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Shear modulation of intercellular contact area between two deformable cells colliding under flow

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Abstract

Shear rate has been shown to critically affect the kinetics and receptor specificity of cell-cell interactions. In this study, the collision process between two modeled cells interacting in a linear shear flow is numerically investigated. The two identical biological or artificial cells are modeled as deformable capsules composed of an elastic membrane. The cell deformation and trajectories are computed using the Immersed Boundary Method for shear rates of 100–400 s⁻¹. As the two cells collide under hydrodynamic shear, large local cell deformations develop. The effective contact area between the two cells is modulated by the shear rate, and reaches a maximum value at intermediate levels of shear. At relatively low shear rate, the contact area is an enclosed region. As the shear rate increases, dimples form on the membrane surface, and the contact region becomes annular. The non-monotonic increase of the contact area with the increase of shear rate from computational results implies that there is a maximum effective receptor-ligand binding area for cell adhesion. This finding suggests the existence of possible hydrodynamic mechanism that could be used to interpret the observed maximum leukocyte aggregation in shear flow. The critical shear rate for maximum intercellular contact area is shown to vary with cell properties such as radius and membrane elastic modulus.

INTRODUCTION

Polymorphonuclear leukocyte (PMN) recruitment to sites of inflammation/infection is orchestrated by the sequential involvement of distinct receptor-ligand pairs: the selectins, integrins and immunoglobulins. According to this model, free-flowing PMNs first loosely attach (tether) and roll on activated endothelium via selectin-ligand interactions, then stop, flatten and squeeze between endothelial cells into the afflicted tissues in an integrin/immunoglobulin-dependent manner (Simon and Green, 2005). The paradigm of the coordinated action of a selectin-mediated tethering followed by integrin-supported firm adhesion has been extended to account for PMN homotypic aggregation in cell suspensions stimulated by bacterial peptides/chemokines typically found in blood vessels proximate to the infected/inflamed tissue (Kuypers, et al., 1990; Simon, et al., 1998).

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Prior work has demonstrated that steady application of a threshold level of shear rate is necessary to support PMN homotypic aggregation in bulk suspensions (Goldsmith, et al., 2001). The presence of the shear threshold phenomenon, by which a reduction of shear rate below a threshold value diminishes the probability of cell adhesion, was also detected during the interaction of free-flowing and surface-adherent PMNs (Kadash, et al., 2004). Moreover, these studies revealed significant deformation during cellular collision.

Biological and artificial cell aggregation can currently be predicted using mathematical models based on the Smoluchowski's collision frequency, which assumes linear trajectory of hard spheres (Smoluchowski, 1917). Given the evidence suggesting that cellular deformation during shear-induced collisions affects the intercellular contact area, and thus, the probability of receptor-ligand bond formation between the interacting cells (Goldsmith, et al., 2001; Kadash, et al., 2004), our attention focuses on the development of mathematical models that incorporate cellular deformation.

Most of the previous theoretical/computational studies involving deformable cells were limited to single cells in shear flow. Barthes-Biesel and colleagues (Barthes-Biesel and Rallison, 1981; Barthes-Biesel and Sgaier, 1985) studied the motion of an elastic capsule in a linear shear flow under the small deformation regime using perturbation analysis, and obtained the deformation and orientation of the capsule in the shear field. Deformation was found to increase with an increase in the capillary number. Large deformation of red blood cell ghosts was simulated by (Eggleton and Popel, 1998) using the Immersed Boundary Method (IBM) that reproduced the tank treading behavior observed experimentally in shear flow (Fischer, et al., 1978). (Lac and Barthes-Biesel, 2005) computed elastic capsule deformation in simple shear flow and hyperbolic flow using the Boundary Element method, and showed that steady shapes were obtained only within stable capillary number ranges. Outside of the stable capillary number ranges, the capsules either go through continuous elongation or a membrane buckling instability develops. Numerical simulations by Pozrikidis (Pozrikidis, 2001) using boundary element method showed that membrane bending stiffness significantly affected capsule deformation in shear flow. Recently, (Bagchi et al, 2005) simulated the aggregation of erythrocytes in two dimensions and showed that rheological cell properties effect the aggregate dynamics.

Although there have been a handful of numerical studies on multiple particle deformation (Loewenberg and Hinch, 1997; Breyiannis and Pozrikidis, 2000; Zinchenko and Davis, 2002), the particles considered in these studies were either liquid droplets or two-dimensional capsules. This paper investigates the effects of fluid shear on the intercellular contact area of two identical cells modeled as three-dimensional elastic capsules. The cell deformation and trajectories are calculated using IBM. The cell contact area and the contact duration obtained from the simulations are relevant to liposome or polymersome interactions as well as homotypic leukocyte aggregation in a linear shear field.

PROBLEM STATEMENT

The off-center binary collision of two cells in an unbounded linear shear flow is simulated using the IBM (Peskin and McQueen, 1989). The cells are modeled as three-dimensional elastic capsules containing a Newtonian liquid, and the fluid flow is governed by the continuity and Stokes momentum balance equations (Eggleton and Popel, 1998; Jadhav, et al., 2005):

$$\nabla \cdot u(x) = 0 \quad (1)$$

$$\rho \frac{\partial u(x)}{\partial t} + \rho u(x) \cdot \nabla u(x) = - \nabla p(x) + \mu \nabla^2 u(x) + F(x) \quad (2)$$

ρ is the fluid density, μ is the internal and external viscosity, $u(x)$ is the velocity vector at position $x(x_1, x_2, x_3)$, p is the pressure, and $F(x)$ is the total force exerted by the elastic membrane onto the fluid. In the Immersed Boundary Method, the computational domain is comprised of an Eulerian Cartesian fluid grid $x(x_1, x_2, x_3)$ and a Lagrangian triangular finite element grid $X(X_1, X_2, X_3)$ that tracks cell motion and deformation (Eggleton and Popel, 1998; Jadhav, et al., 2005):

The force $F(x)$ exerted on the fluid by the membrane is calculated at each time step by the interpolation of the forces obtained on the surface grid node $F(X)$ as follows:

$$F(x) = \sum F(X) \cdot D_h(X - x) \text{ for } |X - x| \leq 2h \quad (3)$$

where h is the uniform fluid grid spacing. Hence, the restoring force of the membrane located at the surface grid node X is distributed onto the fluid grid node x according to the 3-D discrete delta function,

$$D_h(X - x) = \delta_h(X_1 - x_1) \delta_h(X_2 - x_2) \delta_h(X_3 - x_3) \quad (4)$$

and

$$\begin{aligned} \delta_h(z) &= \frac{1}{4h} \left(1 + \cos\left(\frac{\pi \cdot z}{2h}\right) \right) \text{ for } |z| \leq 2h; \\ \delta_h(z) &= 0 \text{ for } |z| > 2h \end{aligned} \quad (5)$$

Similarly, the velocity at the membrane node X is calculated from the velocity at the fluid grid nodes x using the delta function as

$$u(X) = \sum u(x) \cdot D_h(X - x) \text{ for } |X - x| \leq 2h \quad (6)$$

This also implies velocity continuity condition on the membrane surface since its velocity matches that of the fluid. Periodic boundary conditions on the velocity and pressure are imposed, and the fast Fourier Transform method is used to solve the flow equations (Peskin and McQueen, 1989; Jadhav, et al., 2005).

The elastic membrane is assumed to have an initial spherical stress-free shape. The cell membrane mechanics is described by the neo-Hookean membrane model, which assumes that the membrane material is incompressible and isotropic. The strain energy density, W , of a neo-Hookean membrane is given by (Green and Adkins, 1970).

$$W_h = \frac{Eh}{6} (\lambda_1^2 + \lambda_2^2 + \lambda_1^{-2} \lambda_2^{-2} - 3) \quad (7)$$

where λ_1 and λ_2 are the principal stretching ratio, E is the Young's modulus and h is the membrane thickness.

The finite element implementation of the force $F(x)$ calculation of the membrane is based on the model developed by (Charrier, et al., 1989) and (Shrivastava and Tang, 1993). The membrane is discretized into triangular finite elements to obtain the forces acting at the discrete nodes of the membrane surface, which are then distributed onto the fluid grid as described above. Given the displacement of the three nodes of an element, its state of strain (λ_1, λ_2) is obtained. The material properties of the element determine the forces that are required to maintain the element in a given state of strain/stress. The principle of virtual work is used to calculate the forces at the three nodes of an element. The resultant force $F(X)$ on a membrane node X is simply the sum of the forces exerted by the triangular elements attached to that node. An equal and opposite force acts on the fluid in the manner described by the immersed boundary method. Further details of the numerical implementation and validation of the model can be found in (Eggleton and Popel, 1998).

The fluid domain is a cube with a side that is 8 times the cell radius, a , and the uniform grid used in the simulations has 256^3 nodes, and grid spacing of $a/32$. The finite element grid of each cell has 20480 triangular elements. A time step of 10^{-7} seconds was used to ensure numerical stability. The computations require upwards of 2 GBs of memory and run times of two to four weeks depending on the CPUs employed and other hardware characteristics. Our simulations are conducted on an IBM SP60 and SUN Fire Server.

RESULTS AND DISCUSSION

In our simulations, biological or artificial cells with a radius, a , of $3.75\text{ }\mu\text{m}$, equivalent to that of a PMN, are modeled as elastic capsules whose membrane elasticity, Eh , varies from $0.03 - 3\text{ dynes/cm}$ (Jadhav, et al., 2005), and are suspended in medium with fluid viscosity, μ , of 0.8 cP . The membrane stiffness values of $0.3-1.2\text{ dynes/cm}$ have been shown to match the extent of PMN deformation previously observed in vivo (Damiano, et al., 1996; Smith, et al., 2002), while higher values are used to observe the effects of membrane stiffening. The physiological shear rate, G , that cells or liposomes/polymersomes can experience in the venular circulation varies from $100-400\text{ s}^{-1}$. These parameter values give a dimensionless capillary number ($Ca = \mu Ga / Eh$) of $0.0001 - 0.04$. The capillary number compares the relative importance of the hydrodynamic viscous forces causing cell deformation to the modeled cell's elastic tension forces resisting deformation. The simulated results are presented first in terms of this dimensionless capillary number so the behavior becomes independent of the specific values of the cell properties. The dimensionless results can be applied to a wide variety of biological or artificial cells by specifying particular values of membrane elasticity and radius, from which the shear rate can be determined for any given capillary number, as discussed below.

The x_2 -component of velocity of the far field shear flow can be written as: $u = Gx_2$, and the initial offset between the centers of the cells is: $\Delta x_1 = 2.4a$, $\Delta x_2 = 0.24a$, $\Delta x_3 = 0$. At this initial offset, the deformation of the individual cells reaches that of a single isolated cell at the given shear rate, before hydrodynamic interactions are observed. The relatively close initial proximity of the cells greatly reduces the computational time required. A greater offset in the x_1 direction would require the majority of the simulation time to be dedicated to convecting the cells towards each with minimal hydrodynamic interaction (Loewenberg and Hinch, 1997). The simulated trajectory profile as the two modeled cells interact with each other under the influence of a linear shear flow is shown in Figure 1 at a capillary number of 0.04 . The initially stress-free spherical cells deform into oblate spheroid tank-treading cells with negligible hydrodynamic interaction under the influence of the imposed shear flow. As the cells approach each other, the cell contact regions flatten and a thin lubrication gap develops (Fig. 1B). Note that the contact time between capsules scales as $1/\dot{\gamma}$, while lubrication theory predicts that the time for film drainage scales as $a^2/(\dot{\gamma} h_0)$, where h_0 is the film thickness. The ratio of drainage time to contact time scales as $a^2/h_0 \gg 1$. Thus, there is insufficient time for film drainage to occur. Then, the cells start to rotate and spin-off each other with respect to the center point between the cells (Fig. 1C–D). Lastly, the cells separate and continue on their own path as oblate tank-treading spheroids (Fig. 1E). Moreover, there is a permanent shift in the trajectories of the modeled cells after this cell-cell interaction. For example, for L-selectin-mediated receptor-ligand bond formation between PMNs, the bond length is $\sim 70\text{ nm}$, the length of microvillus on the membrane surface is $\sim 350\text{ nm}$. Thus, a minimum separation distance between the two cells of about 800 nm or less is defined to be the contact area. This intercellular contact area represents the available area for cell adhesion; the larger the contact area the greater the possibility for the involvement of multiple receptor-ligand bonds and thus successful adhesion (Gourier, et al., 2004; Jadhav, et al., 2005; Lin, et al., 2006). The time evolution of the contact area with contact time is illustrated in Fig 2A. The contact area first increases, reaches a maximum, and then decreases back to zero when the cells separate at all capillary numbers examined here. Interestingly, Figs. 2B–C indicate that the maximum dimensionless

contact area and the dimensionless contact duration occur at an intermediate capillary number. The existence of the maximum intercellular contact area can be explained by examining the detailed cell shape evolution during the binary-collision process. As the modeled cells make contact, a thin lubrication fluid layer appears and the shape, size and thickness of this gap are influenced by the strength of the shear flow and the membrane deformability (i.e. capillary number). Figure 3 depicts the cell deformation and contact area shape during cell contact. The lubrication layer widens and thickens with increasing capillary number (Fig. 3A). Moreover, dimple formation is more pronounced at large capillary numbers, in which the edge of the lubrication film is significantly thinner than the middle of the film. The increase in size of the lubrication region leads to a bigger contact area circumference, while the formation of dimples leads to the transition from solid to annular shape of the contact area, as shown in Figure 3B. Therefore, the net cell contact area (the shaded area in Figure 3B) shows a maximum value as capillary number increases. It is noteworthy that dimple formation has been simulated in liquid droplets (Zinchenko and Davis, 2002), and observed in experiments (Horn et al, 2006; Zdravkov et al, 2006). Thus, it may represent a characteristic of deformable particles.

Since the capillary number depends on the fluid shear rate G , the cell radius a , and the membrane elasticity Eh , we wished to investigate how specific modulations of these parameters would affect the intercellular contact area and duration. To this end, we first chose to vary the cell membrane elastic modulus from 0.03 dynes/cm to 3 dynes/cm. Our simulations indicate that stiffening the cell membrane increases monotonically the shear rate at which maximal intercellular contact area and contact duration are detected (Fig. 4) and note that shear rates beyond 2000 s^{-1} and $10,000 \text{ s}^{-1}$ are considered supraphysiologic and hemolytic, respectively. Similarly, our analysis predicts that increasing cell size decreases the shear rate at which maximal contact parameters occur at a given membrane elastic modulus (not shown). This analysis can be used to predict the modulation of the homotypic intercellular contact area between biological or artificial cells of different membrane characteristics and varying cell sizes in a linear shear field.

Our key observation of the maximum intercellular contact area as a function of shear rate predicts a hydrodynamic mechanism that would contribute to maximal homotypic cell aggregation. This finding may provide a basis for interpreting experimental observations showing the existence of an intermediate shear rate at which maximal homotypic PMN aggregation occurs (Taylor, et al., 1996; Jadhav, et al., 2001; Jadhav and Konstantopoulos, 2002; Simon and Goldsmith, 2002; Kadash, et al., 2004). However, recent experimental observations also suggest that selectins exhibit a "catch-slip" bond transition, where increasing tensile forces initially prolong, and subsequently diminish bond lifetimes (Marshall, et al., 2003; Yago, et al., 2004). Thus, a kinetic and hydrodynamic mechanism may both contribute to the observed shear threshold phenomenon in which the number of tethered PMNs first increases and then decreases with monotonically increasing shear (Finger et al., 1996; Lawrence, et al., 1997; Hammer, 2005).

Taken altogether, the simulation results presented in this paper provide qualitative evidence of a hydrodynamic mechanism contributing to the maximum homotypic aggregation observed between biological or artificial cells at intermediate shear rates in vitro. Moreover, it can guide the design of artificial cells for in vivo targeted drug delivery applications by prescribing the combination of membrane properties and vesicle size that lead to maximum contact area with biological cells.

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Figure 1. Cell deformation and trajectory shift between two cells in shear flow

The immersed boundary method was used to simulate the hydrodynamic interaction between cells (modeled as elastic capsules) in a linear shear field. The initial offset between the centers of the cells is: $\Delta x_1 = 2.4a$, $\Delta x_2 = 0.24a$, $\Delta x_3 = 0$. The fluid grid used in the computations has 256^3 nodes, and the finite element grid of each cell has 20480 triangular elements (not all shown in the figure above). The parameters in this simulation are $G = 400 \text{ s}^{-1}$, $Eh = 0.03 \text{ dynes/cm}$, $Ca=0.04$ Panels A–E show the time evolution of cell deformation during collisional contact and subsequent separation.

(a)

(b)

(c)

Figure 2. Dimensionless intercellular contact area and contact duration as a function of the capillary number

The intercellular contact area A , nondimensionalized with surface area of the undeformed cell and the intercellular contact duration, B nondimensionalised with shear rate is plotted as a function of the capillary number. The two cells were assumed to be in contact when the distance between the surfaces was less than 800 nm taking into account the radius of PMNs as 3.75 μm , receptor-ligand bond length of approximately 70 nm and surface roughness due to PMN microvilli (microvillus length is 350 nm). The evolution of the contact area as a function of contact duration C , is plotted for capillary numbers ranging from 0.0006 to 0.04.

Figure 3. Profiles of interacting cells and shape of intercellular contact area

Dimple formation in the contact region observed in the plane of shear passing through the centers of interacting cells (a), and the shape of the intercellular contact area (b), shown for different capillary numbers; (A) 0.0006, (B) 0.004, (C) 0.01, (D) 0.02, (E) 0.04

Figure 4. Intercellular contact area and contact duration as a function of the membrane stiffness
 The intercellular contact area A and the intercellular contact duration B are plotted as a function of the shear rate. The two cells were assumed to be in contact when the distance between the surfaces was less than 800 nm taking into account the radius of PMNs as 3.75 μm , receptor-ligand bond length of approximately 70 nm and surface roughness due to PMN microvilli (microvillus length is 350 nm). The values of the membrane elastic modulus are 0.03 dynes/cm, 0.3 dynes/cm, 3 dynes/cm.