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Effect of viscous drag on multiple receptor-ligand bonds rupture force

V.K. Gupta¹

¹University of Maryland Baltimore County, Baltimore, Maryland 21250, USA

Abstract

Monte Carlo simulation of the rupture of multiple receptor-ligand bonds between two PMN cells suspended in a Newtonian fluid is performed. We demonstrate via micro-mechanical model of two cells adhered by multiple receptor-ligand bonds that viscous drag caused by relative motion of cell suspended in a Newtonian fluid modulates transmission of an applied external load to bonds. Specifically, it is demonstrated that at any time the intermolecular bond force is not equivalent to the instantaneous applied force. The difference in the instantaneous applied force and the intermolecular bond force depends on the viscosity of fluid, the size of cell, the applied loading rate, and the number of bonds at any instant of time. Viscous drag acting on cell reduces average bond rupture forces.

I. INTRODUCTION

Cellular adhesion is mediated by a wide variety of cell adhesion molecules (CAMs) also known as receptors and ligands, e.g., E-selectin, L-selectin, P-selectin, PSGL-1 etc., which interact with each other residing on the opposing cells or the extracellular matrix (ECM) [1, 2]. When a CAM binds with other CAM of the same kind, i.e., the receptor serves also as its own ligand, the resulting adhesion is termed homophilic adhesion which normally takes place in the same type of cells. On the other hand, when a CAM binds with other CAM of different kinds, the resulting adhesion is termed heterophilic adhesion which normally takes place between different types of cells or between a cell and ECM [3]. Cells in multicellular organisms adhere to other cells and the ECM through two-dimensional clusters spanning a number range from several (leukocyte rolling) to 10^5 (mature adhesion) adhesion bonds [1]. Cell adhesion on the ECM is often localized to discrete contact regions called focal adhesions that consist of multiple trans-membrane receptor-ligand bonds connecting the actin cytoskeleton of the cell to the ECM [4]. Cellular adhesion plays a pivotal role in diverse biological processes, including thrombosis [5], tumor metastasis [6], arteriosclerosis [7] and inflammation [8, 9]. Changes in cell adhesion can be the defining event in a wide range of diseases, including cancer [10], arthritis [11], osteoporosis, and atherosclerosis [12]. CAMs (proteins and oligosaccharides) on the cell surface mediate cell adhesion via multiple non-covalent interactions (van der Waals, hydrogen bonding, hydrophobic or electrostatic). Multicellular organisms perform many biological functions using multivalent interactions where multiple weak individual bonds between receptor-ligand pairs combine to produce a much stronger interaction [13, 14]. Multivalent bonds feature prominently in a variety of biological processes such as intercellular adhesion [15] and activation of T cells

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[16]. Biomedical researchers also utilize multivalent binding to increase the binding time of pharmaceuticals to their targets [17]. The equilibrium properties of the cooperative effects of such multivalent interactions are well studied both in theory [18–20] and in experiments [21–23].

Adherent cells are constantly exposed to disruptive forces caused either by the cell's own contractile machine or by a variety of external factors such as shear flow in the fluid surrounding the cell and the thermally induced relative motion of the opposing surfaces [24]. Detailed models for specific problems such as the peeling of a membrane [25, 26] have been solved numerically to extract a threshold tension for rupture. A single molecular bond has a binding energy around $10\text{--}25\ k_B T$, where k_B is the Boltzmann constant and T is the absolute temperature [27, 28]. This leads to a finite bond lifetime even in the absence of an external force, i.e., individual receptor-ligand bonds will dissociate sooner or later with or without an applied force [28]. According to experiments based on dynamic force spectroscopy [29–31] and theoretical models by Evans and Ritchie [32], and more recently by Freund [33], bond dissociation can be regarded as thermally assisted escape over a potential energy barrier [34]. In these systems an applied force changes the height of an energy barrier along the dissociation path by an amount proportional to the work done by the applied force leading to a linear decrease of the free energy for dissociation (true only for so called 'slip' bonds) [35]. Consequently, these systems show an exponential increase of the dissociation rate and hence the bond lifetime decreases exponentially with applied force [1]. Although such a statistical description of single molecular bonds is by now well understood and accepted but the collective behavior of multiple molecular bonds can be much more complex and are relatively less understood. Though in single-molecule experiments ruptured bond usually cannot rebind but it can in bond clusters as long as other bonds are still intact [36]. A single bond only has a limited lifetime but a cluster of bonds can have much longer lifetime due to collective effects. Moreover, under real physiological conditions cellular adhesion is usually not based on single molecules, rather on clusters of varying size [37]. Therefore, it is pertinent to study the collective behavior of a cluster of receptor-ligand bonds under applied load.

Bell [1] pioneered a theoretical framework for describing the collective behavior of multiple adhesive bonds by applying the kinetic theory of chemical reactions to predict the thermodynamic competition between bond formation and rupture. Using deterministic model for rupture of multiple parallel bonds loaded with a constant force, Bell [1] predicted that molecular clusters remain stable and have infinite lifetime up to a critical applied load, i.e., stability is lost beyond a critical force.

Using the reliability theory framework Tees et al. [38] derived closed form expressions for the probability density of dissociation of up to four bonds (together with the average and variance of the break-up time) for unstressed bonds, bonds instantaneously exposed to a given force, and bonds exposed to a ramp of force. Tees et al. [38] compared the theoretical calculations obtained from the reliability theory with the results for Monte Carlo simulations of multiple bond dissociation for the cases that cannot be easily solved in closed form. Tees et al. [38] showed that the average lifetime (and hence force) of n bonds scales with the n th harmonic number multiplied by the lifetime (and hence force) of a single bond.

Evans and Williams [39] demonstrated that an equivalent single-bond model provides a good approximation for the strength of multiple bond attachments. Evans and Williams [39] showed that multiple bonds loaded in parallel withstand forces nearly proportional to the number but only in the limit of large number of bonds and very large forces. Williams [40] proposed an analytical model that describes simultaneous rupture of many parallel bonds assuming that the applied load is distributed evenly among closed bonds. Williams [40]

aimed to qualify and validate various statistical methods that have been adopted in an attempt to elucidate the single-molecule event from the rupture of multiple bonds [41–43].

Erdmann and Schwarz [44, 45] extended Bell's work to include fluctuation of number of closed bonds resulting in a more rigorous theory of the bond cluster lifetime based on the one-step master equation in stochastic dynamics. Erdmann and Schwarz [44, 45] studied the stochastic effects of a cluster of uniformly stressed molecular bonds transiting between bound and unbound states under the influence of thermal fluctuation. Based on the assumption of equal sharing of the applied load among all closed bonds, the theory of Erdmann and Schwarz [44, 45] predicted that the cluster lifetime monotonically increases as the cluster grows, i.e., the larger the cluster the more stable it is. Erdmann and Schwarz [44, 45] demonstrated that clusters below a critical size behave like a single molecular bond with a finite bond lifetime. On the other hand, clusters above the critical size survive over a longer period due to the collective effect of clustering. Thus, adhesion size plays a crucial role in the stability of a bond cluster: small clusters can easily switch between adhesion and deadhesion whereas large clusters tend to have a much longer lifetime. Qian et al. [28] extended the work of Erdmann and Schwarz [44, 45] to incorporate the effect of elasticity and nonuniform stress distribution on the stability of a single adhesion cluster under a tensile load applied perpendicular to the cell-ECM interface. Qian et al. [28] predicted a window of cluster size for relatively stable adhesion and an optimal size for maximum strength. Lin and Freund [24] also predicted an optimum cluster size for maximum strength and corresponding to this strength is a maximum lifetime for the cluster. This size is dictated by the competition between the nonuniform force distribution among bonds, which tends to promote smaller cluster, and stochastic response allowing bond reformation, which tends to promote larger clusters [24].

Seifert [46] studied the dynamic behavior of a bond cluster subjected to force that increases with time. On the basis of a scaling analysis of the rate equation for the mean number of bonds Seifert [46] showed that different scaling regimes exist for cluster lifetime as a function of cluster size, loading rate, and rebinding rate. For the case of vanishing rebinding, Erdmann and Schwarz [36] confirmed the three scaling regimes for cluster lifetime as a function of loading rate predicted by Seifert [46]. Further Erdmann and Schwarz [47] showed theoretically that bistability between unbound and bound states of adhesion clusters results from positive feedback mediated by structural rather than biochemical processes, namely by receptor-ligand dissociation and association dynamics that depend nonlinearly on mechanical force and receptor-ligand separation. Erdmann et al. [48] arrived at an extraction of single bond data from multiple bonds rupture based on the superposition of experimentally measured rupture force histograms to those obtained from a one-step master equation model for the stochastic dynamics of bond rupture under load.

Tang et al. [49] have shown that the lifetime of an adhesion cluster under constant external force is closely related to the shape of the effective free energy of the system. Tang et al. [49] demonstrated that there exists a critical force per bond (on- and off-rate model dependent) such that for large cluster size when applied force per bond is greater than the critical force per bond, the lifetime of the cluster is independent of the cluster size N_0 . When applied force per bond is lower than the critical force per bond, the lifetime of the cluster scales as e^{N_0} . When applied force per bond equals the critical force per bond, the lifetime of the cluster scales as $N_0^{1/3}$. Recently, Liang and Chen [50] extended these ideas for a cluster under an external force with a constant loading rate. Liang and Chen [50] demonstrated that the mean rupture force of the cluster is dictated by a (model dependent) characteristic loading rate.

During the past decade tremendous progress has been made on quantitative characterizations of the behavior of bond clusters between rigid media [36–40, 44–51]. Only recently a coupled stochastic-elastic modeling framework has been put forward for bond clusters between elastic media [28, 52–54]. All of these studies consider a situation in which multiple receptor-ligand bonds under applied load are arranged in parallel along the cell-substrate interface in absence of a surrounding fluid media. Consequently, all of these studies do not consider the effect of viscous drag caused by relative motion of cell suspended in a fluid and adhered to another cell or the ECM in their modeling approaches. It is apparent that in absence of drag force, the intermolecular bond force is instantaneously equal to the externally applied force neglecting inertial effects. In presence of viscous drag we might expect this quasi-static force equilibrium at very slow loading rates but not at high loading rates. At very slow loading rates the cell would move with a very small velocity and hence drag force acting on it would be negligible. However, at high loading rates this would not be true. Under real physiological conditions biological cells are constantly exposed to viscous drag force arising from blood flow. Consequently, we need to account for viscous drag force acting on the cell in modeling multiple receptor-ligand bonds system. Hence, in this work we consider a more realistic situation by incorporating viscous drag force acting on the cell in modeling multiple receptor-ligand bonds system relevant to real physiological conditions. Specifically, we consider two spherical PMN (polymorphonuclear leukocytes) cells suspended in a Newtonian fluid and adhered by multiple receptor-ligand molecular bonds. An equal and opposite force is applied on the surface of each cell along the line connecting their centers causing bond stretching and eventually bond rupture. Movement of these cells causes viscous drag force acting on them. We demonstrate through our analytical and numerical model how viscous drag affects transfer of the applied force to the bonds and average bond rupture forces.

II. COMPUTATIONAL METHOD

The adhesion and detachment of multiple receptor-ligand bonds between two PMN cells suspended in a Newtonian fluid is simulated in two steps: (1) assuming both PMN cell and microvilli inelastic (undeformable) we write an analytical expression for time varying bond stretch, (2) knowing bond stretch we simulate the formation and breakage of receptor-ligand bonds using Monte Carlo method [55].

A. Micro-mechanical Model of Detachment of Inelastic PMN Cells

Figure 1 shows our model of two spherical (radius = R) PMN cells each containing a Newtonian fluid of density ρ and viscosity η and are suspended in a medium fluid with the same density and viscosity. These cells are adhered by multiple receptor-ligand molecular bonds which are modeled as a set of parallel linear springs (bond spring constant = σ). The bonds are formed between adhesion molecules concentrated on the tips of PMN microvilli which are microscopic cellular membrane protrusions that increase the surface area of cells, and are involved in a wide variety of functions, including absorption, secretion, cellular adhesion, and mechanotransduction [56, 57]. The initial number of bonds (N_0) between these two cells is controlled by the number of receptor and ligand molecules. As soon as the expected number of bonds (N_0) between these two PMN cells are formed we apply an equal and opposite force $F(t) = R_f t$, where R_f is the loading rate, on the surface of each cell along the line connecting their centers causing bond stretching and eventually bond rupture (see Fig. 1). Both PMN cells and microvilli are modeled as undeformable materials allowing us to write an analytical expression for time varying bond stretch utilizing Newton's second law of motion. Due to symmetry we consider only one cell in writing the following equation:

$$\rho \frac{4}{3} \pi R^3 \frac{d^2 x}{dt^2} = F(t) - N(t) \sigma x(t) - 6 \pi \eta R \frac{dx}{dt}, \quad (1)$$

where $x(t)$ is the bond stretch and $N(t)$ is number of bonds at any time t . The first term on the left, the second, and the third terms on the right side represent inertial force, the intermolecular bond force, and drag force arising from the relative motion between the cell and the surrounding fluid, respectively. At any instant of time the magnitude of the drag force acting on each cell depends on three factors: (i) the viscosity η of the suspension, (ii) the radius R of PMN cell, and (iii) the relative velocity $\frac{dx}{dt}$ of the cell which in turn depends on R_f and $N(t)$. Increasing any of these will result in higher drag force. Letting $a = \rho \frac{4}{3} \pi R^3$, $b = 6 \pi \eta R$, and $c = \sigma$ the above equation becomes

$$a \frac{d^2 x}{dt^2} + b \frac{dx}{dt} + N(t) c x(t) = F(t). \quad (2)$$

The above differential equation can be integrated numerically using the initial conditions $x(0) = x'(0) = 0$. Thus knowing $x(t)$ we can simulate the detachment of receptor-ligand bonds as a function of loading rate using Monte Carlo method [55].

B. Monte Carlo Simulation of Receptor-ligand Interactions

We model the bonds between adhesion molecules (ligand-receptor) located on the microvilli of PMN cells as Hookean springs, so the chemical force on each cell due to each bond, F_b , is given by

$$F_b = \sigma (x_m(t) - \lambda) = \sigma x(t), \quad (3)$$

where σ is the bond spring constant, $x_m(t)$ is the stressed bond length, and λ is the equilibrium bond length. We simulate bond formation and rupture utilizing the Bell model [1, 32]. According to the Bell model the force dependent on-rate, k_f , and off-rate, k_r , are given by [1]

$$k_f = k_f^0 \exp \left[\frac{F_b (x_\beta - 0.5 x(t))}{k_B T} \right], \quad (4)$$

$$k_r = k_r^0 \exp \left(\frac{x_\beta F_b}{k_B T} \right), \quad (5)$$

where x_β is the reactive compliance, $k_B T$ is the thermal energy, and $F_b = \sigma x(t)$ is the force acting on the bond where the bond stretch $x(t)$ is governed by Eq. (1). Note that neglecting both inertia and viscous drag force Eq. (1) reduces to $F(t) = N(t) \sigma x(t)$. Hence, in this case the bond force is given by $F_b = F(t)/N(t)$, i.e., the bond force is the applied force per bond at any instant of time. The reactive compliance controls the degree to which force facilitates bond rupture; a smaller value of x_β means that the bond is less susceptible to rupture by force. Evans and co-workers [58] deduced the two-state model for bond dissociation from a series of dynamic force spectroscopy (DFS) experiments to characterize the catch-slip transition for the P-selectin–PSGL-1 bond. In this model there are two pathways for dissociation: pathway 1 is very fast and dominates at low forces, while pathway 2 is slower

and dominates at high forces. Evans and co-workers [58] assumed that the pathways come from two possible bound states. Dissociation via pathway 1 occurs at a constant off-rate k_{1rup} . For the pathway 2, on the other hand, dissociation occurs with off-rate $k_{2rup}=k_2^0\exp(f/f_\beta)$. The occupancy ratio of two states determines the dominant dissociation pathway. The states were assumed to be in equilibrium at all times (fast equilibrium) with a small difference in energy between state 2 and state 1 (ΔE_{21}). This energy difference sets the equilibrium occupancy ratio, Φ_0 , of state 1 to state 2 at zero force. However, force applied to the bond results a shift in the energy of each state, leading to a change in the energy difference between the states. Then the occupancy ratio of the two states changes exponentially with applied force with a scale of f_{12} . Hence, although pathway 1 may dominate at low forces where equilibrium favors occupancy of state 1, at higher forces, pathway 2 dominates as equilibrium shifts to favor occupancy of state 2. For bonds with this type of catch-slip behavior, the off-rate is given by

$$k_r = \frac{\Phi_0 k_{1rup} + \exp\left(\frac{f}{f_{12}}\right) \left[k_2^0 \exp\left(\frac{f}{f_\beta}\right) \right]}{\Phi_0 + \exp\left(\frac{f}{f_{12}}\right)}. \quad (6)$$

Though the above model was derived for the P-selectin–PSGL-1 bond, experiments have shown similar catch-slip behavior for L-selectin–PSGL-1 bond. The values of the different parameters in the above model for L-selectin–PSGL-1 bond used in our simulations are listed in Table 1.

An essential part of the modeling is a reasonable assumption on how the applied force is distributed among the multiple receptor-ligand bonds formed between two PMN cells. Here we assume that the net applied force is shared equally among these bonds, i.e., a single bond is assumed to rupture with the dissociation rate given by Eq. (5) with F_b being the net applied force per bond at any instant of time. We use Monte Carlo simulation to incorporate the stochastic nature of ligand-receptor interactions. In the simulation during a time interval Δt , the probability (P_b) that a ligand will bind with its complementary receptor is given by [55]

$$P_b = 1 - \exp(-k_f \Delta t). \quad (7)$$

Similarly the probability for bond rupture is given by [55]

$$P_r = 1 - \exp(-k_r \Delta t). \quad (8)$$

At each time step, the probabilities of bond formation and rupture are compared to random numbers (P_{ran1} and P_{ran2}) lying between 0 and 1. $P_b > P_{ran1}$ indicates bond formation whereas $P_r > P_{ran2}$ indicates bond rupture.

C. Numerical Simulation Algorithm

The above Eq. (2) is integrated numerically using the finite difference scheme [59] and the initial conditions $x(0) = x'(0) = 0$ to obtain the bond stretch $x(t)$ at any instant of time. Note that $x(t)$ is dependent on the number of bonds, $N(t)$, at any instant of time. Specifically, as $N(t)$ decreases the bond stretch, $x(t)$, increases. In our simulation experiments as soon as the expected number of bonds (N_0) between the two cells are formed we apply an equal and opposite force $F(t)$ on the surface of each cell along the line connecting their centers causing $x(t)$ to increase and $N(t)$ to decrease due to bond rupture. The applied force $F(t)$ increases

linearly with time simply because $F(t) = R_f t$ while the bond stretch, $x(t)$, increases nonlinearly with time due to the non-linear nature of the Eq. (2) and the number of bonds, $N(t)$, decreases as an integer multiple. Note again that the net applied force is shared equally among all the bonds at any instant of time. In other words at any time step, the net applied force is assumed to be equally distributed among the current number of bond(s). Hence, as more and more bonds rupture, the force on the remaining bonds increases. Bonds break due to stochastic nature with the lowest probability at equilibrium according to Eq. (8). The probability for bond rupture P_r increases as the separation distance between the two cells increases. Knowing $x(t)$ at any instant of time we calculate the probability of a bond rupture P_r according to Eq. (8) in conjunction with the off-rate given by the Bell model Eq. (5). We then perform Monte Carlo simulation at a given time step to check whether or not a bond ruptures according to the criterion described above. This leads to a new value of number of bonds, $N(t)$, at the end of each time step. Using this new value of $N(t)$ and the applied force $F(t)$ we again obtain $x(t)$ numerically and repeat all the steps mentioned above until all the bonds are ruptured, i.e., $N(t)$ becomes zero. Note that we consider irreversible forced bond rupture, i.e., once a bond is ruptured we do not consider its reformation [36]. Once all the bonds are ruptured, i.e., $N(t)$ becomes zero the two cells separate from each other and the simulation is terminated.

D. Deterministic Model for Receptor-ligand Interactions without Rebinding

The above stochastic description of receptor-ligand interactions is useful to obtain (stochastic) average bond rupture time and (stochastic) average bond rupture force for low initial number of bonds $N_0 \sim 10$. For higher initial number of bonds $N_0 > 10$ the stochastic approach becomes computationally very expensive given we need to repeat Monte Carlo simulation of rupture for 10^6 times to get statistically accurate average bond rupture force from distribution of rupture forces. In the deterministic model of receptor-ligand interactions without rebinding the (stochastic) average number bonds $\tilde{N}(t)$ is governed by the following equation [36]

$$\frac{d\tilde{N}}{dt} = -\tilde{N}(t)k_r^0 \exp\left(\frac{x_\beta F_b}{k_B T}\right). \quad (9)$$

Note once again that in presence of both inertia and viscous drag $F_b = \alpha x(t)$ is the force acting on the bond where the bond stretch, $x(t)$, is governed by Eq. (1). While in absence of both inertia and viscous drag $F_b = F(t) = \tilde{N}(t)$, i.e., the bond force is the applied force per bond at any instant of time. Using the above deterministic model we can obtain the cluster lifetime T_{cluster} defined by $\tilde{N}(T_{\text{cluster}}) = 1$ and the corresponding cluster rupture force $F_{\text{cluster}} = F_b(T_{\text{cluster}})$ at a given loading rate [36, 46]. The above Eq. (9) is integrated numerically using the fourth order Runge Kutta time integration scheme [59] and the initial conditions $\tilde{N}(t=0) = N_0$ to obtain the (stochastic) average number of bonds $\tilde{N}(t)$ at any instant of time. Numerical integration is terminated at T_{cluster} defined by $\tilde{N}(T_{\text{cluster}}) = 1$ to obtain the cluster lifetime, T_{cluster} , and the cluster rupture force, F_{cluster} . The cluster lifetime, T_{cluster} , and the cluster rupture force, F_{cluster} , are made dimensionless with the Bell model unstressed off-rate, k_r^0 , and the Bell model force scale, $\frac{k_B T}{x_\beta}$, respectively. We define dimensionless loading rate, $\mu = \frac{R_f x_\beta}{k_0 k_B T}$. For the case of vanishing rebinding and in absence of both inertia and viscous drag, using the above deterministic approach we first confirmed the three scaling regimes for cluster lifetime and cluster rupture force as a function of loading rate predicted by Seifert [46]. We then explore the effect of inertia and viscous drag on these three scaling regimes.

E. Model and Computational Parameters

We simulated adhesion and detachment of multiple receptor-ligand bonds between two inelastic PMN cells using the Bell model and the parameter values listed in Table 1 unless stated otherwise. All of the results presented below are obtained using stochastic description of receptor-ligand interactions unless stated otherwise. We consider two PMN cells adhered by multiple L-selectin–PSGL-1 bonds for which the Bell model parameters are taken from Ref. [62]. The initial center-to-center distance between the two PMN cells is $8.27 \mu\text{m}$. A time step of 10^{-7} s is used in all these simulations. Since the thermally activated escape process is stochastic, the rupture forces differ from one experiment to another, resulting in distribution of rupture forces. For a given N_0 and R_f we repeated Monte Carlo simulation of rupture for 10^6 times to get statistically accurate average bond rupture force from distribution of rupture forces. The initial van der Waals attraction between a pair of microvilli separated by $0.05 \mu\text{m}$ is approximately 0.001 pN (see Eq. A9 in [55]) which is very small hence we do not consider van der Waals attraction in our model simulation. Similarly, the electrostatic and steric stabilization forces have been neglected because these forces exist in biological systems at distances from 50 to 250 Å [55].

III. RESULTS

As soon as force $F = R_f t$ on the cell is applied, it starts moving from its stationary position with an increasing velocity $\frac{dx}{dt}$. The cell velocity $\frac{dx}{dt}$ keeps increasing until it attains a steady velocity (see Fig. 2). Fig. 2 shows time variation of the cell velocity (solid lines) and the number of bonds (dashed lines) obtained from micro-mechanical model simulation at loading rate $R_f = 10^7$ pN/s for the initial number of bonds $N_0 = 5$. Once the cell attains a steady velocity ($\frac{dx}{dt} = \text{constant}$) the inertial force acting on it vanishes. Hence, during this period at any time the force transmitted to the bonds is the applied force less the drag force acting on the cell according to Eq. (1). However, once a bond ruptures the cell again undergoes a transient period during which inertia is non-zero. The cell velocity once again keeps increasing until it attains another steady velocity (see Fig. 2). This entire process repeats until all the bonds are ruptured. It should be noted from Fig. 2 that the time for subsequent rupture of bonds decreases. This is attributed to the fact that once a bond ruptures the net applied force is shared equally among all the remaining bonds at any instant of time, i.e., as more and more bonds rupture, the force on the remaining bonds increases. This leads to an enhanced probability for rupture of the remaining bonds. Consequently, the time for subsequent rupture of bonds decreases. Indeed as seen from Fig. 2 that towards the end the remaining bonds rupture in a very short period of time, in agreement with the similar findings reported in Ref [36]. This leads to a fluctuating cell velocity towards the end of complete rupture of bonds. We should note that in the absence of drag force acting on the cell at any time after initial transient, when the force $F = R_f t$ is applied or when a bond ruptures, the force transmitted to the existing bonds is the applied force at that instant of time.

Fig. 3(a) shows time variation of the drag force acting on the cell obtained from micro-mechanical model simulations for $N_0 = 2$ at three different loading rates $R_f = 10^3$, 10^5 , and 10^7 pN/s. It is seen that at any R_f the drag force increases with time and eventually attains a steady state. This is due to the fact that when the cell reaches its steady velocity it moves at a constant rate and hence the drag force acting on the cell becomes a constant. Further, it is seen that as R_f increases the drag force acting on the cell increases. This is attributed to the fact that increasing R_f increases the velocity of the cell and hence the drag force acting on the cell. Fig. 3(b) shows time variation of drag force acting on the cell obtained from micro-mechanical model simulations at $R_f = 10^7$ pN/s for $N_0 = 1, 2, 5$, and 10 . It is evident that at a given loading rate as the initial number bonds, N_0 , increases the drag force acting on the cell decreases. This is because at a given R_f as we increase N_0 the movement of the cell gets

restrained leading to a reduced cell steady velocity and hence the drag force acting on the cell. It is easy to infer from Fig. 3(b) that as more and more bonds rupture, i.e., $N(t)$ decreases from its initial value $N_0 > 1$, the drag force acting on the cell will increase progressively.

Fig. 4(a) shows time variation of the applied load (solid lines) and the intermolecular bond force obtained from micro-mechanical model simulations at $R_f = 10^3$ pN/s for $N_0 = 1$ (dashed lines), $N_0 = 2$ (dashed dot lines), $N_0 = 5$ (long dashed lines), and $N_0 = 10$ (dashed dot dot lines). The applied force increases linearly with time simply because $F = R_f t$. On the other hand, the intermolecular bond force increases nearly linearly with time. It is seen that at any instant the intermolecular bond force is always lower than the applied load for any N_0 . The intermolecular bonds do not experience the instantaneously applied load at any instant of time. The difference in applied load and the intermolecular bond force is the largest for $N_0 = 1$ (single bond) while it is the lowest for $N_0 = 10$. This is because as we increase N_0 the drag force acting on the cell decreases as shown in Fig. 3(b). The reduction in drag force acting on cell causes more of the applied force to get transmitted to the intermolecular bonds. Consequently, the difference in applied load and the intermolecular bond force decreases as N_0 increases. A similar set of conclusions are drawn from Figs. 4(b)–4(c) where we show time variation of applied load and the intermolecular bond force obtained from micro-mechanical model simulations at $R_f = 10^5$ pN/s and $R_f = 10^7$ pN/s, respectively. It is apparent that the bond rupture force would always be lower than the applied load at any instant of time. Consequently, the rupture force histograms based on the ‘applied force’ would differ from the rupture force histograms based on the ‘bond force’.

From Figs. 4(a)–4(c) we should not misinterpret that the difference in average bond rupture force with and without drag being considered would decrease as N_0 increases at a given R_f . On the contrary it would increase as noted below. From Figs. 4(a)–4(c) we should only infer that the difference in applied load and the intermolecular bond force would be the lowest for the cell adhered with the highest number of bonds at any time because the drag force acting on the cell decreases with increasing number of bonds as seen in Fig. 3(b). Once bonds rupture, i.e., $N(t)$ decreases from its initial value $N_0 > 1$, the difference in applied load and the intermolecular bond force will increase progressively because the drag force acting on the cell will increase progressively as inferred from Fig. 3(b). For a given N_0 and R_f the average bond rupture force is obtained considering all bond rupture events from $N(0) = N_0$ to $N(t) = 0$.

A direct comparison of Figs. 4(a)–4(c) shows that for a given N_0 as we increase the loading rate, R_f , the difference in applied load and the intermolecular bond force increases. This is because for a given N_0 as we increase R_f the drag force acting on the cell increases as shown in Fig. 3(a). This causes less of the applied force to get transmitted to the bonds. Consequently, the difference in applied load and the intermolecular bond force increases as R_f increases for a given N_0 . Once again it should be noted that at a given R_f and $N(t)$ at any time after initial transient the difference in the applied load and the intermolecular bond force is merely the drag force acting on the cell.

Figs. 4(a)–4(c) are obtained using $\eta = 1.0$ cP which corresponds to a Newtonian (water) fluid viscosity. However, the viscosity of the blood varies from 3 cP to 4 cP at physiological temperatures. In Fig. 4(d) we show time variation of the applied force (solid line) and the intermolecular bond force obtained from micro-mechanical model simulations at $R_f = 10^7$ pN/s for $N_0 = 2$ and $\eta = 1$ cP (dashed lines), $\eta = 2$ cP (dashed dot lines), $\eta = 3$ cP (long dashed lines), and $\eta = 4$ cP (dashed dot dot lines). It is apparent from Fig. 4(d) that as we increase the fluid viscosity, η , the difference in applied load and the intermolecular bond force increases. This is because as we increase η the drag force acting on the cell increases.

This causes less of the applied force to get transmitted to the bonds. Consequently, the difference in applied load and the intermolecular bond force increases as η increases for a given R_f and N_0 .

As noted above the rupture force histograms based on the ‘applied force’ would differ from the rupture force histograms based on the ‘bond force’ and hence the respective calculated average rupture forces. In this work we chose to calculate average rupture forces based on the bond force, $F_b = \alpha x(t)$, since this would be more relevant in measuring the bond kinetics [64]. Figs. 5(a)–5(d) show the effect of viscous drag on the average bond rupture forces as a function of loading rates obtained from the micro-mechanical model simulations for $N_0 = 1, 2, 5$, and 10 , respectively. It is seen that for single bond ($N_0 = 1$) the viscous drag does not affect the average bond rupture forces for $R_f = 10^2 - 5 \times 10^7$ pN/s for the system considered in this work. For loading rates $R_f > 5 \times 10^7$ pN/s the average bond rupture forces obtained with drag being considered are lower than the respective average bond rupture forces obtained without drag being considered. Moreover, for loading rates $R_f > 5 \times 10^7$ pN/s the difference in these two forces increases as the loading rate increases. From Figs. 5(a)–5(d) it is clear that there exists a critical loading rate at which the difference in the average bond rupture forces with and without drag being considered starts appearing. For a given N_0 the viscous drag does not affect the average bond rupture forces below the critical loading rate. On the other hand the viscous drag reduces the average bond rupture forces increasingly as the loading rate is increased progressively above the critical loading rate for a given N_0 . Further, at a given loading rate, R_f , as the initial number of bonds, N_0 , increases the difference in the average bond rupture forces with and without drag being considered increases. A direct comparison of Figs. 5(a)–5(d) shows that as we increase N_0 the critical loading rate decreases. Specifically, for $N_0 = 1, 2, 5$, and 10 , the critical loading rates are $R_f = 5 \times 10^7, 10^5, 5 \times 10^4$, and 10^4 pN/s, respectively for the system considered in this work. It is apparent that for higher initial number of bonds, $N_0 > 10$, the difference in average bond rupture forces with and without drag being considered would appear even for slow loading rates (see Fig. 10). A similar set of conclusions are drawn from Figs. 6(a)–6(d) where we show the effect of viscous drag on the average bond rupture forces as a function of loading rates obtained from the micro-mechanical model simulations using the two-state (catch-slip) model for $N_0 = 1, 2, 5$, and 10 , respectively. It is apparent that irrespective of the kinetic model (Bell or catch-slip) used the viscous drag acting on the cell reduces average bond rupture forces.

We performed Monte Carlo simulations using the bond spring constant $\sigma = 4$ dyn/cm for L-selectin–PSGL-1 bonds taken from the Ref. [61]. In order to assess the sensitivity of σ on the average bond rupture forces we performed two additional sets of Monte Carlo simulations using the bond spring constant $\sigma = 2$ dyn/cm and $\sigma = 1$ dyn/cm. Fig. 7 shows the effect of viscous drag on the average bond rupture forces as a function of loading rates obtained from the micro-mechanical model simulations for $N_0 = 10$ at $\sigma = 4$ dyn/cm (solid lines), $\sigma = 2$ dyn/cm (dashed lines), and $\sigma = 1$ dyn/cm (dashed dot lines). It is seen from Fig. 7 that at a given loading rate the average bond rupture forces obtained without drag being considered are practically insensitive to changes in the bond spring constant. On the other hand at a given loading rate the average bond rupture forces obtained with drag being considered slightly decrease as the bond spring constant decreases. In other words as we decrease the bond spring constant the difference in average bond rupture forces with and without drag being considered slightly increases especially at higher loading rates.

Fig. 8 shows variation of the (stochastic average) number of bonds as a function of time obtained from the deterministic model simulation (solid lines) at $R_f = 10^7$ pN/s, $N_0 = 100$. Bond breakage is synergistically regulated by thermally induced spontaneous dissociation and occurs stochastically with a characteristic bond lifetime that is the reciprocal of the

unstressed off-rate [38]. However, in forced dissociation an applied load causes bond stretching and hence lowers the chemical activation barrier to increase the probability of bond rupture according to Eq. 5 and Eq. 8. In other words once a bond ruptures the net applied force is shared equally among all the remaining bonds at any instant of time, i.e., as more and more bonds rupture, the force on the remaining bonds increases. This leads to an enhanced probability for rupture of the remaining bonds. Hence, it is seen from Fig. 8 that initially bond rupture is nearly linear with time. However, once number of bonds drop to about 90 the bond rupture is non-linear with time due to bond stretching leading to enhanced probability in bond rupture according to Eq. 5 and Eq. 8. Further, it is seen that there is a precipitous drop in the number of bonds from about 60 to 0 for the same reason. In Fig. 8 we also show representative trajectories for the number of bonds as a function of time obtained from the Monte Carlo simulations (dashed lines) at $R_f = 10^7$ pN/s, $N_0 = 100$. Due to stochastic nature inherent in Monte Carlo simulation these trajectories differ from each other. Furthermore, it is seen that each trajectory deviates (two-sided) from the (stochastic average) number of bonds as a function of time implying that stochastic average of many such trajectories would be in good agreement with the (stochastic average) number of bonds as a function of time obtained from the deterministic model simulation, in agreement with the similar findings reported in Ref [36].

Seifert [46] predicted that for the case of vanishing rebinding in the regime of slow loading rates, $\mu < 1$, the cluster lifetime $T_{\text{cluster}} = \ln N_0$ in absence of both inertia and viscous drag. While in the intermediate loading rates, $1 < \mu < N_0$, the cluster lifetime scales as $T_{\text{cluster}} \sim \ln(N_0/\mu)$. On the other hand in the regime of fast loading rates, $\mu > N_0$, the cluster lifetime scales as $T_{\text{cluster}} \sim (N_0/\mu) \ln(\mu/N_0)$. The corresponding scalings for the cluster rupture force for the case of vanishing rebinding and in absence of both inertia and viscous drag are $F_{\text{cluster}} = \mu \ln N_0$, $F_{\text{cluster}} \sim \mu \ln(N_0/\mu)$, and $F_{\text{cluster}} \sim \mu(N_0/\mu) \ln(\mu/N_0)$, respectively. Figure 9(a) shows dimensionless cluster lifetime, T_{cluster} , as a function of μ/N_0 for $N_0 = 10, 10^2$, and 10^3 obtained from the deterministic model simulation for the case of vanishing rebinding and in absence of both inertia and viscous drag (solid lines). The three scaling curves of Seifert [46] are shown as broken lines. It is seen from Fig. 9(a) that for slow loading rates, $\mu < 1$, the different curves plateau at the value $\ln N_0$ for a given N_0 . While for the intermediate loading rates, $1 < \mu < N_0$, and sufficiently large N_0 , these different curves collapse onto a universal curve which is approximated by $0.84 \ln(0.35 N_0/\mu)$ [36]. On the other hand in the regime of fast loading rates, $\mu > N_0$, these different curves collapse onto another universal curve, $(N_0/\mu) \ln(\mu/N_0)$. The corresponding dimensionless cluster rupture force, F_{cluster} , as a function of μ/N_0 for $N_0 = 10, 10^2$, and 10^3 obtained from the deterministic model simulation for the case of vanishing rebinding and in absence of both inertia and viscous drag is shown as solid lines in Fig. 9(b) and the three scaling curves of Seifert [46] as broken lines. It is seen from Fig. 9(b) that for slow loading rates, $\mu < 1$, the cluster rupture force obtained from the deterministic model simulation exactly matches with that predicted by Seifert [46]. While in the intermediate loading rates, $1 < \mu < N_0$, the scaling curves of Seifert [46] becomes an increasingly bad fit as we decrease N_0 . On the other hand in the regime of fast loading rates, $\mu > N_0$, the cluster rupture force obtained from the deterministic model simulation are reasonably in good agreement with the scaling curves of Seifert [46]. Results similar to those shown in Fig. 9 were originally presented by Erdmann and Schwarz [36] and they confirmed the three scalings of Seifert [46] for the case of vanishing rebinding and in absence of both inertia and viscous drag. In this work we have reconfirmed the results of Erdmann and Schwarz [36] and the three scalings of Seifert [46].

Figure 10(a) shows dimensionless cluster lifetime, T_{cluster} , as a function of μ/N_0 for $N_0 = 10, 10^2$, and 10^3 obtained from the deterministic model simulation for the case of vanishing rebinding and in absence of both inertia and viscous drag (solid lines). The corresponding T_{cluster} obtained considering both inertia and viscous drag is shown as symbols. It is

apparent from Fig. 10(a) that incorporation of both inertia and viscous drag into the model does not appreciably change the cluster lifetime. However, the influence of both inertia and viscous drag on the cluster rupture force, F_{cluster} , is very strong as shown in Fig. 10(b). Figure 10(b) shows dimensionless cluster rupture force, F_{cluster} , as a function of μ/N_0 for $N_0 = 10, 10^2$, and 10^3 obtained from the deterministic model simulation for the case of vanishing rebinding and in absence of both inertia and viscous drag (solid lines). The corresponding F_{cluster} obtained considering both inertia and viscous drag is shown as symbols. It is apparent from Fig. 10(b) that the incorporation of both inertia and viscous drag into the model causes a significant reduction in cluster rupture forces especially at higher μ/N_0 for a given N_0 . This is attributed to the fact the drag force acting on the cell increases as the dimensionless loading rate, μ/N_0 , increases for a given N_0 as seen from Fig. 3(a). This causes a significant reduction in the intermolecular bond force leading to a significant reduction in cluster rupture forces especially at higher μ/N_0 for a given N_0 . Further, it is seen from Fig. 10(b) that for $N_0 = 10$ the difference between the cluster rupture force obtained with and without considering both inertia and viscous drag starts at around $\mu/N_0 = 10^0$. Once again it is clear that there exists a critical loading rate at which the difference in the cluster rupture force with and without both inertia and drag being considered starts appearing. For a given N_0 the viscous drag does not affect the cluster rupture force below the critical loading rate. On the other hand the viscous drag reduces the cluster rupture force increasingly as the loading rate is increased progressively above the critical loading rate for a given N_0 . Specifically, for $N_0 = 10, 100$, and 1000 the critical loading rates obtained from the deterministic model simulations for the system considered in this work are $R_f = 10^4, 7 \times 10^3$, and 10^3 pN/s, respectively. Further, at a given μ/N_0 as the initial number of bonds, N_0 , increases the difference in the cluster rupture force with and without both inertia and drag being considered increases. It is apparent from Fig. 10 that as we increase N_0 the critical loading rate decreases, an observation similar to seen from Fig. 5. A direct comparison of Fig. 9 and Fig. 10 clearly indicates that for the case of vanishing rebinding the three scaling regimes for the cluster lifetime predicted by Seifert [46] are not affected by the incorporation of both inertia and viscous drag into the model. However, the incorporation of both inertia and viscous drag into the model causes a significant deviation from the corresponding scalings for the cluster rupture force especially at higher loading rates.

IV. CONCLUSION

The detachment of two PMN cells suspended in a Newtonian fluid and adhered by multiple L-selectin–PSGL-1 bonds as a function of applied loading rate was simulated using a Monte Carlo method. We demonstrated that viscous drag caused by relative motion of cell suspended in a Newtonian fluid modulates transmission of an applied external load to bonds. It is demonstrated that at any time the intermolecular bond force is not equivalent to the instantaneous applied force due to viscous drag. The difference in the instantaneous applied force and the intermolecular bond force varies with the viscosity of the fluid, the size of cell, the applied loading rate, and the number of bonds at any instant of time. Consequently, there is not a constant off-set between the applied load and the force transmitted to bonds. Average bond rupture forces were based on 10^6 Monte Carlo simulations. We showed that viscous drag acting on cell reduces average bond rupture forces. For a given initial number of bonds there exists a critical loading rate below which the viscous drag does not affect the average bond rupture forces while it does for loading rates higher than the critical loading rate. As we increase initial number of bonds the critical loading rate decreases. Consequently, it is anticipated that for large ($> 10^3$) initial number of bonds the viscous drag will lower the average bond rupture forces even for very slow loading rates.

To the best of our knowledge, this is the first study dealing with the model of multiple receptor-ligand bonds system in presence of viscous drag acting on the cell. All of the previous studies mimic models of multiple receptor-ligand bonds system in absence of viscous drag acting on the cell. Incorporation of viscous drag relevant to real physiological conditions in these modeling approaches will alter their findings due to bond force modulation as demonstrated in this work. It is apparent that in absence of viscous drag the entire work done by the applied force only affects the free energy of the bond. However, when viscous drag is taken into consideration part of the entire work done by the applied force is lost in the form of viscous dissipation. We should note that for receptor-ligand bonds system considered in this work viscous dissipation depends on the size of cell, the viscosity of the media, the number of bonds, and the applied loading rate. Viscous dissipation will modify the effective free energy of a bond cluster resulting in a modified cluster dissociation dynamics. Furthermore, modeling cell as an elastic (deformable) material would also contribute to an additional force modulation due to viscoelasticity arising from the complex interplay of cellular deformation and viscous drag acting on it [65]. Hence, it is important to consider all these factors in modeling multiple receptor-ligand bonds system relevant to real physiological conditions.

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Highlights

Monte Carlo simulation of the rupture of multiple bonds between two PMNs is performed

Viscous drag acting on cells reduces intermolecular bond forces

The modulation of bond force leads to reduced average bond rupture forces

The three scaling regimes for rupture force and time of Seifert [46] are examined

Figure 1. Schematic of two PMN cells detachment (not drawn to scale) through binding between PSGM-1 (receptor) and L-selectin (ligand) molecules concentrated on the tip of PMN microvilli.

Figure 2.

Time variation of the cell velocity (solid lines) and the number of bonds (dashed lines) obtained from micro-mechanical model simulation at loading rate $R_f = 10^7$ pN/s for the initial number of bonds $N_0 = 5$.

Figure 3. Time variation of drag force acting on cell (a) for $N_0 = 2$ at three different R_f (b) for $N_0 = 1, 2, 5, 10$ at $R_f = 10^7$ pN/s obtained from micro-mechanical model simulations for the model parameters listed in Table 1.

Figure 4.

Time variation of applied force (solid line) and intermolecular bond force for $N_0 = 1$ (dashed lines), $N_0 = 2$ (dashed dot lines), $N_0 = 5$ (long dashed lines), and $N_0 = 10$ (dashed dot dot lines) at (a) $R_f = 10^3$ pN/s (b) $R_f = 10^5$ pN/s (c) $R_f = 10^7$ pN/s obtained from micro-mechanical model simulations for the model parameters listed in Table 1. Panel (d) shows time variation of applied force (solid line) and intermolecular bond force for $N_0 = 2$ at $R_f = 10^7$ pN/s and $\eta = 1$ cP (dashed lines), $\eta = 2$ cP (dashed dot lines), $\eta = 3$ cP (long dashed lines), and $\eta = 4$ cP (dashed dot dot lines).

Figure 5.

Average bond rupture force as a function of loading rate for (a) $N_0 = 1$, (b) $N_0 = 2$, (c) $N_0 = 5$, and (d) $N_0 = 10$ obtained from the micro-mechanical model simulations utilizing the Bell model for the model parameters listed in Table 1.

Figure 6.

Average bond rupture force as a function of loading rate for (a) $N_0 = 1$, (b) $N_0 = 2$, (c) $N_0 = 5$, and (d) $N_0 = 10$ obtained from the micro-mechanical model simulations utilizing the two-state (catch-slip) model for the model parameters listed in Table 1.

Figure 7.

Effect of bond spring constant on the average bond rupture force as a function of loading rate for $N_0 = 10$ at $\sigma = 4$ dyn/cm (solid lines), $\sigma = 2$ dyn/cm (dashed lines), and $\sigma = 1$ dyn/cm (dashed dot lines) obtained from the micro-mechanical model simulations utilizing the Bell model for the model parameters listed in Table 1.

Figure 8.

Number of bonds as a function of time obtained from the deterministic model simulation (solid lines) at $R_f = 10^7$ pN/s, $N_0 = 100$. A few representative trajectories for the number of bonds as a function of time obtained from the Monte Carlo simulation at $R_f = 10^7$ pN/s, $N_0 = 100$ are shown as dashed lines.

Figure 9.

Solid lines: deterministic results for (a) cluster lifetime T_{cluster} and (b) cluster rupture force F_{cluster} for the case of vanishing rebinding and in absence of both inertia and viscous drag as a function of μ/N_0 for $N_0 = 10, 10^2$, and 10^3 . Broken lines: curves for all three scaling regimes.

Figure 10.

Solid lines: deterministic results for (a) cluster lifetime T_{cluster} and (b) cluster rupture force F_{cluster} for the case of vanishing rebinding and in absence of both inertia and viscous drag as a function of $\mu=N_0$ for $N_0 = 10, 10^2$, and 10^3 . Symbols: corresponding results in presence of both inertia and viscous drag.

TABLE I

Parameter values used in the model

Parameter	Definition	Value	Reference
R	PMN radius	$3.75 \mu\text{m}$	[60]
L_{mv}	Length of microvillus	$0.35 \mu\text{m}$	[57]
λ	Receptor-ligand bond length	$0.07 \mu\text{m}$	[60]
k_f^0	Unstressed on rate (Bell model)	3 s^{-1}	[62]
k_r^0	Unstressed off rate (Bell model)	8.6 s^{-1}	[62]
x_β	Reactive compliance (Bell model)	$0.16 \text{ \AA}$	[62]
α	Bond spring constant	4 dyn/cm	[61]
k_{1rup}	Off-rate (pathway 1) (Two-state model)	150 s^{-1}	[63]
k_2^0	Unstressed off-rate (pathway 2) (Two-state model)	5 s^{-1}	[63]
f_β	Force scale (Two-state model)	110 pN	[63]
ΔE_{12}	Equilibration parameter (Two-state model)	5 pN.nm	[63]
f_{12}	Equilibration parameter (Two-state model)	10 pN	[63]
η	Fluid viscosity	1.0 cP	
ρ	Fluid density	1 g/cc	
T	Temperature	310 K	