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Computational Study of Cell Adhesion and Rolling in Flow Channel by Meshfree Method

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Abstract

Tethering and rolling of circulating leukocytes on the surface of endothelium are critical steps during an inflammatory response. A soft solid cell model was proposed to study monocytes tethering and rolling behaviors on substrate surface in shear flow. The interactions between monocytes and micro-channel surface were modeled by a coarse-grained molecular adhesive potential. The computational model was implemented in a Lagrange-type meshfree Galerkin formulation to investigate the monocyte tethering and rolling process with different flow rates. From the simulation results, it was found that the flow rate has profound effects on the rolling velocity, contact area and effective stress of monocytes. As the flow rate increased, the rolling velocity would increase linearly, whereas the contact area and average effective stress in monocyte showed nonlinear increase.

Keywords

Cell tethering; Cell rolling; Meshfree method; Human monocyte; Shear flow; Numerical simulation

1. Introduction

Cell migration is a fundamental biological process throughout all the stages of animal life, from its commencement to its end (Frascoli et al. 2013, Li and Sun 2014). A variety of complex mechanisms, such as embryonic morphogenesis, wound healing, and immune response all require the orchestrated movement of cells in certain directions. For instance, in the human immune system, the movement and circulation of white blood cells (leukocytes) on the endothelial layer is highly coordinated during an inflammatory response (Muller 2013, Simon and Green 2005), in which the cells will undergo a multistep process. Firstly, the leukocyte adheres to the surface of endothelium, then the leukocyte will start to roll along the endothelial cell surface, finally the leukocyte will squeeze through the capillary wall to the inflammation sites. Through studying rolling of leukocytes on artificial lipid bilayers, Lawrence and Springer (1991) found that selectin-mediated rolling is a prerequisite for activation-induced adhesion strengthening through integrins at physiologic shear stress. In fact, rolling of leukocytes in shear flow involves a complex balance of forces arising from

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cell-substrate interaction and hydrodynamic shearing effect (Lauffenburger and Linderman 1993, Pappu et al. 2008).

To study leukocyte tethering and rolling behavior on the surface of microvasculature in shear flow, many experiments, theoretical analysis and numerical simulations have been conducted. Through characterizing molecular bases of selectin interactions, Somers et al. (2000) demonstrated that the adhesion molecules of the selectin family mediate the initial tethering and rolling of leukocytes. A study on the interplay between adhesive, contractile and protrusive force indicated that cells migrate by the sole force of actin-network expansion which promotes protrusive flowing of the leading edge (Lämmermann et al. 2008). The study of leukocyte deformation found that the increase of the contact area between leukocyte and substrate leads to the increase of adhesion (Lawrence and Dong 1999). From experiment observation, faster rolling was captured when deformation of cell was increased in shear flow (McCarty et al. 2003, Ramachandran et al. 2004, Sheikh and Nash 1998). The study of static and dynamic lengths of neutrophil microvilli indicated that leukocyte rolling might be influenced by the viscoelasticity of the microvilli and the rate of tether elongation of neutrophils (Chen and Springer 1999, Shao et al. 1998). Through investigating the effects of adhesive ligand density on mobility of neutrophils, it was found that neutrophils will switch their motile phenotype from kerotocyte-like to amoeboid-like as ligand density is increased (Henry et al. 2014, Henry et al. 2016). Besides experiments, significant progress has also been made in theoretical analysis and numerical simulations to understand the receptor-mediated cell adhesion and rolling process. By using a rigid cell model, the fluid drag on leukocytes was studied (Brooks and Tozeren 1996, Chapman and Cokelet 1998, Gaver and Kute 1998). In these studies, it was found that the fluid drag on individual cell decreased as the number of adherent leukocytes increased. In addition, the adhesive dynamics simulation model (ADSM) (Chang and Hammer 2000) was developed to study the leukocyte rolling process and to investigate the effects of cell concentration on the rolling velocity (King and Hammer 2001), in which the cell was modeled as a rigid sphere. To consider the cell deformability and its influence on cell tethering and rolling behavior, the elastic ring enclosing incompressible viscous fluid cell model was utilized to investigate the effects of wall shear stress on the HL-60 cell rolling (Dong and Lei 2000). Through numerical analysis, it was found that both cell rolling velocity and cell-surface contact area increase as flow shear stress increases. A 2D compound drop model was used to study the effects of intracellular viscosity and interfacial tension on the rolling of leukocytes (N'dri et al. 2003). The effect of leukocyte adhesion on flow pattern in microvessel was studied by modeling cell as a compound liquid drop surrounded by a hyperelastic membrane (Pappu et al. 2008). The roles of cell and microvillus deformation and receptor-ligand binding kinetics in leukocyte rolling were analyzed to predict the catch-slip bond behavior (Pawar et al. 2008). The effect of cytoplasmic viscosity on leukocyte adhesion and rolling in a parallel plate flow chamber was studied to observe the velocity and shape changes of rolling leukocytes in vitro and in vivo (Khismatullin and Truskey 2012).

Although the tethering and rolling of leukocytes in shear flow have been broadly studied, the migration process are still not fully understood because cell adhesion and rolling behavior on endothelium in shear flow are influenced by many factors. A major challenge in computational simulation is the presence of the disparate length scales between the adhesion

bond, which is at nanoscale and dimension of cells, which is at microscale. To provide some insight into monocyte adhesion and rolling in a shear flow channel, the aim of current work was to develop computational models and simulation tools. A deformable cell model is used to represent cell scaffold and cell plasma aggregates to study monocytes (largest type of leukocyte) tethering and rolling behavior in a shear flow channel by meshfree method. In this study, the monocyte was modeled as a hyperelastic solid and the cell-substrate interaction was modeled by a coarse-grained potential. A reduced unit was used in the simulation calculation. The effects of different flow rates on the monocyte rolling velocity, contact area and effective stress were analyzed. Through this study, it was found that the flow rate has significant influence on the rolling velocity, contact area and effective stress during the monocyte tethering and rolling process.

2. Meshfree Galerkin formulation and the Computational Algorithm

The numerical simulations were conducted by using Reproducing Kernel Particle Methods (RKPM) (Li and Liu 2007, Liu et al. 1997). Through correcting the original Smooth Particle Hydrodynamics (SPH) kernel function (Lucy 1977), the correction function is introduced in the RKPM method. The interpolation approximation function for $u(x)$ in a domain Ω can be described as:

$$u^h(x, t) = \int_{\Omega} C(x, \bar{x}) k(x - \bar{x}) u(\bar{x}) d\Omega \quad (1)$$

where $C(x, \bar{x}) = b^T(x) P(x, \bar{x})$ is the correction function; $k(x - \bar{x})$ is the SPH kernel function.

In the above correction function, $P^T(x, \bar{x}) = \{P_1(x, \bar{x}), P_2(x, \bar{x}), \dots, P_n(x, \bar{x})\}$ is an independent polynomial basis with $P_1(x, \bar{x}) = 1$. The $b(x) = P^T(0) M^{-1}(x)$ is a coefficient vector.

Here:

$$P^T(0) = [1, 0, 0, 0]$$

$$M(x) = \int_{\Omega} P(x - \bar{x}) P^T(x - \bar{x}) k(x - \bar{x}) d\Omega$$

Based on the kernel integration Eq.(1), the discretization form of a numerical interpolation can be obtained:

$$u^h(x, t) = \sum_{I=1}^{np} C(x, \bar{x}) k(x - \bar{x}) U_I(t) W_I = \sum_{I=1}^{np} N_I(x) U_I(t) \quad (2)$$

where W_I is integration weight.

From the strong form of the balance of linear momentum, the weak form of the balance of linear momentum under finite strain condition can be derived as:

$$\int_{\Omega_0} \rho_0 \ddot{\mathbf{u}} \delta \mathbf{u} d\Omega + \int_{\Omega_0} \mathbf{P} \delta \mathbf{F} d\Omega = \int_{\Omega_0} \rho_0 \mathbf{B} \delta \mathbf{u} d\Omega + \int_{\Gamma_t} \bar{\mathbf{T}} \delta \mathbf{u} dS + \int_{\Gamma_t} \mathbf{f}^a \delta \mathbf{u} dS + \int_{\Gamma_t} \mathbf{f}^r \delta \mathbf{u} dS \quad (3)$$

where Ω_0 , Γ_t are the volume and external traction boundary, respectively; ρ_0 represents the material density in the reference configuration; $\mathbf{P}$ is the first Piola-Kirchhoff stress tensor; $\mathbf{F}$ is the deformation gradient; $\mathbf{B}$ is the body force; $\bar{\mathbf{T}}$ denotes the external driving traction vector; $\mathbf{f}^a$ is the cell-channel adhesive force; $\mathbf{f}^r$ is the resistance drag force.

Following the standard meshfree discretization procedure (Li and Liu 2007), the following discrete equations of motion can be obtained:

$$\mathbf{M} \ddot{\mathbf{u}} = \mathbf{F}^{ext} - \mathbf{F}^{int} \quad (4)$$

$$\mathbf{F}^{ext} = \mathbf{F}^d + \mathbf{F}^a + \mathbf{F}^r + \mathbf{F}^b \quad (5)$$

where $\mathbf{M}$ is lumped mass matrix; $\mathbf{F}^{ext}$ is external force array including external driving force $\mathbf{F}^d$, cell-channel adhesion force $\mathbf{F}^a$, resistance drag force $\mathbf{F}^r$ and body forces $\mathbf{F}^b$; $\mathbf{F}^{int}$ denotes internal force array arising from the current state of stress.

$$M_{IJ} = \int_{\Omega_0} \rho_0 N_I N_J d\Omega \quad (6)$$

$$F_I^d = \int_{\Gamma_t} \bar{T}_i N_I e_i dS \quad (7)$$

$$F_I^a = \int_{\Gamma_t} f_i^a N_I e_i dS \quad (8)$$

$$F_I^r = \int_{\Gamma_t} f_i^r N_I e_i dS \quad (9)$$

$$F_I^b = \int_{\Omega_0} \rho_0 b_i N_I e_i d\Omega \quad (10)$$

$$F_I^{int} = \int_{\Omega_0} P_{iJ} N_{I,J} e_i d\Omega \quad (11)$$

3. Model Description

In this study, the monocyte was placed in a micro-channel. We assume the fluid was pumped into the micro-channel from left-hand side and flow to the right-hand side. The surface of the micro-channel is a ligand-coated surface. Under fluid driving, the monocyte will tether and roll over the micro-channel surface. To investigate the tethering and rolling process, a RKPM meshfree method was adopted for numerical simulation. A schematic diagram of a typical human monocyte cell in shear flow channel is shown in Fig. 1.

3.1 Cell-substrate Interaction Model

During the monocyte tethering and rolling process in the fluid channel, the monocyte and substrate will firstly form interaction bonds between cell and micro-channel surface (or substrate surface). Then, the monocyte will start to roll over the substrate surface in shear flow. A specific interaction between the cell surface and substrate is the ligand-receptor interaction. To model the ligand-receptor interaction, many adhesion models were developed in the literatures (Fan and Li 2015, Farsad and Vernerey 2012, Liu et al. 2007, Sauer and Li 2007, Zhu 2000, Zhu et al. 2000). To capture the ligand-receptor bonding behavior, we adopted an adhesive potential function given by Seifert (Seifert 1991), which is also used by Roy and Qi (Roy and Qi 2010) and Zeng and Li (Zeng and Li 2012):

$$\varphi(r) = \sigma \left[\left(\frac{\varepsilon}{r} \right)^4 - 2 \left(\frac{\varepsilon}{r} \right)^2 \right] \quad (12)$$

where σ is the energy depth; r is the separation between the monocyte surface and the ECM substrate; ε is the equilibrium position.

Thus, the adhesive force vector of ligand-receptor bond can be calculated as:

$$\mathbf{F}(r) = -\frac{\partial \varphi}{\partial \mathbf{r}} = \frac{4\sigma}{\varepsilon} \left[\left(\frac{\varepsilon}{r} \right)^5 - \left(\frac{\varepsilon}{r} \right)^3 \right] \frac{\mathbf{r}}{r} \quad (13)$$

Considering ligand-receptor bond density at the contact surface, the adhesive force between the cell membrane and the substrate surface may be calculated as follows:

$$\mathbf{f}^a(r, x) = N_b \mathbf{F}(r) = N_b \frac{4\sigma}{\varepsilon} \left[\left(\frac{\varepsilon}{r} \right)^5 - \left(\frac{\varepsilon}{r} \right)^3 \right] \frac{\mathbf{r}}{r} \quad (14)$$

where N_b is the surface bond density.

3.2 Interstitial Flow Model

In the fluid channel such as vascular microenvironment, the fluid flow will impose a flow shear stress on the monocyte. To describe the physical force from fluid flow in the rectangular micro-channel, the maximum shear stress is defined as (Chung et al. 2014):

$$\bar{T} = \frac{6\mu Q}{H^2 W} \quad (15)$$

where μ is dynamic viscosity; Q is the volumetric flow rate; L is the length of channel; H is the height of the micro-channel; W is the width of the micro-channel.

3.3 Fluid Resistance Force

Drag force depends on the properties of the fluid and the size, shape, and speed of the monocyte. The resistance force on the monocyte is proportional to the cell movement speed, and can be expressed as (Frascoli et al. 2013):

$$\mathbf{f}^r = -3\pi D_0 \eta \mathbf{V} \quad (16)$$

where η is the effective viscosity of the viscoelastic medium, D_0 is the monocyte diameter and $\mathbf{V}$ is the cell velocity vector.

3.4 Monocyte Material Model

For cell modeling, hyperelastic material models have been extensively used (Jean et al. 2005, Monteiro et al. 2011, Zeng and Li 2011b). In our study, a modified Mooney-Rivlin hyperelastic material model (Fried and Johnson 1988) was used to represent monocyte's scaffold and plasma aggregates, which exhibits nonlinear response. The strain energy density function W for the modified Mooney-Rivlin model is given as (Zeng and Li 2011a, Zeng and Li 2013):

$$W = C_1 \left(I_1 - 3I_3^{1/3} \right) + C_2 \left(I_2 - 3I_3^{2/3} \right) + \frac{1}{2} \lambda (\ln I_3)^2 \quad (17)$$

where C_1 , C_2 , and λ are material constants; I_1 , I_2 , I_3 are three invariants of the right Cauchy-Green tensor, which are defined as:

$$I_1 = \text{tr}(\mathbf{C}) \quad (18)$$

$$I_2 = \frac{1}{2} \left[(\text{tr}(\mathbf{C}))^2 - \text{tr}(\mathbf{C}^2) \right] \quad (19)$$

$$I_3 = \det(\mathbf{C}) \quad (20)$$

where tr is trace operator; $\mathbf{C} = \mathbf{F}^T \mathbf{F}$ is the right Cauchy-Green deformation tensor.

Thus, the corresponding constitutive relation of second Piola-Kirchhoff stress $\mathbf{S}$ can be expressed in terms of the three invariants of the right Cauchy-Green tensor:

$$\mathbf{S} = 2 \left[(C_1 + C_2 I_1) \mathbf{I} - C_2 \mathbf{C} - (C_1 I_3^{1/3} + 2C_2 I_3^{2/3} - \lambda \ln I_3) \mathbf{C}^{-1} \right] \quad (21)$$

So, the first Piola-Kirchhoff stress tensor $\mathbf{P}$ can be easily obtained from the second Piola-Kirchhoff stress: $\mathbf{P} = \mathbf{S} \cdot \mathbf{F}^T$, which can be substituted into the meshfree Galerkin formulation to calculate the internal nodal force. The elastic properties of monocyte can be determined by constants C_1 , C_2 , and λ .

4. Numerical Simulation

4.1 Reduced Unit

We applied the proposed model to study human monocyte tethering and rolling in a flow channel. For a 2D problem, the monocyte was modeled as a circular plate with a diameter of D_0 and the channel was modeled as two pieces of thin rectangle plates, as shown in Fig. 1. In this study, there exist two distinct length scales: one is cellular length-scale, which is at micrometer size; the other is the ligand-receptor bond length, which is at nanometer size. To bridge these two different length scales involved in monocyte tethering and rolling process, a set of reduced units was used. The simulation results were reported using a normalizing scheme similar to the scheme of Liu et al (Liu et al. 2007): the length was normalized by the

diameter of the cell D_0 , energy by $E_0 = \sigma$, force by $F_0 = \frac{E_0}{D_0}$, stress by $\sigma_0 = \frac{F_0}{D_0^2}$, density by $\rho_0 = \frac{F_0}{D_0^4}$.

4.2 A Typical Case Study

In the meshfree computation, a total of 4455 particles were used in discretization of the human monocyte. The meshfree dilation parameter are selected as $(\rho_x = 2.0 \Delta_x, \rho_y = 2.0 \Delta_y)$. The initial density for monocyte is $\rho_0 = 1.0 \times 10^3 \text{ kg/m}^3$ and the material constants for the hyperelastic cell model are $C_1 = 0.6 \text{ KPa}$, $C_2 = 0.06 \text{ KPa}$, $\lambda = 2 \text{ KPa}$ (Ravetto et al. 2014). The parameters of ligand-receptor bond were set as $N_b = 3,000 (1/\mu\text{m}^2)$, $\sigma = 0.024 (pN \cdot \mu\text{m})$ and $\varepsilon = 100 \text{ nm}$ (Liu et al. 2007, Roy and Qi 2010). The volumetric flow rate $Q = 4.0 \text{ ml/min}$, the micro-channel length $L = 17000 \mu\text{m}$, and height $H = 100 \mu\text{m}$.

The Fig. 2 showed the contour of shear strain distribution in the monocyte during tethering and rolling process. In Fig. 2, it can be seen that the contact area between the monocyte and the substrate surface became flat and increased during tethering process ($t = 6.1 \text{ s}$, 6.2 s and

6.3s). Meanwhile, the shear strain became larger during tethering process as shown in Fig. 2. When $t > 6.3s$, the tethered microvillus broke and the monocyte started to roll over the substrate surface. The contact area and shear strain was reduced during the rolling process. Subsequently, the monocyte was tethered again and the cell was firmly adhered to the substrate surface ($t = 7.0s$ and $7.1s$).

In addition, the monocyte rolling process was captured from simulation. As shown in Fig. 3, the position of one spot was highlighted by elliptical shape to indicate the monocyte rotation. It was clearly shown that the monocyte rolled forward over the substrate in shear flow.

From the simulation calculation, we assessed the cell rolling velocity and acceleration at cell center point. In Fig. 4(a), it showed that approximately when $t > 5s$, the rolling velocity starts to stabilize. The rolling velocity from our simulation was around $7.5 \mu m/s$, which is in the range ($3 \sim 9 \mu m/s$) of experimental observations of lymphocyte in a flow channel (Murai et al. 2013). In Fig. 4(b), it can be seen that the acceleration showed dynamic features and its value alternated between positive and negative values.

In addition, the deformation and contact area of the monocyte in the rolling process were examined. As shown in Fig. 5, it showed that at initial steps, the monocyte was firstly elongated due to the pressure from shear flow and resistant drag force, then it tethered and spread over the substrate, and started to roll. This process presented the monocyte tethering, spreading and rolling behavior. For every single migration process, the monocyte experienced tethering and spreading over substrate, and rapid formation and dissociation of ligand-receptor bonds at the front and rear edge of the rolling monocyte, which can be seen from the dynamic variation of cell deformation and contact area as illustrated in Fig. 5(a) and (b).

4.3 Cell Response to Different Flow Rates

To assess the effects of shear flow rate on the monocyte tethering and rolling, the influence of different shear flow rates on the rolling velocity was examined. In Fig. 6, it can be seen that as the flow rate increased, the cell rolling velocity increased. We also observed that the rolling velocity increased linearly as the flow rate increased, which is consistent with the observation of Jadhav et al (Jadhav et al. 2005). In addition, the simulation results also showed that the contact area increased as the flow rate increased. But the contact area increased nonlinearly as the flow rate increased, as shown in Fig. 7.

In the meanwhile, since our cell model can deform, we can plot the effective stress. The effective stress is defined as:

$$\sigma_e = \frac{1}{\sqrt{2}} [(\sigma_1 - \sigma_2)^2 + (\sigma_2 - \sigma_3)^2 + (\sigma_3 - \sigma_1)^2]^{1/2} \quad (22)$$

As the flow rate increased, we observed that the average effective stress in cell increased, as shown in Fig. 8.

5. Discussions and Conclusions

The human monocyte tethering and rolling behavior in a fluid micro-channel was studied by using RKPM meshfree method. In current study, the monocyte was modeled as hyperelastic material and a coarse-grained potential force was proposed to model the cell-substrate interactions. The current model successfully captured the monocyte tethering and rolling behavior in shear flow. Through this study, we observed that the monocyte rolling velocity increased linearly with the increase of flow rate, and the contact area and the average effective stress in cell increased nonlinearly with the increase of flow rate.

Experimental observations indicated that leukocytes roll faster on selectins and detach quickly as wall shear stress is increased (Yago et al. 2002). From our simulation, we found that the contact area increased as the flow rate increased (Fig.7), which will result in the increase of the adhesion force between cell and substrate (Lawrence and Dong 1999). Thus, monocyte tends to adhere quickly onto the substrate. Due to the increase of flow rate, the pushing force behind monocyte will increase, which could cause cell to detach and roll forward faster. Hence, the rolling velocity of monocyte will increase as the flow rate increases (Fig.6), which is consistent with experimental observation (Yago et al. 2002) and finite element simulation (Dong and Lei 2000). In Fig.6(a), we observed that monocyte exhibited stable rolling in different flow rates, which maybe the reason that cell presents its receptors in accessible positions with more uniform distribution on the surface to confer stable rolling. On the other hand, it can be seen that the effective stress inside monocyte increased as flow rate increased as shown in Fig.8, which indicated that the stress state in monocyte is directly related to the cell microenvironment.

It should be noted that monocyte's rolling behavior is a complex biological phenomenon. In the current study, it is only intended to study the mechanical behaviors of monocyte under different shear flow rates. Considering monocyte as a deformable body may help us understand biomechanical and biophysical behavior of monocyte during tethering and rolling process. It has been shown in this study that the flow rate has significant influence on the monocyte behaviors, such as contact area and deformability. It also influences the mechanical stress inside monocyte, which might related to health problems, such as injury or damage in cells. The current work is a primitive study of monocyte tethering and rolling behavior by using RKPM meshfree method. It may not explain the real monocyte behaviors inside the blood vessel, which requires an in-depth study. In our future study, we will consider fluid-structure interaction through integration of the immersed boundary method (Zhang et al. 2004), in which the fluid and solid sub-domains are enforced via the interpolation of the velocities and the distribution of the forces with the RKPM delta function. Therefore, we could extend our current model to simulate transendothelial migration by RKPM meshfree method. The current study provides a numerical tool and may open a door for the study of cell extravasation behavior with cell deformability in more realistic settings.

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Fig. 1. Schematic diagram of the boundary condition for the monocyte tethering and rolling

Fig. 2. Snapshots of shear strain contour in cell during the tethering and rolling process: (a) $t=6.1s$, (b) $t=6.2s$, (c) $t=6.3s$, (d) $t=6.5s$, (e) $t=7.0s$, (f) $t=7.1s$

Fig. 3. Snapshots of cell rolling process in fluid channel (the highlighted red point is the marked spot to detect the cell rolling behavior): (a) $t=6.1s$, (b) $t=6.2s$, (c) $t=6.3s$, (d) $t=6.5s$, (e) $t=7.0s$, (f) $t=7.1s$

Fig. 4. Instantaneous rolling velocity and acceleration of cell center point along horizontal direction:(a) Instantaneous rolling velocity (b) Instantaneous rolling acceleration

Fig. 5.
Instantaneous deformation and contact area of cell rolling: (a) Instantaneous deformation (b)
Instantaneous contact area

Fig. 6.
The effect of flow rate on the cell rolling velocity

Fig. 7.
The effect of flow rate on the contact area

Fig. 8.
The effect of flow rate on the average effective stress in monocyte