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# A computational study of leukocyte adhesion and its effect on flow pattern in microvessels

Vijay Pappu, Sai K. Doddi, Prosenjit Bagchi *

*Department of Mechanical and Aerospace Engineering, Rutgers University (The State University of New Jersey), 98 Brett Road, Piscataway, NJ 08554, USA*

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ABSTRACT

Three-dimensional computational modeling and simulation are presented on the adhesive rolling of deformable leukocytes over a P-selectin coated surface in parabolic shear flow in microchannels. The computational model is based on the immersed boundary method for cell deformation and Monte Carlo simulation for receptor/ligand interaction. The simulations are continued for at least 1 s of leukocyte rolling during which the instantaneous quantities such as cell deformation index, cell/substrate contact area, and fluid drag remain statistically stationary. The characteristic 'stop-and-go' motion of rolling leukocytes, and the 'tear-drop' shape of adherent leukocytes as observed in experiments are reproduced by the simulations. We first consider the role of cell deformation and cell concentration on rolling characteristics. We observe that compliant cells roll slower and more stably than rigid cells. Our simulations agree with previous in vivo observation that the hydrodynamic interactions between nearby leukocytes affect cell rolling, and that the rolling velocity decreases inversely with the separation distance, irrespective of cell deformability. We also find that cell deformation decreases, and the cells roll more stably with reduced velocity fluctuation, as the cell concentration is increased. However, the effect of nearby cells on the rolling characteristics is found to be more significant for rigid cells than compliant cells. We then address the effect of cell deformability and rolling velocity on the flow resistance due to, and the fluid drag on, adherent leukocytes. While several earlier computational works have addressed this problem, two key features of leukocyte adhesion, such as cell deformation and rolling, were often neglected. Our results suggest that neglecting cell deformability and rolling velocity may significantly overpredict the flow resistance and drag force. Increasing the cell concentration is shown to increase the flow resistance and reduce the fluid drag. The reduced drag then results in slower and more stable rolling of the leukocytes with longer pause time and shorter step distance. But the increase/decrease in the flow resistance/fluid drag due to the increase in the cell concentration is observed to be more significant in case of rigid cells than compliant cells.



## 1. Introduction

Adhesion of circulating leukocytes to the vascular endothelium is a critical step in inflammatory response. Circulating leukocytes bind to the walls of post-capillary vessels by adhesion molecules, and then roll slowly in an irregular stop-and-go motion (Alon et al., 1995, 1997, 1998; Chen and Springer, 1999; Kim and Sarelius, 2004; Lawrence et al., 1997; Lawrence and Springer, 1991; Moore et al., 1995; Smith et al., 1999; Springer, 1995; Yago et al., 2002). Subsequently, leukocytes firmly adhere and then transmigrate to the sites of inflammation. Adhesion molecules of selectin family, P-, E-, and L-selectins, are known to mediate tethering and rolling of leukocytes. L-selectins are expressed on leukocytes, whereas P- and E-selectins are expressed on activated endothelium. P-selectin-glycoprotein-ligand-1 (PSGL-1) is a common ligand that is known to bind to all three selectins. Flow chamber studies have also shown tethering and rolling of leukocytes over selectin coated surfaces (Alon et al., 1995, 1997, 1998; Dong et al., 1999; Dong and Lei, 2000; Lawrence et al., 1997; Lawrence and Springer, 1991; Lei et al., 1999; Smith et al., 1999).

Rolling and adhesion of leukocytes require a balance of the hydrodynamic dispersal force and the adhesion force between the cell and the substrate. The micro environment of blood flow in a post-capillary vessel, such as erythrocyte–leukocyte interaction (Munn et al., 1996; Thompson et al., 1989), hematocrit, and erythrocyte aggregation, plays a critical role in determining the efficiency of leukocyte margination and rolling adhesion (Abbitt and Nash, 2003; Pearson and Lipowsky, 2000; Migliorini et al., 2002; Schmid-Schonbein et al., 1980; Sun and Munn, 2005). Equally important are the rheological properties of the cells

* Corresponding author. Tel.: +1 732 445 3656; fax: +1 732 445 3124.
*E-mail address:* pbagchi@jove.rutgers.edu (P. Bagchi).

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(Caputo and Hammer, 2005; Dong et al., 1999; Dong and Lei, 2000; Lei et al., 1999; Lomakina et al., 2004) and the biophysical parameters of the receptor/ligand bonds (Alon et al., 1995, 1997, 1998; Chang and Hammer, 2000; Chang et al., 2000; Chen and Springer, 1999; Dembo et al., 1988; Hammer and Apte, 1992; Kim and Sarelius, 2004; Lawrence et al., 1997; Lawrence and Springer, 1991; Smith et al., 1999; Yago et al., 2002). While circulating leukocytes maintain a spherical shape, adhesively rolling leukocytes are known to deform (Damiano et al., 1996; Dong et al., 1999; Dong and Lei, 2000). Stable rolling of the cells at high shear rates is attributed to increased number of receptor/ligand bonds caused by increased cell/substrate contact area (Chen and Springer, 1999; Yago et al., 2002).

Leukocyte adhesion to endothelium causes several changes in the local microvascular flow pattern (King et al., 2004; Thompson et al., 1989). The protrusion of an adherent leukocyte into the vascular lumen results in a decrease in the effective lumen area and leads to an increase in resistance to blood flow, and hence a decrease in volumetric blood flow rate. In vivo studies have shown significantly elevated flow resistance in post-capillary vessels due to adherent leukocytes. Using FMLP (formyl peptide)-mediated leukocyte-endothelium adhesion in cat mesentery, House and Lipowsky (1987) observed up to 150% increase in flow resistance in vessels of 25 μm diameter. Sutton and Schmid-Schonbein (1992) observed up to 60% increase in flow resistance in rat gracilis muscle when leukocytes were activated. Adherent leukocytes also result in deflection of streamlines in microcirculation, and thus affect the flow of erythrocytes, platelets, and biomolecules in blood stream. King et al. (2004) measured the deflection angle of tracer particles in presence of adherent leukocytes in vivo and showed that it increased with increasing leukocyte concentration. Reduced flow rate due to leukocyte adhesion may also lead to increased erythrocyte aggregation (Das et al., 2000). In sickle blood, increased leukocyte adhesion was shown to trigger upstream plugging of sickle erythrocytes and their adhesion to vascular endothelium causing further increase in the flow resistance (Frenette, 2004).

Due to the aforementioned biological importance of leukocyte adhesion, several investigators have developed theoretical models to predict flow resistance due to, and fluid drag on, adherent leukocytes. Chapman and Cokelet (1996–1998) used a three-dimensional (3D) model to simulate flow past single and multiple adherent leukocytes. They showed that the flow resistance depended on the leukocyte to vessel diameter ratio, and the cell concentration. Further computational studies by Das et al. (2000) and Sun and Munn (2005) also predicted increased flow resistance due to leukocyte adhesion. Using a two-dimensional (2D) model, Gaver and Kute (1998) computed the fluid drag on a rigid hemisphere which served as a model for an adherent leukocyte, and showed that the fluid drag increased with decreasing vessel size. Brooks and Tozeren (1996) considered 3D simulation of flow past an array of adherent cells which were modeled as rigid spheres, hemispheres, and inclined cones. The fluid drag was shown to decrease as the shape varied from a sphere to a cone. Their results, as well as those by Chapman and Cokelet (1996–1998), also showed that the fluid drag on individual cell decreased as the number of adherent leukocytes increased. Reduction of the fluid drag acting on multiple adherent leukocytes in proximity has a significant bearing on the leukocyte rolling as the force exerted on each receptor/ligand bond is expected to decrease and the bond lifetime to increase which may result in smoother rolling of the cells. King et al. (2003) have shown in vivo that the hydrodynamic interactions among nearby leukocytes affected the rolling velocity which decreased inversely with the cell-to-cell separation distance.

While a lot has been learned from the aforementioned computational models in terms of flow resistance and fluid drag, two key features of leukocyte adhesion, such as cell deformation and slow rolling, were neglected therein (Brooks and Tozeren, 1996; Chapman and Cokelet, 1996–1998; Das et al., 2000; Gaver and Kute, 1998). While circulating leukocytes maintain a spherical shape, adherent leukocytes assume the shape of a tear-drop (Damiano et al., 1996; Dong et al., 1999; Dong and Lei, 2000). Deformation of an adherent leukocyte increases the free lumen area and hence reduces the resistance to blood flow. Thus it is likely that the flow resistance is overpredicted by the model of Chapman and Cokelet (1996–1998). Deformation also reduces the shear stress, and the fluid drag acting on the cells, and hence increases the lifetime of the selectin bonds. Therefore, accurate prediction of the flow resistance and fluid drag is important in understanding the mechanics of cell adhesion, and the micro-environment surrounding the cells.

Among several computational models, the adhesive dynamics simulation (ADS) pioneered by Hammer and co-workers made a significant contribution to the theoretical understanding of leukocyte rolling (Bhatia et al., 2003; Caputo and Hammer, 2005; Caputo et al., 2007; Chang and Hammer, 2000; Chang et al., 2000; Hammer and Apte, 1992; King and Hammer, 2001a, b, 2003; King et al., 2005; Krasik and Hammer, 2004). In ADS, leukocytes are modeled as rigid spheres, and the receptor/ligand interaction is simulated by stochastic Monte Carlo simulation. King (2005), King and Hammer (2001a, b, 2003), King et al. (2003, 2004, 2005a, b), and Lee et al. (2007) have extended ADS technique to develop the multiparticle adhesive dynamics (MAD) that included hydrodynamic interactions among multiple rigid leukocytes. Recent works by Hammer and co-workers have incorporated microvilli deformation within the framework of ADS (Caputo and Hammer, 2005). Rolling adhesion of deformable leukocytes was considered in two-dimensions by Dong and co-investigators by modeling a leukocyte as a viscous liquid drop surrounded by an elastic ring (Dong et al., 1999; Dong and Lei, 2000; Lei et al., 1999). They showed that the fluid drag on an adherent leukocyte decreased with increasing cell deformation, and vessel size. Kan et al. (1998) and N'Dri et al. (2003) modeled leukocytes as 2D compound liquid drops to study the effect of cell nucleus on deformation. The role of viscoelasticity and microvilli extension during leukocyte adhesion and rolling were considered in a recent 3D model developed by Khismatullin and Truskey (2004, 2005). These authors also simulated deformation of adherent leukocytes in parallel-plate flow chambers, and computed the time-dependent drag. Jadhav et al. (2005) developed a 3D model for rolling leukocytes by coupling cell deformation with stochastic simulation of receptor/ligand interaction. Jin et al. (2007) studied the lateral migration of leukocytes in a parallel-plate channel using direct numerical simulations based on finite element and level set methods. The effect of the cell nucleus was considered by two-layer models for the cell. A recent review on modeling deformable cell interaction under flow, including leukocyte adhesion, is provided by Verdier et al. (2008).

In this article, we present a 3D computational model to simulate rolling adhesion of multiple deformable leukocytes over P-selectin coated surface in parabolic shear flow in microchannels. The model is based on the immersed boundary method (IBM) for cell deformation (Mittal and Iaccarino, 2005; Peskin and McQueen, 1989; Tryggvason et al., 2001) and Monte Carlo simulation for receptor/ligand interaction following Bhatia et al. (2003), Caputo and Hammer (2005), Caputo et al. (2007), Chang and Hammer (2000), Chang et al. (2000), Dembo (1994), Dembo et al. (1988), Hammer and Apte (1992), King and Hammer (2001a, b, 2003), King et al. (2003, 2005a, b), King (2005), and Lee et al. (2007). The simulations are continued for at least 1 s during which leukocyte