MODELING AND SIMULATION OF PLATELET FLOW IN MICROVESSELS

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ABSTRACT

For the simulation of the flow of platelets in the bloodstream of microvessels, the blood mixture is considered as a continuous fluid that flows with a time-invariant flow rate within a vessel of rigid walls. Due to their large size, red blood cells (RBCs) accumulate toward the centerline of the vessel, leaving around them a layer "free of erythrocytes" (CFL – Cell Free Layer). Hence, hemodynamics in microcirculation can be simulated as a two-phase flow consisting of concentrated red blood cells towards the center of a tube, and plasma flowing in the absence of erythrocytes peripherally. Regarding platelets, their flow is affected by the movement of the RBCs because they are relatively much smaller in size, and therefore a large proportion of them migrate toward the vessel walls. In order to estimate the radial platelet distribution, the Convection-Diffusion equation is solved using a model proposed by Eckstein and Belgacem[1] which accounts for the shear-induced diffusion mechanism caused by cell interactions within the blood flow. Blood viscosity is defined using the Casson model[2] which is a generalized non-Newtonian viscosity model of flowing blood that depends on the Hematocrit – defined as the local volume fraction of red blood cells in the blood – and the local shear rate. Additionally, we take into consideration the platelets' effect on the viscosity by applying Einstein's model[3] for low concentration spherical particles in a fluid. This simulation is implemented for various hematocrit levels, platelet counts, vessel radii and wall shear rates. Its solution gives precise results for the radial distribution of platelets, which are in accordance with the experimental data, indicating the conditions in which their margination is facilitated or not.

INTRODUCTION

Platelets are vital components of blood, responsible for hemostasis and wound healing, the complex processes that prevent blood loss. Under physiological conditions, these processes are responsible for keeping blood in a fluidic state and constantly repair the walls of veins and arteries by forming solid plugs which consist of aggregated platelets on the injured wall. However, in pathological blood flow, such a plug might have continuous growth, turning into a clot, which can lead to total occlusion of a vessel. This is a very serious medical symptom called Thrombosis that can lead to conditions such as heart attack or stroke.

Several investigations have been conducted in order to understand platelet rheology and analyze the pathological conditions under which a clot may be formed. Research has shown that platelets flow in close proximity to the vessel walls[5].This lateral platelet movement is caused by continuous rebounding collisions between erythrocytes[6]. As a result, platelet concentration is several times higher near the vessel wall compared to that at the center of the vessel. This discrepancy increases proportionally to the hematocrit and shear rate values[7].Modeling the platelet margination is the first step in order to study the pathological conditions that can lead to Thrombosis.

In several investigations, researchers have developed mathematical models for the simulation of platelet flow. These allow the study of the rheological behavior of platelets in various flow

conditions and the extraction of platelet concentration profiles. Some of the most important models are: The phenomenological Drift-Diffusion model which has been developed by Eckstein et al. and describes the margination of platelets derived from experiments[1], the Fokker-Plank approach proposed for modeling the platelet margination by Fogelson et al.[8] and the mechanistic model proposed by Rivera et al. derived from the kinetic theory for multicomponent suspensions at low Reynolds number[4].

In this study, we develop a computational model for blood flow under steady-state conditions, which accounts for the platelet margination. The model considers the Convection-Diffusion equation for platelets, together with the momentum balance with the adoption of a shear-thinning viscosity model. Consequently, it can be applied for estimation of the platelet concentration, hematocrit, velocity and viscosity profiles in various flow conditions.

BLOOD COMPOSITION

Blood is a dense suspension of red blood cells, platelets and white blood cells in a protein-rich solvent called plasma. The most abundant cell type in the blood is red blood cells (about 99% in number), while the rest are platelets, which are smaller in size and lesser in number, and white blood cells. In the table below the main characteristics of blood components are listed.

Table 1. *Volume fraction, cells number per volume and main diameter range for the 3 blood cell types.*

Blood component	Volume fraction (% v/v)	Cells number per liter of blood	Main Diameter (μm)
Red blood cells (RBCs)	30-45%	**Male**:4.3-5.9 × 10^{12}/L **Female**: 3.5-5.5 × 10^{12}/L	6-8
Platelets(PLTs)	0.06-0.09%	150-400 × 10^{9}/L	2-3
White blood cells(WBCs)	0.01%	4.5-11.0 × 10^{9}/L	10-12 (Neutrophils 63%)
Plasma	~55%		

BLOOD RHEOLOGICAL PROPERTIES

Blood plasma has similar rheological properties to water as it is a protein suspension in 91-92 w/w% water. Physiological values of plasma viscosity range between 1.10-1.35 mPa·s [9]. However, the rest of the blood's components (RBCs, Platelets, and WBCs), have more complex rheological behavior.

While RBCs flow, they migrate toward the centerline of the vessel leaving a cell-depleted layer between the wall and the migrated cells. The formation of this cell depleted layer or Cell-Free Layer (CFL) is the outcome of several physical phenomena that take place within the flow. Specifically, in the vessels, flowing plasma forms a Poiseuille-like velocity profile with a gradually increasing potential along the radial distance, and since the largest probability for a particle to be found is where the potential field is smallest, RBCs tend to move toward the centerline of the flow. At the same time, this accumulation towards the center is limited by frequent particle-particle interactions, which lead to a net migration toward the walls, preventing red cells from being packed in the center. On the other hand, platelets flow in close proximity to vessel walls since they are affected by RBC movement. Specifically, for platelets, the central region is quite limited due to the cumulation of erythrocytes, but the depleted layer allows more freedom of movement for them, leading to a higher probability for a platelet to be found close to the vessel walls.

METHODOLOGY

A way to simulate platelet motion and distribution is the continuous approximation (CM), where blood cells and platelets are assumed to have negligible volume and be part of a dilution with spatially varying concentration levels in the vessel. The continuous models (CM) for concentrated suspensions of platelets are derived from the solution of the Convection-Diffusion equations. The continuous models have the advantage of being easily implementable and compatible with a vast set of available analytical and numerical solution techniques. Continuous models work properly when they are used for suspension motion characterization in microscale where the particles are significantly smaller in comparison with the length scale of the flow.

PLATELET CONVECTION-DIFFUSION EQUATION

In most cases, the diffusivity of particles transported in a flow can be described using a Brownian dynamics approximation. However, this approach does not account for the mechanism of platelet margination. This phenomenon can be qualitatively described by the shear-induced diffusion mechanism. A way to approach this mechanism analytically is that of Eckstein and Belgacem[1] and Fogelson et al.[8] who introduced a drift term in the potential field J_r of the Convection-Diffusion Equation:

$$\frac{\partial C_{pl}}{\partial t} + \nabla\left(v C_{pl}\right) = J_r \quad (1)$$

where C_{pl} is the local concentration of platelets, and $\boldsymbol{v}$ is the local velocity vector. To define J_r, Eckstein and Belgacem[1] suggested a functional form for the drift that has the property of leading to platelet concentration profiles similar to experimentally determined ones, and assumed that the field potential is invariant over the length of the channel, but varies radially.

Hence, J_r can be written as:

$$J_r = \frac{\partial \Phi}{\partial r} C_{pl} + \mathrm{D_{iff}} \nabla C_{pl} \quad (2)$$

where, $\frac{\partial \Phi}{\partial r}$ or $\Phi'(\mathrm{r})$ is the local drift in the r-direction, $\mathrm{D_{iff}}$ is the diffusion coefficient, and C_{pl} is the local concentration of platelets. $\Phi'(\mathrm{r})$ can be calculated using a fitted function of experimental data of platelet concentration profiles, and the following analytical expression [8]:

$$\Phi'(\mathrm{r}) = -\mathrm{D_{iff}} \frac{\frac{\partial Ceq(r)}{\partial r}}{C_{eq}(r)} \quad (3)$$

Apparently, the application of the above equations in steady state provides the same concentration profile with the experimental data curve. In this study, the main concern is to extract a general form of this drift function that accounts for various flow conditions. This can be achieved by seeking analytical relationships that reflect the available experimental data. Eckstein and Belgacem[1], suggested a beta-functional form that provides a visually pleasing approximation to the observed concentration profiles that would mimic the shape of individual experiments. This function has the following form:

$$C_{eq}(\mathrm{r}) = C_0\,[1 + \mathrm{K}\, r^m (1 - \mathrm{r})^{\mathrm{n}})] \quad (4)$$

Thus, the Drift function takes the form of:

$$\Phi'(\mathrm{r}) = -\mathrm{D}_{\mathrm{iff}} \frac{\mathrm{K}\,(\mathrm{m}-1) r^{m-1}(1-\mathrm{r})^{\mathrm{n}} + \mathrm{K}\,(\mathrm{n}-1) r^{m}(1-\mathrm{r})^{\mathrm{n}-1}}{[1+\mathrm{K}\, r^{m}(1-\mathrm{r})^{\mathrm{n}})]} \quad (5)$$

where r is the relative lateral position, K is a parameter that set the relative amplitude of the shape, C_0 is the normalizing platelet concentration at the centerline, and m and n are exponents. The number of these undefined variables can be reduced, because the platelet mass in the width of the channel is conserved which in other words means that the integral of the **eq.4** is equal to 1. In that way, the variable C_0 can be written as a function of m, n and K. The relationship for C_0 is:

$$C_0 = \frac{1}{1+K\cdot\frac{\Gamma(m+1)\cdot\Gamma(n+1)}{\Gamma(m+n+2)}} \text{ , where } \Gamma(z) = \int_0^1 x^{z-1} e^{x} dx \quad (6)$$

In the "results and discussion" section, relations extracted from experiments for K, m and n are presented.

MOMENTUM EQUATION

To calculate the velocity field, we apply the Sriram et al.[10] model. Microcirculation is represented by a two-layered fluid model, consisting of a core region of erythrocytes, and a peripheral layer of plasma, which is assumed to be a Newtonian fluid. The model also determines the location of the Cell-Free Layer (CFL) from an empirical law, and the core-hematocrit. The viscosity in the central region is given by the Casson model[2], and the plasma viscosity is assumed to follow the Newtonian law. The momentum balance equation that governs the flow is the Cauchy equations for steady axisymmetric laminar flow, which in steady state takes the form:

$$\frac{1}{\mathrm{r}}\frac{d}{d\mathrm{r}}\left(\mathrm{r}\,\eta_b\,\frac{d\mathrm{U}_{z,b}}{d\mathrm{r}}\right) = -\frac{dP}{dz} \quad , \; r = [0, \lambda] \quad (7)$$

$$\frac{1}{\mathrm{r}}\frac{d}{d\mathrm{r}}\left(r\,\eta_p\,\frac{d\mathrm{U}_{z,p}}{d\mathrm{r}}\right) = -\frac{dP}{dz} \quad , \; r = [\lambda, R] \quad (8)$$

Where $\frac{dP}{dz}$ is the pressure drop, λ is the point of the interface of blood and plasma, $\eta_{\mathrm{b}}(\eta_p, H_c, \dot{\gamma})$ is the blood viscosity given by Casson model[2], $U_{\mathrm{z,b}}(\mathrm{r})$ is the velocity of RBCs in the core region, η_{p} is the plasma viscosity, and $U_{\mathrm{z,p}}(\mathrm{r})$ is the plasma velocity in CFL.

BLOOD FLOW MODEL

Regarding the estimation of the platelet's impact on the CFL viscosity, we apply an equation proposed by Einstein[3] who was the first to calculate the effective viscosity μ_s of a dilute suspension of equal sized, rigid, non-interacting, neutrally buoyant, spherical particles in a fluid of viscosity μ_0. A dilute suspension is a suspension where the inter-particle distance is much larger than the particle size. Under this condition the effective viscosity μ_s of the suspension relates to that of the suspending fluid μ_0 by:

$$\mu_s = \mu_0(1 + \tfrac{5}{2}\varphi) \quad (9)$$

where in the present study μ_0 is the viscosity of the blood plasma and φ is the local volume fraction of platelets.

RESULTS AND DISCUSSION

A representative case on the determination of the platelet distribution using experimental data is shown Fig.1. These experiments were conducted by Waters et al.[11],and were carried out in conditions where all quantities were kept constant except the hematocrit, which varied from 15% to 44%. The other quantities were the platelet bulk concentration (C_{bulk}), which was equal to $78 \cdot 10^9$cells/L, and the wall shear-rate constant at 400 s^{-1}. A second step in our method is to determine the parameters involved in **Eq.4.** Second order polynomials were used for determining the dependence of m, n, ln(K) on systemic hematocrit. Thus, the value of the beta-function constants can be determined for hematocrits ranging between 15-44% (**Fig. 2**).

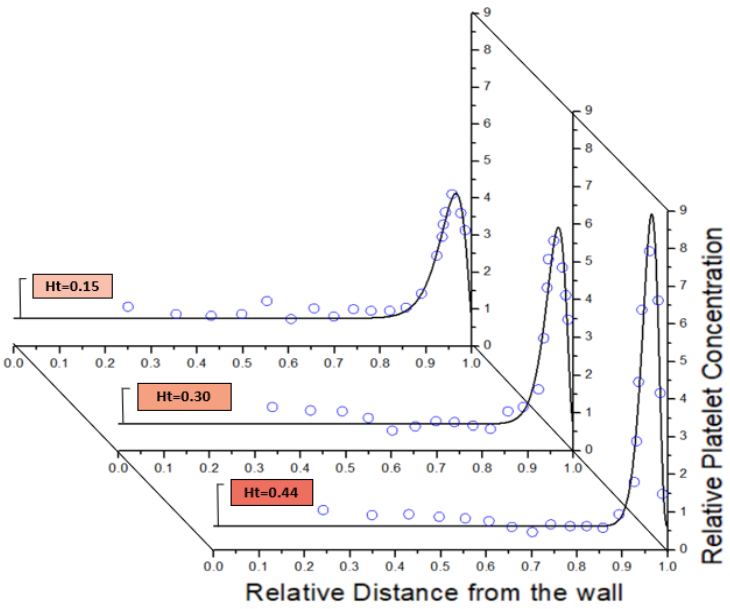


Figure 1. *The beta-function fitting to the experimental results[11] with varying haematocrit values.*

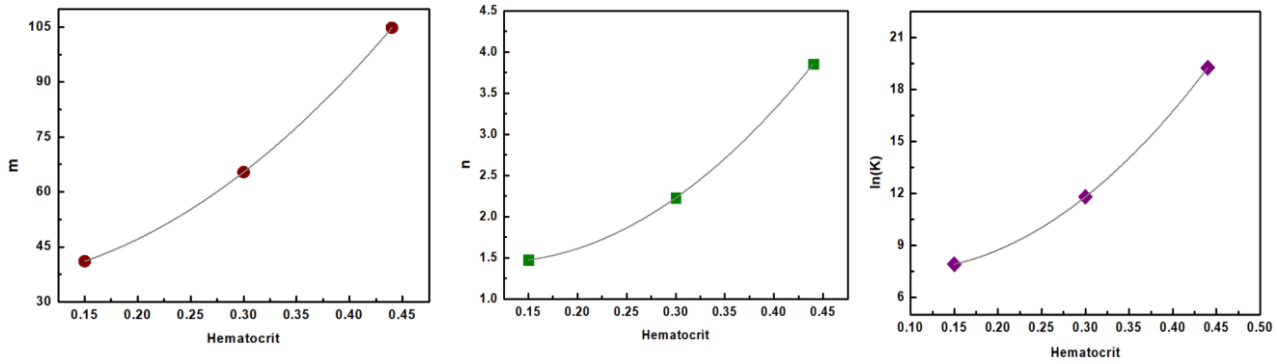
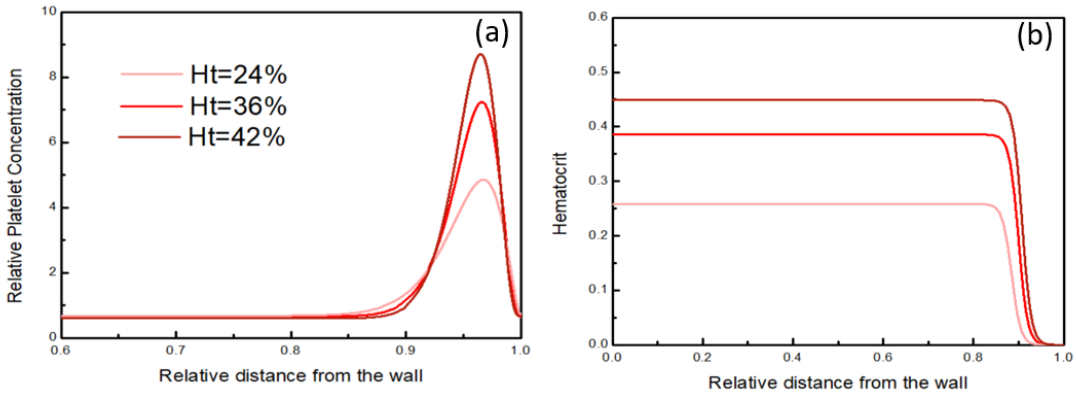


Figure 2. *The second-order polynomial fitted curves for the beta-function parameters m, n and ln(K).*

Finally, the drift term can be determined for any hematocrit value by using **eq.5**. Having determined the drift term, the model can now be applied by solving the momentum equation and the Convection-Diffusion Equations for both platelets and RBCs in steady state or time-dependent flow conditions. Fig.3 shows the local hematocrit profile, the platelet relative concentration profile, the blood velocity profile and the blood viscosity profile versus the normalized distance.



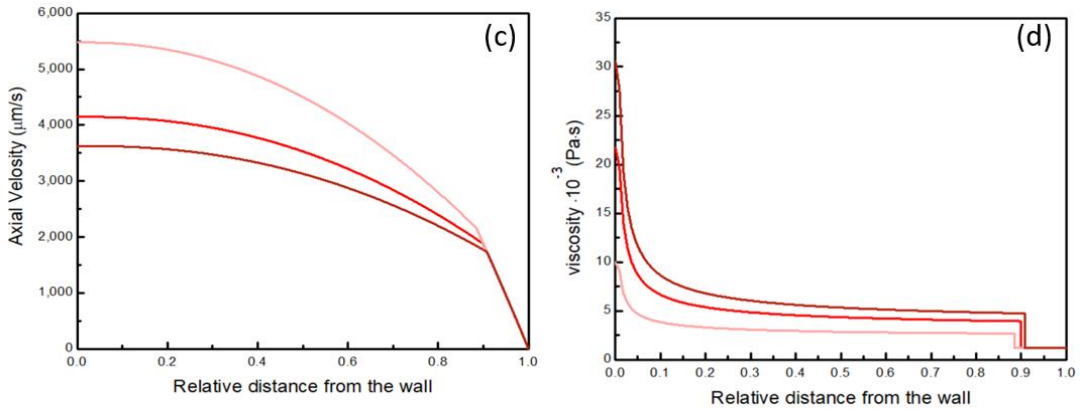


Figure 3. *Results derived from the simulation for 3 different hematocrits 24%, 36%, and 42%; (a) the platelet relative concentration profile($C(r)/C_{bulk}$), (b) the local hematocrit profile, (c) the blood velocity profile, and (d) the blood viscosity profile all represented in normalized tube diameter.*

CONCLUSION

In conclusion, it is important to mention that from these experiments [11], an increase of the hematocrit value results in a more intense accumulation of platelets. For instance, when the hematocrit is 45%, the platelet concentration near the vessel wall can reach a value up to 9 times higher than the bulk platelet concentration. Inspecting the viscosity and velocity profiles, it is easy to conclude that the higher the hematocrit, the larger the viscosity is. This leads to lower blood velocities. Furthermore, although we have adopted the Einstein model [3] to determine the impact of platelet volume fraction on the CFL viscosity, its effect is negligible. This is happening due to the low concentration of the platelets. It should be mentioned that this research can contribute to personalized diagnosis and treatment of the circulatory system diseases, a subject that is a future goal in the field of Biomedical Engineering.

ACKNOWLEDGMENTS

This work is financially supported by the “Karatheodori” scholarships program (E565).

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