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MECHANISM OF CELL TRANSPORT IN A MICROCHANNEL WITH BINDING BETWEEN CELL SURFACE AND IMMOBILIZED BIOMOLECULES

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ABSTRACT

Recent trends in micro and nano fabrication techniques have opened a new era for microfluidic based immunosensing devices. In immunosensing microfluidic device, the buffer solution transports the different biomolecules and cells. The interaction between the cell and surface of the microchannel takes place during this transport. In the present study, the effect of interaction between the cell and the immobilized biomolecule on the cell transport is analyzed theoretically. A single cell transport is studied with the interaction between the cell surface and the microchannel wall. The type of immobilized biomolecule on the surface and the surface properties of the cell decide the interaction force between cell and biomolecule. In the present analysis, the interaction force between the cell and modified microchannel is considered as a bond force between ligand and receptor. The bond force is equated as an additional rolling friction to investigate the effect of bond force on the cell transport behavior. The coefficient of rolling friction is determined through non-dimensional analysis. The non-dimensional governing equation is solved to investigate the effect of different operation parameters on cell velocity. The cell velocity experiences a resistance while attaining the maximum velocity. This resistance depends on different operating parameters and forces acting on the cell. It is observed that, higher cell density delays the attainment of maximum cell velocity. It is also observed that, the value of maximum cell velocity is function of Reynolds number and bond length. Finally, it is demonstrated that, the bond density and contact area have no effect on the cell velocity behavior beyond the maximum bond density.

Keywords: cell transport, cell-surface interaction, functionalized surface

NOMENCLATURE

A_c	Area exposed to the fluid flow
F	Force
N	Normal reaction
R	Radius
V	Volume
a	Radius of contact area
t	Time
m	Mass
v	Velocity
ρ	Density
μ	Coefficient of friction

Non-dimensional parameters

Re	Reynolds number $\left(\frac{\rho v_f R_c}{\mu}\right)$
R_l^*	Bond length$(\frac{R_c}{l_b})$
R_a^*	Radius of contact area$(\frac{R_c}{a})$
N_b^*	Bond density $(N_b \pi a^2)$
t^*	Time$\left(\frac{\mu_f}{\rho_f R_c^2}\right) t$

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v_c^* Velocity $\left(\frac{\rho R_c}{\mu}\right) v_c$

ρ^* Density $\left(\frac{\rho_f}{\rho_c}\right)$

Subscript

R Rolling
b Bond
c Cell
d Drag
h Hydraulic
f Fluid
t Total
x x-direction
y y-direction

INTRODUCTION

The fundamental understanding of cell transport behavior helps to interpret the several bio technological process. Recent developments in micro fabrication techniques have opened new avenues for biomedical devices on microfluidic platform [1–3]. The modification of microfluidic channel surface is essential step to immobilize the biomolecules of interest. The end application of such microfluidic devices dictate the surface modification techniques. The surface modification adds a new functional groups or binding agents on the surface of microchannel. This additional binding agent or functional group immobilizes the specific biomolecules which changes the surface properties of a microchannel wall. The modified surface properties of microchannel affect the transport of a cell. The interaction between the cell surface and the immobilized biomolecule takes place by several mechanism like antigen antibody bonding, hydrophobic interaction, electrostatic interaction, etc. The cell transport with surface reaction has been studied extensively for biomedical interest [4]. However, the literature is not particularly focused on the microfluidic prospective. In microfluidic devices during the biomolecule or cell quantification, the ligand-receptor bonding is used for the separation of specific biomolecule. In present study, theoretical analysis is made to investigate the cell transport on a modified surface with ligand-receptor bond effect.

In most of the lab-on-a-chip devices the modification of the surface is needed to isolate the biomolecule of interest [5]. The surface property of the channel wall influences the transport of cell and subsequently the device performance. Different approach for the surface modifications in microfluidic immunosensing chip is reviewed by Henares et al. [6]. In the present study, the biomolecule of interest is a cell and the interaction between the cell surface and the microchannel surface is modeled to investigate the cell transport. The molecule on cell membrane is usually referred as a receptor and the complementary molecule on the substrate is called as a ligand [7]. The type of ligand-receptor pair and biomolecule depend on the end application of the device. Different possibilities of biochemical activities between the biomolecule surface and the surface of the microdevice are explained elaborately by Zhu and Snyder [8]. Several theoretical [9–11] and experimental [12] studies analyzed the fluid flow influence on the transport of the cell. Starting from Hammer and Lauffenburger [9] to till date by Kuusela and Alt [13], different approach have been proposed to investigate the cell transport behavior with adhesion. Parameters affecting the cell adhesion and its importance is elaborately discussed by Bell [14]. The review of cell adhesion in a microfluidic device can be found elsewhere [15].

Hammer and Lauffenburger [9] considered a cell as a spherical body and the analysis is performed based on the results of spherical body in a shear flow. The additional force due to ligand-receptor bonding is considered through the total bond force in the analysis. The bond numbers and bond density for bond force calculation are derived through bond kinetics. In the present study similar approach is used to investigate the cell rolling transport but instead of additional bond force on the surface, the additional resistance to the transport of the cell is considered. The specific adhesion due to bonding between ligand and receptor is modeled as an additional rolling resistance on the cell. The outcome of the model shows the cell rolling under different operating conditions. This model will also provide a simple expression for the resistance offered to the cell transport.

Mathematical Formulation

Theoretical approach for predicting the cell velocity under different operating parameter is presented here. In most of immunosensing and lab-on-a chip devices, the surface properties of at least one surface are modified for immobilizing the biomolecule. This immobilized biomolecules serve the purpose of ligands for the receptors on the surface of the cell in a bulk solution. The specific adhesion of cell depends on various parameters viz; bond formation rate and binding affinity between ligand and receptor, contact area, bond density, fluid environment, cell properties etc. [7, 16]. Figure 1(a) shows a spherical cell with bonding between the receptor on the cell surface and the ligand on the modified substrate of the channel. The force body diagram(FBD) for the cell rolling with hydrodynamic force(F_h) and equivalent bond force(F_b) is shown in Fig 1(b). In the present analysis, a novel approach is used to represent F_b. An additional surface force due to F_b on the cell is equated to the rolling friction. The FBD for the rolling friction and the modified cell rolling with normal bond force(N) and rolling resistance(μ_R) is presented in Fig 1(c) and 1(d), respectively. The change in bond density(N_b) due to bond formation and dissociation is ignored i.e., bond kinetics is ignored. Hence, the bonds are evenly stressed and the bond force(F_b) is independent of bond orientation, which dictates that each bond has equal strength.

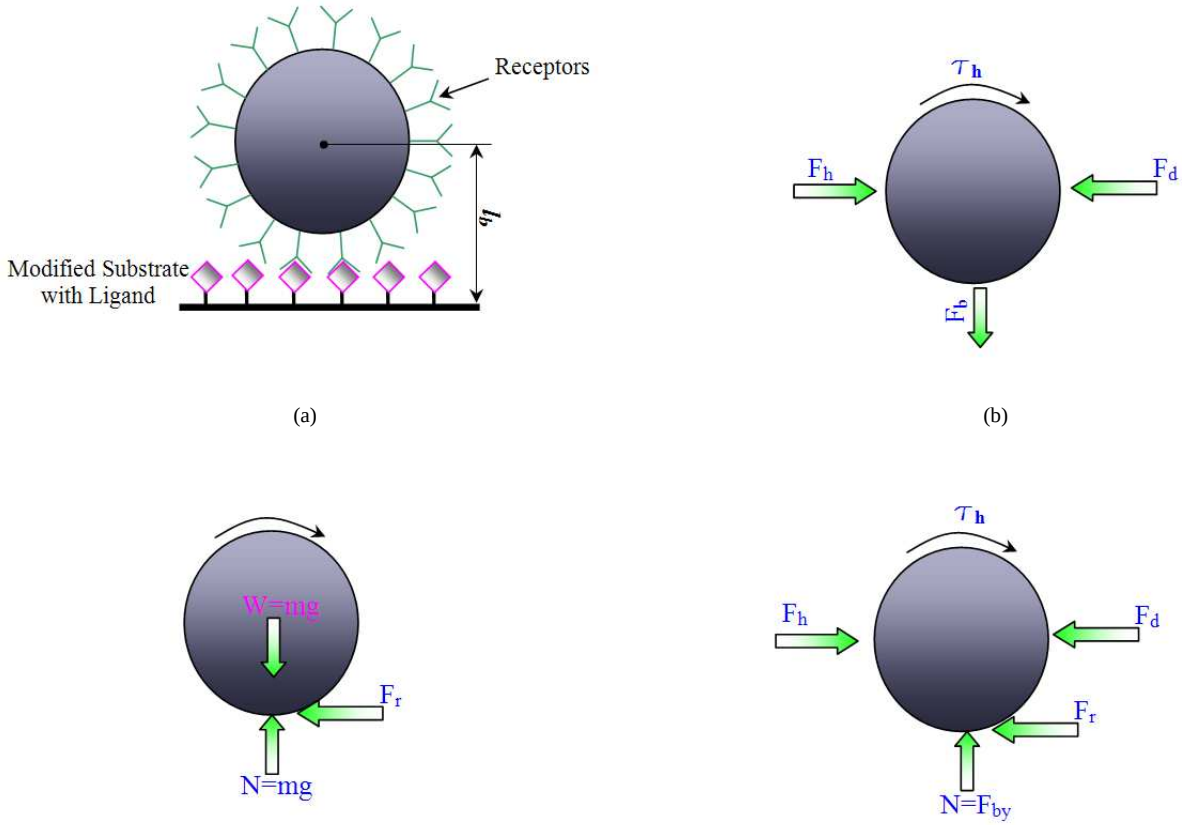

Figure 1. Schematic of (a) single cell on a modified surface with ligand-receptor bonding; (b) different forces acting on a cell; (c) rolling friction; (d) cell with bond force as a friction force

The cell is assumed as a spherical body therefore, the expression for the hydraulic force(F_h) and torques(τ_h) on spherical body under Poiseuille flow placed near the wall can be used. Happel and Brenner [17] have derived the following expression for the F_h and τ_h,

$$F_h = 6\pi\mu_f R_c v_f \left[\frac{1 - \frac{1}{9R_l^{*2}}}{1 - 0.6526R_l^* + 0.3160R_l^{*3} - 0.242R_l^{*4}} \right] \quad (1)$$

$$\tau_h = \frac{8}{3}\pi\mu_f R_c^2 v_f R_l^* \left[1 + 0.075R_l^* + 0.049R_l^{*2} \right] \quad (2)$$

where, $R_l^* = \frac{R_c}{l_b}$ in which R_c and l_b represent the radius of cell and the distance between cell center and wall, respectively. Suffix f is express the fluid properties. The velocity of fluid(v_f) is taken at the l_b.

Hammer and Lauffenburger [9] calculated the total force on the cell due to bonding between ligand and receptors assuming cell at mechanical equilibrium. The force balance shows that, the hydrodynamic and bond forces in flow direction are equal in magnitude with opposite direction($F_{bx} = -F_h$). The other component which is normal to the hydrodynamic force is given by Eq.(3) in which a is radius of the contact area.

$$F_{by} = -\frac{3\pi}{4a}\left[\tau_h + F_b R_c\right] \quad (3)$$

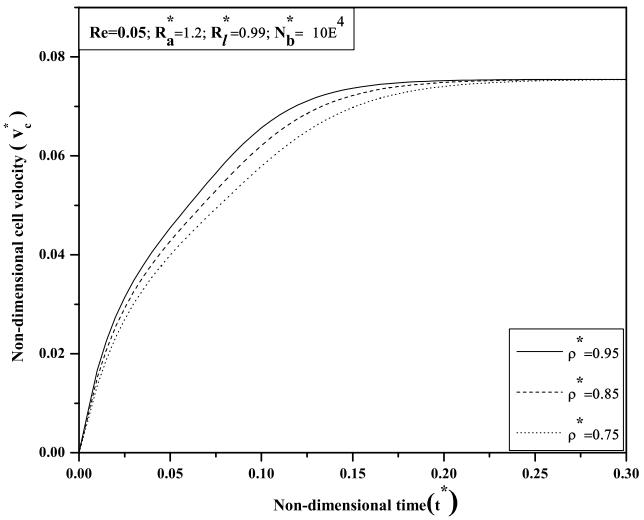

Figure 2. Variation in non-dimensional cell velocity(v_c^*) for different density ratio(ρ^*)

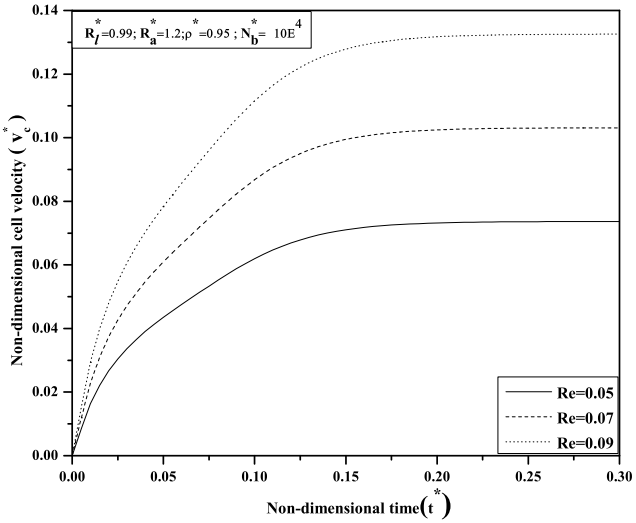

Figure 3. Variation in non-dimensional cell velocity(v_c^*) for different Reynolds numbers(Re)

$$F_{bt} = \sqrt{F_{bx}^2 + F_{by}^2} \tag{4}$$

As shown in Fig. 1, the bond force is represented as a normal reaction(N) for rolling friction with coefficient of rolling friction μ_r. It is assumed that, the normal reaction on the cell is equivalent to F_{by}. The difference in the cell rolling behavior with and without ligand-receptor bonding mainly depends on the bond force(F_{bt}) which is function of individual bond force(f_b), bond density(N_b), velocity(v_c) and mass of cell(m_c). This group of parameters has a major role in deciding the cell transport behavior. Hence, the coefficient of rolling friction must be representation of non-dimensional group consisting of these parameters. Performing Buckingham-π analysis, the μ_r can be expressed as,

$$\mu_r = \frac{f_b}{v_c^2 m_c \sqrt{N_b}} \tag{5}$$

where, N_b is the bond density which is equivalent to number of bonds per unit contact area. In the present analysis, the bond density is calculated by multiplying the ligand density to contact area(πa^2). The individual bond force(f_b) is calculated using [9],

$$f_b = \frac{F_t}{\pi a^2 N_b} \tag{6}$$

The linear momentum equation of cell of mass m_c with acceleration a_c can be written as,

$$m_c a_c = \sum F = F_h - \mu N - F_d \tag{7}$$

where, F_d is the drag force on cell which is given by,

$$F_d = C_d \rho_f |v_c - v_f|(v_c - v_f)\frac{A_p}{2} \tag{8}$$

The drag coefficient(C_d) for laminar flow is widely used as $\frac{24}{Re}$. A_p is the area exposed to fluid flow which is assumed as half of the entire sphere surface area.

From Eqs. (1) to (8), the momentum equation can be rewritten as,

$$m_c \frac{dv_c}{dt} = \mu_f R_c V_f \left[I_1 + \mu_r R_a^* \left(I_2^{'} + I_1^{'}\right)\right] - C_d \rho_f |v_c - v_f|(v_c - v_f)\frac{A_p}{2} \tag{9}$$

where, $R_a^* = \frac{R_c}{a}$, $I_1 = 6\pi \left[\frac{1-\frac{1}{9R_l^{*2}}}{1-0.6526R_l^* + 0.3160R_l^{*3} - 0.242R_l^{*4}}\right]$
$I_2 = \frac{8}{3}\pi R_l^* \left[1 + 0.075R_l^* + 0.049R_l^{*2}\right]$ and $I_1^{'} = \frac{3\pi}{4a} I_1; I_2^{'} = \frac{3\pi}{4} I_2$.

Non-dimensional form of the governing equation is,

$$\frac{dv_c^*}{dt^*} = \alpha_1 \left[I_1 + \mu_r R_a^* \left(I_2^{'} + I_1^{'}\right)\right] - \alpha_3 |v_c^* - Re|(v_c^* - Re) \tag{10}$$

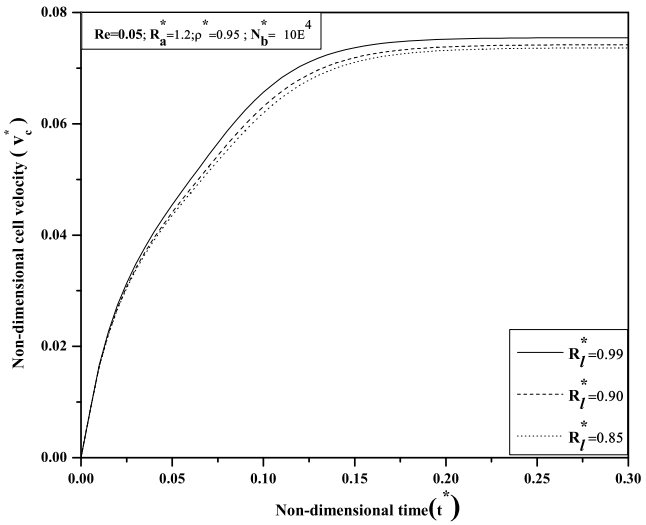

Figure 4. Variation in non-dimensional cell velocity(v_c^*) for different non-dimensional bond length(R_l^*)

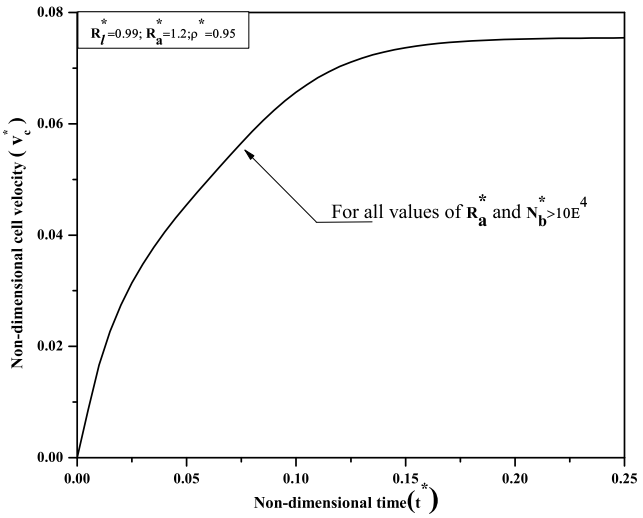

Figure 5. Variation in non-dimensional cell velocity$(v_c^*)$for $N_b^* > 10^4$

where, $\alpha_1 = \left(\frac{\rho_f}{\rho_c}\right)\left(\frac{R_c^3}{vol_{cell}}\right)Re$, $\alpha_2 = \frac{\pi^{0.5}\alpha_1^2}{(\pi a^2 N_b)^{1.5}}$ and $\alpha_3 = \frac{48\pi\alpha_1}{Re^2}$. Non-dimensional time and cell velocity are defined as $v_c^* = \left(\frac{\rho R_c}{\mu}\right)v_c$, $t^* = \left(\frac{\mu_f}{\rho_f R_c^2}\right)t$, respectively and *Re* is the Reynolds number defined based on cell radius with fluid properties i.e., $Re = \frac{\rho v_f R_c}{\mu}$. The non-dimensional density $\left(\rho^* = \frac{\rho_f}{\rho_c}\right)$ is the ratio of the fluid density to the cell density and the rolling friction in terms of non-dimensional parameter is $\mu_r = \frac{\alpha_1\alpha_2}{v_c^*}$. Non-dimensional bond density(N_b^*) is defined as the product of contact area(πa^2) and the bond densityN_b. Equation (10) governs the cell transport behavior and the finite difference method is used to obtain the solution for this equation.

Results and Discussion

In this section the parametric study is performed to investigate the effect of several operating parameters on the cell transport behavior. The operating range of different non-dimensional parameter is obtained from literature [9, 10, 12]. Figure 2 shows the variation in the non-dimensional velocity under different density ratios. With the decrease in density ratio, the mass of cell increases, which in turn reduces the velocity of the cell. Since the inlet velocity i.e. *Re* of the flow is constant therefore, the constant maximum velocity in each case is also observed. The attainment of plateau at constant maximum velocity in each case is observed. The variation in attainment of the plateau depends on the density value. For the higher cell density i.e., lower ρ^*, the delay in attainment of the maximum velocity is observed as compare to the lower cell density case.

The variation in maximum velocity with different *Re* is presented in Fig.3. The resistance offered by bond and drag forces decides the delay in attainment of maximum velocity. Since the resistance due to bond and the drag forces in all the cases is same therefore, the attainment of different maximum velocity at the same instance is observed for all the cases. The variation in maximum velocity under different R_l^* is also observed as shown in Fig.4. In hydrodynamic flow i.e., for spherical body(without bonding with the surface) in a Poiseuille flow, the hydrodynamic force reduces as the distance between body and wall increases. In the present analysis, the distance between the wall and the cell is represented as a bond length. R_l^* represents the ratio between the cell radius and the distance between cell center and wall. As bond length increases, i.e, increment in R_l^* reduces the the bond force and subsequently increases the resistance to cell transport. Different bond length results into different resistance and hence different maximum velocities for different R_l^* are observed. As R_l^* decreases, the resistance force increases, which reduces the maximum velocity as depicted in Fig.4 .

The non-dimensional bond density N_b^* is an important parameter for predicting the rolling resistance and hence the cell velocity. There is an upper limit for the number of bonds for constant contact area and corresponding bond density can be defined as maximum bond density. The variation in the velocity profile for corresponding non-dimensional maximum bond density$(N_{b\,max}^*)$ is presented in Fig. 5. It is observed that, varia-

tion in N_b^* above 10^4 does not change the behavior of cell velocity. Similar results are obtained for different R_a^* with $N_b^* = 10^4$. Thus 10^4 is the upper limit for N_b^* i.e., $N_{b\,max}^* = 10^4$ for analyzed set of operating parameters.

During the cell transport in Poiseuille flow, it is observed that, the density of cell(ρ^*), external flow parameter(Re), bond dimension(R_l^*) and contact area(R_a^*) influence the behavior of the cell transport. It is also demonstrated that, the amount of deviation in attaining the maximum velocity is function of all mentioned parameters. In the present study, the parametric study is performed on constant bond density during transport process. The transient variation in the bond numbers during the cell transport will be taken up in near future. The transient variation in bond will dictate the change in bond density and bond dimensions and subsequently the bond force on the cell.

Conclusion

Theoretical model for investigating the cell transport in a Poiseuille flow with modified channel surface is presented. The non-dimensional governing equation considering hydrodynamic, bond and drag forces is derived. The bond force is considered as an additional rolling resistive force. A rolling friction factor is determined based on the parameters which represent the cell transport with bonding. The parametric study is performed to trace out the effect of different operating conditions on the cell transport. It is observed that, the cell velocity attains the maximum velocity and attainment of maximum velocity depends on the operating parameters. It is demonstrated that, the denser cell delays the attainment of the maximum cell velocity. Variation in bond length and the inlet velocity decides the range of maximum velocity. It is also reported that, for variation in the cell velocity the bond density should be less than maximum bond density.

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