3-D Front-tracking Simulation of Receptor-Ligand Mediated Cell Adhesion to Surfaces

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The adhesion of cells to surfaces in the presence of flow is a major step in many biological responses and disease processes. For example in immune responses, activated leukocytes (white blood cells) step out of blood stream and adhere to the vascular endothelium through receptor-ligand binding, which is critical for the subsequent diapedesis and defense against infection and diseases. Tumor cells focally interact with ligand-bearing endothelium and transmigrate to the underlying tissue sites, serving as a mechanism for cancer spreading. The molecular mechanisms underlying the adhesion process has received a great deal of attention (Ley 1996, Simon & Green 2005, Hammer & Apte 1992, King & Hammer 2001). Distinct adhesion molecules have been implicated in different steps of leukocyte adhesion cascades (Butcher 1991, Springer 1990). Although the molecular binding in the nanoscale contact region critically regulates the adhesion process, the microscale flow and cell morphology serve to balance the adhesive force, also controlling the adhesion process. In vivo and in vitro research has found that leukocyte deformation increases the area of contact between leukocytes and the endothelium. The rolling velocity increases and reach a plateau with increasing shear rates as a result of increased deformation (Firrell & Lipowsky 1989). Additional complexity exists due to cell deformation. A lift force of purely hydrodynamic origin acts on adhered leukocytes as on any other deformable particles in shear near a wall (Abkarian et al 2002, Cantat & Misbah 1999, Leal 1980, Lorz et al 2000, Seifert 1999, Smart & Leighton 1991, Smith & Seifert 2005). In contrast to a rigid sphere in a zero Reynolds number wall bounded shear flow, a deforming drop experiences lateral migration away form the wall (Goldsmith & Mason 1962, Karnis & Mason 1967, Leal 1980). The hydrodynamic lift force on a vesicle (enclosed membrane) bounded by nonspecific forces was studied using lubrication theory in the bound region (Cantat & Misbah 1999, Seifert 1999). Such a hydrodynamic lift critically couple with the molecular bindings in modulating the actual adhesion process. However, a detailed investigation of the coupled physics has not been pursued.

We use a front-tracking finite difference code (Li & Sarkar 2005a, 2005b, 2005c, 2005d, Sarkar & Schowalter 2001a, 2001b) as the over-arching platform to solve the fluid flow outside and inside the cells, and describe their deformation. The fluid inside the cell can be modeled with spatially varying viscoelastic constitutive equations. The stresses due to the cell’s bilayer membrane are modeled with an elastic constitutive equation. The cell membrane is considered as a two-dimensional fluid layer (Singer & Nicolson 1972). The interfacial stress is determined by the initial membrane configuration and its history of deformation. We use a neo-Hookean constitutive model for the membrane (Jadhav et al 2005). The cell membrane is discretized by a mesh of triangular elements. During deformation, the elements remain flat and the constitutive relation is applied to each element. We do not consider the bending stresses at this point. The total force exerted by the surrounding fluid acting on each membrane node is computed by adding the forces exerted by all the elements attached to the node.

The forces due to molecular bindings between leukocytes and endothelium are modeled with linear springs governed stochastic rate equations (Bell 1978, Chang & Hammer 2000, Dembo et al 1988). The cell-wall interactions are mediated by bindings of linear springs (Bell 1978, Dembo et al 1988, Hammer & Tirrell 1996). The formation and rupture of bonds is determined by a stochastic rate law. The probabilities of formation and rupture of a bond are given by

\[ P_1 = 1 - \exp(-k, \Delta t) \]
\[ P_2 = 1 - \exp(-k, \Delta t) \]

(1)
Monte Carlo sampling method is used to simulate random bond associations and dissociations. The reaction rates $k_r$ and $k_d$ are determined by the spring force applied on the bond and the sensitivity to the applied load. The forces exerted by the receptor-ligand bonds and the elastic membrane are distributed over the grid points in the neighborhood of the interface. We use an ADI (alternating direction implicit) scheme for the diffusion term, and a multigrid method for the pressure solution resulting in substantial computational advantage.

We use a novel robust algorithm for non-Newtonian constitutive equations (Sarkar & Schowalter 2000) that could solve the complex multi-phase flow containing a deformable drop. The algorithm combines an analytical integration by parts of the local time derivative part to arrive at the finite difference scheme for the time derivative. An ordinary finite difference algorithm is proved inadequate for the front-tracking finite difference implementation of the multi-phase non-Newtonian stress (Sarkar & Schowalter 2000). The novel difference scheme results in a natural splitting of the elastic and the viscous stresses (Perera & Walters 1977, Rajagopalan et al 1990, Sun et al 1996, 1999). It allows preserving the elliptic nature of the problem and thus enhances stability.

As a validation of our method, the simulation compare well with the analytical results of Goldman et al (1967) for a purely hydrodynamic (no chemical binding) problem of a rigid sphere of radius $a$ rolling at a distance $h$ above wall in shear (Fig. 1, variable are nondimensional). Rigidity was simulated by an extremely high value of membrane elasticity. The long-time steady-state velocity matches well with the analytical result. In Figure 2 (all variables are nondimensional), we consider a deformable sphere (initial $h/a=1.2$), and compare its relative slip and lateral migration velocities with analytical (Leal 1980) and boundary element simulation (BEM) (Uijttewaal et al 1993). The results match well in the range of low capillary number (small deformations). The migration velocity matches well with BEM simulation for all the capillary number considered. The results demonstrated our capability to study the lift effects due to cell deformations.

We further investigate the lift effects on the leukocyte induced by its deformation. In Fig. 3, we show three time-shots of chemically adhered leukocyte adhering and rolling along the plate. The simulation provides us with information about each microvillus, its state of binding, number of bonds, and contact area. We will use it to compute the total force due to molecular binding. At adherence, the vertical component of this force equals the hydrodynamic lift force. Figures 4 and 5 (all variables are nondimensional) shows cell translational velocity and total number of bonds formed for three different values of membrane elasticity. More compliant cells experience larger lift due to larger deformation, leading to earlier detachment (displayed by the faster increase of displacement at low $Eh$ in Fig 4) of leukocytes. However, larger deformation also induces larger contact

![Figure 1](image1.png)  
**Figure 1.** Comparison of the rolling velocity of a highly stiff cell near a wall in shear with analytical solution by (Goldman et al 1967).

![Figure 2](image2.png)  
**Figure 2.** Comparison of the migration and slip velocity of a deformable cell in a wall bounded shear with analytical solutions and BEM simulations.

![Figure 3](image3.png)  
**Figure 3** Cell rolling at three consecutive times mediated by ligand receptor interactions in a wall bounded shear flow.
area leading to more bonds formation (displayed by the larger number of bonds for low \( Eh \) as \( t<2 \)). Such competing dynamics have been systematically investigated. We also investigate the effects of lift on the transition between different adhesion states for varying parameters. Different adhesion states in presence of leukocyte deformation are identified on several state diagrams.

**REFERENCE**


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