Theoretical and Applied Mechanics Letters 5 (2015) 216–221

Contents lists available at ScienceDirect

Theoretical and Applied Mechanics Letters

journal homepage: www.elsevier.com/locate/taml

Letter

Combined modeling of cell aggregation and adhesion mediated by receptor–ligand interactions under shear flow

Yu Du [a,b,c], Shuang Peng [a,b,c], Yuhong Cui [d], Shouqin Lü [a,b,c], Yan Zhang [a,b,c], Mian Long [a,b,c,*]

[a] Center of Biomechanics and Bioengineering, Institute of Mechanics, Beijing 100190, China
[b] Key Laboratory of Microgravity (National Microgravity Laboratory), Institute of Mechanics, Beijing 100190, China
[c] Beijing Key Laboratory of Engineered Construction and Mechanobiology, Institute of Mechanics, Beijing 100190, China
[d] Department of Mechanics, Tianjin University, Tianjin 300072, China

HIGHLIGHTS

- Combine the dynamics of cell aggregation and adhesion under shear flow.
- Parametric analysis of cell collision and adhesion efficiency.
- Interplay between cell aggregation and adhesion near the wall.

ARTICLE INFO

Article history:
Received 20 July 2015
Received in revised form
6 September 2015
Accepted 29 September 2015
Available online 23 October 2015
*This article belongs to the Biomechanics and Interdiscipline

Keywords:
Cell adhesion
Aggregation
Kinetics
Shear flow

ABSTRACT

Blood cell aggregation and adhesion to endothelial cells under shear flow are crucial to many biological processes such as thrombi formation, inflammatory cascade, and tumor metastasis, in which these cellular interactions are mainly mediated by the underlying receptor–ligand bindings. While theoretical modeling of aggregation dynamics and adhesion kinetics of interacting cells have been well studied separately, how to couple these two processes remains unclear. Here we develop a combined model that couples cellular aggregation dynamics and adhesion kinetics under shear flow. The impacts of shear rate (or shear stress) and molecular binding affinity were elucidated. This study provides a unified model where the action of a fluid flow drives cell aggregation and adhesion under the modulations of the mechanical shear flow and receptor–ligand interaction kinetics. It offers an insight into understanding the relevant biological processes and functions.

Blood cell aggregation and adhesion to endothelial cells under shear flow are crucial to many biological processes such as thrombi formation, inflammatory cascade, and tumor metastasis. For example, homotypic aggregation of activated platelets induced by high shear stress or by chemokines is involved in many diseases such as atherosclerosis and thrombosis [1] while heterotypic aggregation between platelets and neutrophils (PMNs) is responsible for thrombosis progression [2] and acute myocardial infarction [3]. In inflammatory cascade, flowing PMNs adhere to the endothelium of post-capillary venule to mediate the sequential transmigration and phagocytosis at the target site [4]. Tumor cells also interact with leukocytes in blood flow, e.g., between PMNs and melanoma cells [5–8] or colon carcinoma cells [9,10], to facilitate tumor metastasis.

Homotypic or heterotypic aggregation of blood cells is mainly governed by blood flow and binding kinetics of interacting molecules. A body of experimental evidence, via flow chamber assay and cone–plate viscometer [11,12], demonstrates that shear-induced aggregation of PMNs and transfected cells is shear-rate dependent [12]. The underlying cellular adhesive molecules, e.g., β_2 integrin and intercellular adhesive molecule 1 (ICAM-1), is found to play a key regulating role [5]. On the other hand, theoretical models based on population balance equation [13] have been developed to test the size distribution of cell aggregates and predict the aggregation dynamics in a uniform shear field for homotypic aggregation of human blood platelets [14] or PMNs [13,15], as well as for heterotypic aggregation of platelets and PMNs [16] or PMNs and tumor cells [5]. Noting that these measurements and models are referred to as the flow field in a free stream of a blood vessel, the impact of presence of endothelium monolayer on cell aggregation as well as cell adhesion mediated by the interactions of blood cells and endothelial cells should be taken into account.

* Corresponding author at: Center of Biomechanics and Bioengineering, Institute of Mechanics, Beijing 100190, China.
E-mail address: mlong@imech.ac.cn (M. Long).

http://dx.doi.org/10.1016/j.taml.2015.09.004

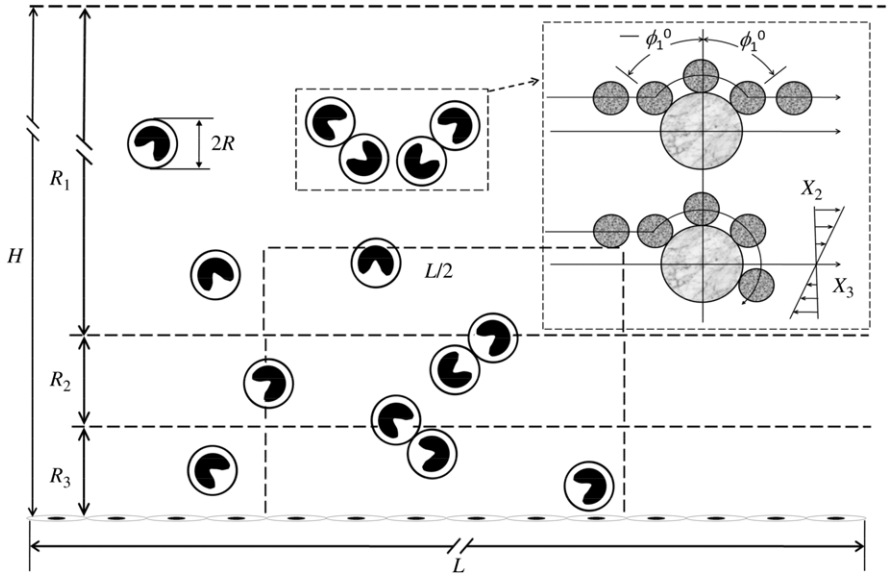

Fig. 1. Schematic of cell aggregation and adhesion under shear flow. Cell aggregation and adhesion occur in a chamber of 20 (L) × 1.0 (H) mm, in which three regions, R_1, R_2, and R_3 with a height of 0.96, 0.02, and 0.02 mm are considered separately. *R indicates the cell radius assumed to be a sphere.*

Cell–cell interactions become more complicated when the flowing cells are marginalized to the vicinity of the endothelium. In addition to the similar dynamics of shear-induced aggregation of blood cells arising in free stream, the marginalized cells occasionally collide with the endothelium and result in rolling over, tethering onto, and crawling along endothelial cells. Again, cell adhesion and detachment are governed by binding kinetics of interacting molecules under shear flow. For instance, PMNs or beads bearing selectin and/or integrin receptors are driven to flow over the ligand-immobilized or—expressed substrate or cells and the shear stress dependence of rolling velocity, tether rate, and "stop-and-go" frequency have been determined experimentally using a flow chamber assay [17,18]. Using a (gas-driven) micropipette adhesion assay, not only adhesion dynamics between the two cells is quantified but binding kinetics of the receptor–ligand interactions is also determined under zero force. By contrast, theoretical models of cell adhesion have been developed, as observed that cell adhesion is governed by cell margination from free stream, cellular Brownian motion and molecular diffusion near endothelium, and binding kinetics of two contact molecules [19]. Evidently, these models are different from those for cell aggregation in free stream, since the endothelial cells are lined stably as a monolayer.

Although cell aggregation and adhesion dynamics are well studied separately, their integration under blood flow has been poorly understood. Here we develop a model to combine both the cell aggregation in free stream and the cell adhesion in the vicinity of the endothelium. Using two-body collision theory and a binding kinetics model for a small system, the impacts of shear flow and binding kinetics of interacting molecules are analyzed. Comparison of the predictions with measured data validates our model.

As shown in Fig. 1, "blood flow" in a chamber with a length of L and a height of H is segregated into three regions: *Region* 1 (R_1) denotes the body flow along the main stream with a height of r_1, where "blood cells" are able to collide freely with each other and form aggregates; *Region* 2 (R_2) is referred to as the transient flow with a height of r_2, where the cells are close to but do not interact with vessel wall; *Region* 3 (R_3) represents the local flow with proximity to the blood vessel with a height of r_3, where the cells are able to contact with the wall and induce cell adhesion.

In a two-dimensional (2D) Couette flow along X_3-axis with a flow velocity $v = G \times X_2$, sphere collision occurs due to the velocity gradient or shear rate, G. Based on Smoluchowski two-body collision theory in colloidal dynamics [13], the collision frequency depends on sphere concentration C, shear rate G, and sphere radius R (*inset* in Fig. 1). In the case of uniformly distributed spheres, two-body collision frequency per unit volume, f, in the three-dimensional (3D) case, $f = 16R^3GC^2/3$, is simplified as the value per unit area in the 2D case:

$$f = 2R^2GC^2. \tag{1}$$

The two-body collision brings the spheres into contact and provides the opportunities for surface-presented receptors and ligands to bind with each other. Supposing two spheres collide at $\phi_1 = -\phi_1{}^0$ ($\phi_1{}^0$ is the initial contact angle; *inset* in Fig. 1) in a mirror-image manner, which is a so-called transient doublet. Yet the doublet will remain attached under hydrodynamic force until all the bonds break up, which is named a non-separating doublet.

For a transient doublet rotating from $-\phi_1{}^0$ to $\phi_1{}^0$, the contact duration, τ, is given by:

$$\tau = (5/G)\{\tan^{-1}[(\tan\phi_1{}^0)/2]\}. \tag{2}$$

It is known that shear flow applies a normal force ($F_N = \alpha_N\eta R^2G\sin^2\theta_1\sin 2\phi_1$) and a shear force ($F_S = \alpha_S\eta R^2G[(\cos 2\theta_2\cos\phi_2)^2 + (\cos\theta_2\sin\phi_2)^2]^{1/2}$) to the doublet, where α_N and α_S are force coefficients as a function of the dumbbell geometry and η is the medium viscosity [13]. Noting that shear force F_S is neglected as it has little effect on the break-up of the doublet [13,19], the applied force yields in the 2D case,

$$F_N = \alpha_N\eta R^2G\sin 2\phi_1. \tag{3}$$

To predict the fate of existing bonds in a doublet so formed, a probabilistic model based on small system kinetics [20] is developed, which describes the binding kinetics of a small number of receptor–ligand bonds, n (1, 2, 3, . . . , N, where N is the maximum number of bonds able to be formed between two spheres) [5,19,21,22]:

$$\begin{aligned} dp_n/dt &= A_c m_r m_l k_f p_{n-1} - (A_c m_r m_l k_f + n k_r{}^{(n)})p_n \\ &\quad + (n+1)k_r{}^{(n+1)}p_{n+1}. \end{aligned} \tag{4}$$

Here, p_n is the probability of having n bonds at time t, m_r and m_l are the respective site densities of receptors and ligands, $k_r{}^{(n)}$ and k_f are the respective reverse rate for nth bond and forward rate, and