $G_0 \leq G \leq G_1$, as shown in the case of $\mathcal{M} = 0.1$ in Fig. 3a) simultaneously coexists on the phase plane. Although, the presence of this bistable phase have been reported in several in vitro experiments on cell-wall adhesion (Brunk and Hammer 1997; Yago 2002; King et al. 2005) and some cases of cell-cell adhesion (Coombs et al. 2004), a quantitative description of this phase for the specific case of two deforming cells immersed in an ionic fluid, is missing. Figure 6 presents the boundaries of the adhesion, the fragmentation region and the bistable region which are computationally tracked as a continuation of the limit points of $g^*$. Further description of this bistable phase is outlined later.

In the present study, three different types of adhesion-fragmentation kinematics are found. For example, for nearly rigid cells (Fig. 3a, $\mathcal{M} = 0.01$), the transition from adhesion to fragmentation phase (and vice-versa) is irreversible and discontinuous. For this curve, the adhesive effects are strong for low shear rates (i.e., $g^*$ has a stable steady-state branch with $g^* > 0.5$ in the shear rate range $G < 0.5$ s$^{-1}$). As the shear rate increases beyond the critical value, $G = 0.5$, the system abruptly jumps to a steady-state branch in the fragmentation phase (i.e., $g^* < 0.5$) and remains in this phase even

Fig. 2 Hydrodynamic speed of two identical, hard spheres (results highlighted with ‘◦’) compared with the theoretical results (O’Neill and Majumdar 1970) (solid curve)
Surface deformation and shear flow…

Fig. 3  Steady state transition curves of the sticking probability function, \( g^*(x^* = 0.5) \), versus the shear rate, \( G \), for different (a) membrane stiffness, \( \mathcal{M} \), (b) screening lengths, \( \delta \), and (c) binder stiffness, \( \lambda_0 \). Three different adhesion-fragmentation transitions are detected when the membrane stiffness is changed: (1) continuous reversible transition (dash-dot curve); (2) continuous irreversible transition (dashed curve); and (3) discontinuous irreversible transition (solid curve).  

(a) \( \mathcal{M} = 0.01 \), \( \mathcal{M} = 0.1 \), \( \mathcal{M} = 0.9 \)

(b) \( \delta = 0.5 \), \( \delta = 1.0 \), \( \delta = 2.0 \)

(c) \( \lambda_0 = 10^{-5} \), \( \lambda_0 = 10^{-3} \), \( \lambda_0 = 10^{-1} \)

if the fluid shear rate is reduced below this critical value. For deformable cells (Fig. 3a, \( \mathcal{M} = 0.1, 0.9 \)), this transition is reversible with flow, and either changes continuously (\( \mathcal{M} = 0.9 \) curve) or discontinuously through the bistable region (\( \mathcal{M} = 0.1 \) curve).

Figure 3b, c, respectively, presents the effects of the different ionic conditions in the surrounding fluid affecting only the screening length, \( \delta \) (in the present study), and the binder stiffness coefficient, on the flow-kinematic phase space. Strong surface adhesion is observed in highly ionic fluids (i.e., fluids represented by shorter screening lengths, \( \delta \), Fig. 3b) and with elastic binders (i.e., binders with lower stiffness coefficient, Fig. 3c). A shorter screening length implies a smaller separation distance between the interacting surfaces, and hence a strong adhesion. Similarly, elastic binders aid bond formation which favors surface adhesion. Another observation is the absence of any qualitative differences within the curves in Fig. 3b,c, a finding which is consistent with previous theoretical predictions (Hammer and Tirrell 1996).

Physically, the abrupt hysteretic transitions in the sticking probability curves between the adhesion and the fragmentation regimes (i.e., the transition curves in Fig. 3) is explained by the relation between the magnitude of the total nanoscale bind-
The nonlinear relation between the nanoscale forces and the fluid shear rate as well as the cell deformability is justified as follows. With increasing shear rate the binders are advected away from the vertical alignment, the \( z \)-component of the torsion force, \( \mathbf{F}_T \), as well as the surface force, \( \mathbf{F}_C \), pushes the cells farther away. However, for sufficiently large separation distances, the bonds stretch and the extension forces, \( \mathbf{F}_E \) (\( \propto D^* \)), tend to pull the cells close to each other. All these forces depend on the minimum separation, \( D^* = D^*(G, \mathcal{M}, \delta) \), (Fig. 4b), which varies nonlinearly with the fluid shear rate, the cell surface deformability and the ionic conditions in the fluid, and thus accounts for this non-linear variation versus the separation distance. Further, we numerically verified that the maximum of the total nanoscale forces is attained at a critical shear rate, \( G_c \) (e.g., as shown in Fig. 4a), when the separation gap, \( D^* \), reaches close (i.e., within 1% numerical accuracy in the \( l_\infty \) norm) to its asymptotic value, as shown in Fig. 4b. Numerical results indicate that this critical shear rate is attained when the total nanoscale binding forces, \( F_{\text{Tot}} \), are at their peak. Further, the peak of these forces and the critical shear rate increase with increasing cell deformability (i.e., from \( F_{\text{peak}}^{\text{Tot}} = 0.25 \) and \( G_c = 0.45 \) (at \( M = 0.01 \)), to \( F_{\text{peak}}^{\text{Tot}} = 0.68 \) and \( G_c = 1.87 \) (at \( M = 0.1 \)), to \( F_{\text{peak}}^{\text{Tot}} = 0.87 \) and \( G_c = 2.12 \) (at \( M = 0.9 \))), which leads to the conclusion (similar to those documented in another article (Jadhav et al. 2005)) that deformable cells exhibit strong adhesion.

We investigated the effects of the cell surface deformability (Fig. 5a) as well as the Debye length (Fig. 5b) on the hydrodynamic speed of the cells. At nearly zero
shear rate, the hydrodynamic speed does not vary significantly with the deformability coefficient, $\mathcal{M}$. In contrast, pronounced differences were observed at higher shear rates. In particular, the hydrodynamic speed for nearly rigid cells ($\mathcal{M} = 0.01$, Fig. 5a) and cells immersed in weakly ionic fluids ($\delta = 2.0$, Fig. 5b) increased appreciably. Conversely, only a modest increase in the hydrodynamic speed of more compliant cells ($\mathcal{M} = 0.1, 0.9$ curves in Fig. 5a) or cells immersed in strong electrolytic solvent ($\delta = 0.5, 1.0$ curves in Fig. 5b) occurred with increasing shear, a fact which is explained below and corroborated with the previous in silico experiments (Jadhav et al. 2005).

Altogether, cell deformation induced by the hydrodynamic forces (due to fluid flow) modulates the ligand-mediated cell adhesion kinetics. Deformable cells exhibit compact binding with a higher magnitude of binding forces, (Fig. 4a), remain closer to each other (Fig. 4b) and move slowly (Fig. 5a). In the case of compliant cells, we attribute these features due to an enlarged contact area (Eq. (20)) resulting in an increase in the overall magnitude of the microscale forces inside the gap between the cells (e.g., notice the variation of the hydrodynamic speed versus cell surface deformability in Fig. 5a). Similarly, a highly ionic aqueous environment results in a strong surface adhesion and hence a reduced hydrodynamic speed (e.g., compare the curves in Fig. 5b), an observation reported earlier by Jadhav et al. (2005).

Figure 6 identifies the domain of adhesion (region I), bistability (region II) and fragmentation (region III), within a selected range of materials parameters used in our numerical calculations (Table 1). Bistability is an intrinsic property of any biophysical system exhibiting hysteretic transitions, such as the adhesion-fragmentation transitions as shown in Fig. 3. As the flow shear rate increases from zero to a critical shear rate (e.g., $G_1$, as shown for the case of $\mathcal{M} = 0.1$ in Fig. 3a), majority of (initially bound) ligands unbind (i.e., $g^*$ drops below 0.5). If the shear rate decreases below this critical value the process is reversed, the cells surfaces reattach (i.e., the value of $g^*$ rises above 0.5) but this happens at a critical shear rate different than the previous threshold (e.g., $G_0$, as shown for the case of $\mathcal{M} = 0.1$ in Fig. 3a). The solid lines in Fig. 6 highlights the locus of all such ($g^*, G$) critical-points enclosing the bistable region in the material parameter space. The dashed lines correspond to the nullcline $g^* = 0.5$. 

![Figure 5](image_url)

**Fig. 5** Effect of a cell surface deformability and b fluid ionic conditions, on the hydrodynamic speed of the cells in shear flow. The material parameter for these simulations is fixed at $\lambda_0 = 10^{-3}$ N m$^{-1}$. a Hydrodynamic speed at $\delta = 1.0$ b Hydrodynamic speed at $\mathcal{M} = 0.1$. 
Cell adhesion bistability occurs from a tug-of-war between two kinetic processes taking place within the contact area, bond formation which aids adhesion and bond rupture (Lauffenburger and Linderman 1993). As seen in Fig. 6, the factors affecting adhesion are low fluid shear rate and elastic binders (i.e., lower stiffness coefficient, $\lambda_0$) which assists bond formation, deformable membrane surface (or larger value of the membrane stiffness coefficient, $M$) which leads to increased attachment area, higher magnitude of the total hydrodynamic force (Fig. 4a) and a lower hydrodynamic speed (Fig. 5a), and strong fluid ionic conditions (i.e., lower screening length, $\delta$) which reduces the separation distance between the cell surfaces.

Bistability has been reported in a variety of experiments, especially those involving cell-wall adhesion. Brunk and Hammer (1997) detected bistability in an in vitro set-up of cell-free assay characterized by a single bond type ($\alpha$-selectin and its ligands), mimicking rolling neutrophils over stimulated endothelial surface. Yago (2002) gave further evidence of bistability via numerical simulations of neutrophils rolling on a carbohydrate selectin-ligand substrate under flow—a phenomenon later corroborated by King et al. (2005). The current study provides a theoretical description of the existence of the bistable phase in the adhesion-fragmentation phase diagram of the ligand mediated, deformable, charged, cell-cell adhesion in an ionic aqueous environment, for the first time.

### 4 Conclusions and discussion

Section 2 presented a unified, multiscale model for the adhesion of two spherical, deforming cells via tiltable, elastic ligands in an ionic fluid subject to a homogeneous shear flow. Section 3 demonstrated that the transition between the adhesion and the fragmentation phases are either reversibly continuous, reversibly discontinuous, or irreversible, depending on the deformability of the cell surface, the strength of the ionic fluid medium and the stiffness of the binding ligands. In particular, deformable
cells exhibit strong adhesion. We attribute this partly due to the increased cell-cell contact area as well as a rise in the magnitude of the hydrodynamic forces experienced inside the gap between the cells. Strong ionic fluid conditions favor adhesion via the strengthening of the microscale forces as well as the reduction in the cell separation gap. A bistable region signifying the coexistence of both the aggregation and the fragmentation domains in deforming, two-cell experiments immersed in an ionic fluid, was numerically detected for a selected range of material and fluid parameters (Fig. 6).

Although the proposed model is able to describe the key features in cell adhesion, several issues still need to be addressed. For example, nonlinearity of the nanoscale forces can significantly modify the nano-micro hydrodynamic force balance thereby modifying the adhesion region. Our approach excludes spatial inhomogeneity arising through the material parameters, effects of catch behaviour ($\kappa_r^* > 1.0$), non-equilibrium binding effects, stochasticity and the discrete number of bonds (Zhu 2000), cellular viscoelasticity (needed to fully describe the cell rheology as mentioned by Dembo et al. (1988)), electro-viscous drag on the spherical surfaces surrounded by ionic solution (Jia et al. 2006) (which modifies the fluid velocity across the channel between the cells), as well as shearing forces large enough to tear the binding ligands from their anchoring surface (Varenberg and Gorb 2007). All these effects can lead to several non-trivial behaviours (including the possible absence of hysteresis in flow-phase transition) that deserves a full numerical investigation in the near future.

Acknowledgments Authors thank Dr. Edward Green in the Department of Mathematical Sciences, Adelaide University, for providing useful insights at later stages of the model development. We are also grateful for the two anonymous reviewers providing their detailed criticism which has helped improve the clarity of this article.

References

Bäbler MU, Morbidelli M (2007) Analysis of the aggregation-fragmentation population balance equation with application to coagulation. J Colloid Interface Sci 316(2):428–441
Bihr T, Seifert U, Smith AS (2012) Nucleation of ligand-receptor domains in membrane adhesion. Phys Rev Lett 109(25):1–5
Brunk DK, Hammer DA (1997) Quantifying rolling adhesion with a cell-free assay: E-selectin and its carbohydrate ligands. Biophys J 72(6):2820–2833
Coombs D, Dembo M, Wofsy C, Goldstein B (2004) Equilibrium thermodynamics of cell-cell adhesion mediated by multiple ligand-receptor pairs. Biophys J 86(3):1408–1423
Coreazzi S, Fioretto D, Scirtortino F (2012) Chemical and physical aggregation of small-functionality particles. Soft Matter 8(44):11207–11216
Cox R, Brenner H (1967) The slow motion of a sphere through a viscous fluid towards a plane surface. Part II. Small gap widths, including inertial effects. Chem Eng Sci 22:1753–1777
Davis RH, Schonberg JA, Rallison JM (1989) The lubrication force between two viscous drops. Phys Fluids 1:77–81
Davis RH, Zinchenko AZ (2009) Motion of deformable drops through granular media and other confined geometries. J Colloid Interface Sci 334(2):113–123
Dembo M, Torney DC, Saxman K, Hammer D (1988) The reaction-limited kinetics of membrane-to-surface adhesion and detachment. Proc R Soc Lond Ser B 234(1274):55–83
Duval JFL, Pinheiro JP, Van Leeuwen HP (2008) Metal speciation dynamics in monodisperse soft colloidal ligand suspensions. J Phys Chem A 112(31):7137–7151
Forest MG, Sircar S, Wang Q, Zhou R (2006) Monodomain dynamics for rigid rod and platelet suspensions in strongly coupled coplanar linear flow and magnetic fields. II. Kinetic theory. Phys Fluids 18(10):103102 1–14

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Gilbert B, Lu G, Kim CS (2007) Stable cluster formation in aqueous suspensions of iron oxyhydroxide nanoparticles. J Colloid Interface Sci 313(1):152–159
Gregory J (2006) Particles in water: properties and processes. CRC Press, Boca Raton
Haber S, Hetsonri G, Solan A (1973) On the low reynolds number motion of two droplets. Int J Multiph Flow 1(1):57–71
Hammer DA, Tirrell M (1996) Biological adhesion at interfaces. Ann Rev Mater Sci 26(1):651–691
Hodges SR, Jensen OE (2002) Spreading and peeling dynamics in a model of cell adhesion. J Fluid Mech 460:381–409
Jadhav S, Eggleton CD, Konstantopoulos K (2005) A 3-D computational model predicts that cell deformation affects selectin-mediated leukocyte rolling. Biophys J 88(1):96–104
Jadhav S, Eggleton CD, Konstantopoulos K (2007) Mathematical modeling of cell adhesion in shear flow: application to targeted drug delivery in inflammation and cancer metastasis. Curr Pharm Des 13(15):1511–1526
Jia Z, Gauer C, Wu H, Morbidelli M, Chittofrati A, Apostolo M (2006) A generalized model for the stability of polymer colloids. J Colloid Interface Sci 302(1):187–202
Jones DA, Smith CW, McIntire LV (1996) Leukocyte adhesion under flow conditions: principles important in tissue engineering. Biomaterials 17(3):337–347
Kim S, Karrila SJ (2005) Microhydrodynamics: principles and selected applications. Dover Publications, New York
King MR, Sumagin R, Green CE, Simon SI (2005) Rolling dynamics of a neutrophil with redistributed L-selectin. Math Biosci 194(1):71–79
Korn C, Schwarz US (2006) Efficiency of initiating cell adhesion in hydrodynamic flow. Phys Rev Lett 97(13):1–4
Lauffenburger DA, Linderman JJ (1993) Receptors: models for binding, trafficking and signalling. Oxford University Press, New York
Mani M, Gopinath A, Mahadevan L (2012) How things get stuck: kinetics, elastohydrodynamics, and soft adhesion. Phys Rev Lett 108(22):226104–226108
Marshall BT, Long M, Piper JW, Yago T, McEver RP, Zhu C (2003) Direct observation of catch bonds involving cell-adhesion molecules. Nature 423(6936):190–193
Moncho-Jordá A, Odriozola G, Martínez-López F, Schmitt A, Hidalgo-Álvarez R (2001) The DLCA–RLCA transition arising in 2D-aggregation: simulations and mean field theory. Eur Phys J E 5(4):471–480
Moss MA, Anderson KW (2000) Adhesion of cancer cells to endothelial monolayers: a study of initial attachment versus firm adhesion. J Adhes 74:19–40
Odriozola G, Moncho-Jordá A, Schmitt A, Callejas-Fernández J, Martínez-García R, Hidalgo-Álvarez R (2007) A probabilistic aggregation kernel for the computer-simulated transition from DLCA to RLCA. Europhys Lett 80(6):797–803
O’Neill ME, Majumdar SR (1970) Asymmetrical slow viscous fluid motions caused by the translation or rotation of two spheres. Part II: asymptotic forms of the solutions when the minimum clearance between the spheres approaches zero. Zeitschrift angewandte Mathematik und Physik ZAMP 21(2):180–187
Reboux S (2008) Multiscale models for cellular adhesion and deformation. PhD thesis, University of Nottingham
Reboux S, Richardson G, Jensen OE (2008) Bond tilting and sliding friction in a model of cell adhesion. Proc R Soc A Math Phys Eng Sci 464(2090):447–467
Shao JY, Ting-Beall HP, Hochmuth RM (1998) Static and dynamic lengths of neutrophil microvilli. Proc Natl Acad Sci 95(12):6797–6798
Sircar S, Bortz DM (2013) Impact of flow on ligand-mediated bacterial flocculation. Math Biosci 245(2):314–321
Somasundaran P, Runkanan V, Kapur P, Stechemesser H, Dobiáš B (2005) Flocculation and dispersion of colloidal suspensions by polymers and surfactants: experimental and modeling studies. Coagul Flocculation 126:767–803
Springer TA (1995) Traffic signals on endothelium for lymphocyte recirculation and leukocyte emigration. Ann Rev Physiol 57(1):827–872
Varenberg M, Gorb S (2007) Shearing of fibrillar adhesive microstructure: friction and shear-related changes in pull-off force. J R Soc Interface R S 4(15):721–725
Yago T (2002) Distinct molecular and cellular contributions to stabilizing selectin-mediated rolling under flow. J Cell Biol 158(4):787–799
Zhu C (2000) Kinetics and mechanics of cell adhesion. J Biomech 33(1):23–33