EFFECT OF LEUKOCYTE RHEOLOGY ON THE VALUE OF THE CRITICAL ADHESIVE BOND FORCE

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INTRODUCTION

Adhesion of to vascular endothelium is a prerequisite for circulating leukocytes to migrate into tissues. This event involves a multi-step process that includes: (i) rolling of the cell along the blood vessel wall, (ii) margination (firm adherence of the cell to the blood vessel wall), and finally (iii) diapedesis or emigration (cell squeezes through the capillary wall). This three-step stage is mediated by a series of different endothelial cell-leukocyte adhesion molecules [1]. Adhesion of leukocytes to substrate involves the coupling of disparate length and time scales between molecular mechanics and macroscopic transport [2]. Models of cell adhesion do not use full cellular information. Hydrodynamic flow surrounding the cell exerts forces on the adhesion bonds, which can shorten their lifetime or even extract the receptor molecule from the cell surface [3-5].

Most of the previous studies consider the cell as a solid body, so the only parameter that can affect adhesion bond force and bond lifetime is the imposed inlet velocity. In this study, modeling the cell as a compound drop, we will study the effect of cell rheology on adhesion bond force and bond lifetime.

DESCRIPTION OF THE MULTI-SCALE MODEL

In order to form a comprehensive modeling framework to treat the disparate scales between cell deformation (μm) and bond length (nm), a multi-scale model to account for both macroscopic (continuum) and microscopic (ligand-receptor) levels of phenomena is needed. In our multi-scale model, the macroscopic component deals with the deformation of the cell while the microscopic part takes care of the adhesion aspect, and a numerical procedure is used to transfer information between the two components. The detail description of this method can be found in Shyy et al. [2].

A 2D dimensional representation of a cell modeled as a Newtonian compound drop is studied in a planar channel under an imposed flow as shown in the Figure 1. The flow is assumed to be uniform at the entrance of the channel, as it is the case when a flow enters the orifice of a parallel plate chamber. This is done to generalize the problem so that no assumption has to be made concerning the velocity profile of the flow as it approaches the cell. The cell is attached to one side of the channel wall with adhesive bonds governed by the kinetics model proposed by Dembo et al. [6].

The macroscopic model is governed by the incompressible Navier-Stokes equations. Blood is considered as a Newtonian fluid. The flow equations are solved using the projection method.

The microscopic model is based on the model proposed by Dembo et al. [6] who considered the bond as a spring. They derived a simple kinetic equation to derive the bond density. The kinetic equation is solved using a 4^{th} order Runge-Kutta method.

The computational procedures for the above-described cell adhesion problem consist of the following key elements: (i) field equation solvers for mass and momentum conservation, (ii) interfacial movement in response to cell and surrounding fluid interactions, and (iii) communication between the field equation solvers and the interfacial treatment. In the present approach, the field equations are solved using fixed Cartesian grid, while the interface moves through the mesh based on discrete, massless markers. This approach forms the so-called Eulerian-Lagrangian technique [2]. The advantage of the fixed grid approach is that grid topology remains simple while large distortions of the interface take place.

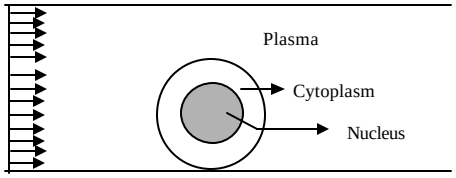

Figure 1. Schematic of the problem statement

RESULTS

A leukocyte is modeled as a compound drop. The compound drop model describes better the structure of a lymphocyte, but it is still a good model for evaluating the effect of key parameters on the rheology and adhesion of leukocytes in general. For that reason, we take the nucleus to be 44% of the volume of the cell, and the rheological properties (viscosity and surface tension) of the nucleus to be 10 times that of the cytoplasm and cellular membrane.

The viscosity ratios between the plasma, cytoplasm, and nucleus are defined as follows:

$$a = \frac{m_c}{m_0} \quad and \quad b = \frac{m_n}{m_c} \tag{1}$$

where μ_0 is the plasma viscosity, μ_c is the cytoplasm viscosity, and μ_n is the nucleus viscosity.

The force of rupture (critical bond force) of a single bond, F_{br}, is determined as a function of bond lifetime. This force is the force reaches by the bond before it breaks. In all the computations, N_r and N_l are the receptor and ligand densities respectively; γ is the cell surface tension and f_σ is the slippage constant.

Critical Bond Force as a Function of Bond Lifetime

In the work of N'Dri et al. [7], the values of the bond molecule force vary from 250 to 400 pN for a range of shear flows between 2 and 20 dyne/cm^2 and a spring constant $\bar{s} = 0.1$. These results are shown in Figure 2 for α = 100. The value of $\bar{s} = 0.1$ corresponds to a dimensional value of 0.5 dyne/cm. Figure 2 demonstrates a linear relationship between bond lifetime and force of rupture.

$$t = 0.0013 F_{b_r} - 0.206 \tag{2}$$

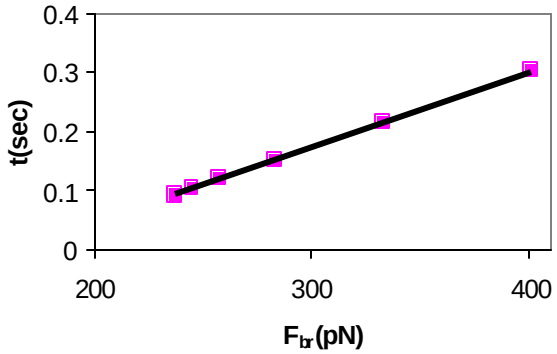

Figure 2. Bond lifetime as a function of the bond force F_{br}
$\bar{N}_r$ = 0.02 , $\bar{N}_l$ = 1.0 , $\bar{s}$ = 0.1 , f_s = 0.04 , $\bar{g}$ =1.2, b = 10 .
The dot points correspond to the numerical results and the line is a curve fitting

In N'Dri [8], a bond lifetime was computed as a function of the cell viscosity and cell surface tension. Using eq. (2) and the bond lifetime computed in [8], the critical bond force can be determined.

Effect of Cell Viscosity

In this study, the inlet velocity and the cell surface tension are kept constant. The parameter α is varied. Increasing α increases the critical bond force as shown in Figure 3.

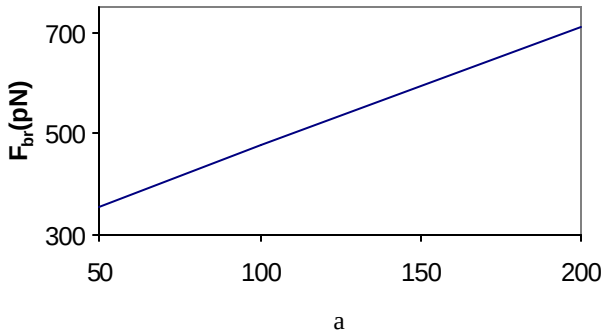

Figure 3. Effect of the cell viscosity on the bond rupture force. $\bar{N}_r$ = 0.02 , $\bar{N}_l$ = 1.0 , $\bar{s}$ = 0.1 , f_s = 0.04 , $\bar{g}$ =1.2, b = 10

Effect of Cell Surface Tension

In this computation, the cell viscosity and the inlet velocity are kept constant, only the cell surface tension varies. It is found that the critical bond force decreases as the cell surface tension increases (Figure 4).

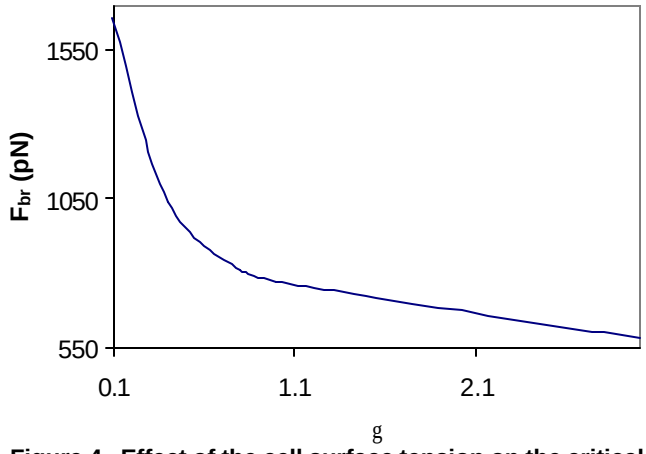

Figure 4. Effect of the cell surface tension on the critical bond force.
$\bar{N}_r$ = 0.02 , $\bar{N}_l$ = 1.0 , $\bar{s}$ = 0.1 , f_s = 0.04 , $\bar{g}$ =1.2, b = 10 .

CONCLUSION

In this study, we have shown that cell deformability affects cell adhesion. A computation of the bond length before breakage agreed with published results [3,4] and lies between 0.25 and 0.85 μm. The unique of cell deformability is that critical bond force varies not only with inlet velocity but also with cell rheology. This knowledge can help not only in the selection of biomaterial for biomedical implants but also for the understanding of cell's function and behavior in health and disease.

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