mathematics

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Numerical Modeling of Thrombocyte Interaction Mechanics with a Blood Vessel Wall

Raimondas Jasevičius [1,2,3]

[1] Institute of Mechanical Science, Faculty of Mechanics, Vilnius Gediminas Technical University, Plytinės Str. 25, 10105 Vilnius, Lithuania; raimondas.jasevicius@vilniustech.lt
[2] Department of Mechanical and Materials Engineering, Faculty of Mechanics, Vilnius Gediminas Technical University, Plytinės Str. 25, 10105 Vilnius, Lithuania
[3] Department of Biomechanical Engineering, Faculty of Mechanics, Vilnius Gediminas Technical University, Plytinės Str. 25, 10105 Vilnius, Lithuania

Abstract: A platelet (thrombocyte) can be in two states, activated and inactivated. The paper analyzes the interaction of an inactive platelet cell with the wall of a blood vessel. The goal is to analyze and represent the dynamics of platelet cell interaction when a thrombus has not yet formed. The discrete element method (DEM) can be used for the presented model. The paper presents an analysis of the dependence of force and displacement. This test is an introduction to more advanced tests when a blood clot forms.

Keywords: thrombocyte; platelet; inactivated; interaction; vessel; discrete element method

MSC: 37M05; 37N15; 70K40; 74H15; 92B05; 92C05; 92C10; 92C17

Citation: Jasevičius, R. Numerical Modeling of Thrombocyte Interaction Mechanics with a Blood Vessel Wall. *Mathematics* **2023**, *11*, 4814. https://doi.org/10.3390/math11234814

Academic Editors: Ionuț Gabriel Ghionea, Cristian Ioan Tarbă and Saša Ćuković

Received: 12 October 2023
Revised: 23 November 2023
Accepted: 27 November 2023
Published: 29 November 2023

1. Introduction

When conducting numerical studies, especially when the object in question (platelets) may be associated with a system (blood clot), the interaction of the object in question remains important from a mechanical point of view and as already mentioned, since it may have the ability to stick together, the effect of adhesion also becomes important. Therefore, below is a review of works that focus on the main points mentioned. The purpose of this review is to present several notable articles highlighting the importance of platelet research and to present important findings from scientists. First, work related to platelet interactions is discussed. The interaction of the platelet and vessel wall in health and disease was studied by Löwenberg et al. [1], where it is stated that the interactions of platelets with the vascular endothelium are mediated by various cellular receptors. The interaction and adhesion of platelets to vessel walls was studied by de Groot and Sixma [2]. They noted that platelet thrombi are not only formed when a vessel is breached; also, after superficial injury of the intact endothelial cell layer, thrombus formation starts with a platelet–vessel wall interaction.

The interaction of the platelet with activated endothelial was studied by Coenen et al. [3], they noted the vital importance of elucidating the mechanisms of platelet thrombus formation after injury to the vessel wall, as well as the fact that platelets also act as modulators of inflammatory processes. An analysis of the interaction between platelets and endothelium from pathophysiology to new therapeutic options was presented by Hamilos et al. [4]. They noted that platelets, together with the endothelium, play an important role in inflammation and the progression of atherosclerosis.

In the following, works devoted mainly to the adhesion effect will be discussed. The molecular basis of platelet adhesion and aggregation was presented by Groot et al. [5]. The clinical implications of the platelet–vascular interaction were studied by Mangiacapra and Barbato [6], where it was noted that platelet–vessel wall interactions have important

clinical implications, especially in patients treated with percutaneous coronary intervention. Adhesion influences platelet movement and behavior. The mechanisms of adhesion in platelet function were studied by Ruggeri and Mendolicchio [7]. The importance of platelets and platelet adhesion was analyzed by Kisucka et al. [8], they noted that platelets and their adhesive function are critical as they stimulate the growth of new blood vessels while preventing excessive bleeding. The glycobiology of interactions between platelets and endothelial cells was studied by Etulain and Schattner [9]. They noted that under normal conditions platelets do not interact with the walls of blood vessels. The interaction of platelets and endothelial cells in vitro was analyzed by Wilson [10]. It was mentioned there that in vitro factors derived from both platelets and endothelial cells influence each other's function.

2. Problem Formulation

When studying biological objects or structures, many problems arise. One of the urgent problems is related to the human circulatory system, its condition, which directly affects human health and life expectancy. One of the biological objects in the circulatory system are platelets. The process in which a platelet cell is involved is the formation of a thrombus. The coagulation (formation of a blood clot) can be considered as a beneficial phenomenon that allows to repair a damaged blood vessel, and on the other hand, as a negative phenomenon when the formed thrombus breaks away from the surface of the vessel (embolus) and clogs small blood vessels while traveling through the circulatory system. This study is the first step towards the process of thrombosis, when one of the essential components of this process—a platelet—interacts with the surface of a blood vessel. In order to find out how a platelet behaves during the formation of a thrombus, it is important to first find out how a platelet behaves under normal conditions, when a thrombus has not yet formed. In this work, the interaction of platelets with the wall of a blood vessel will be investigated. During the interaction, the platelet is considered inactivated. In numerical simulations, a platelet can be considered as a particle. Taking into account the model features of the interaction of particles (Jasevičius and Kruggel-Emden [11]; Jasevičius et al. [12–15]) Newton's second law, and the method of discrete elements, the developed model, originally intended for analyzing the motion of micro-objects, can be adapted to describe the motion of a biological cell. Applying the established model, this study will allow the description of platelet interactions taking into account the platelet mechanical parameters taken from known physical experiments. This study is the start of further studies that will examine the interaction of an already activated platelet and when more platelets interact.

3. Methodology

Newton's second law is applied to describe the movement of a platelet (thrombocyte), Jasevičius et al. [11–15].

$$m_i \frac{d^2 \mathbf{x}_i}{dt^2} = \mathbf{F}_i(t) \tag{1}$$

where m_i is the mass, and the vector $\mathbf{x}_i$ is the position of the i-th thrombocyte. Vector $\mathbf{F}_i(t) = \sum_j \mathbf{F}_{i,j}(t)$ is the net force. It is added and acts at the center of thrombocyte (platelet) i during interaction. The integration of Equation (1) for the thrombocyte at time $t + \Delta t$ (here Δt time step) is obtained numerically by applying the 5th order Gear's predictor-corrector algorithm.

During the interaction (Figure 1) of the platelet, different processes can be considered during approach, deformation and detachment (retraction). Figure 1 presents a model of the interaction of the cell in various situations. Figure 1a represents the interaction when the cell is separated from the surface, in other situations where the sticking process began during unloading (Figure 1b) or during the detachment/separation (Figure 1c). Then the sticking process could occur during unloading (U-A) at point A′ (Figure 1b) or during detachment (A-D) at point D′ (Figure 1c). Such a sticking process may be important as a

part of the thrombus formation. The sticking process in this work is not analyzed. Such investigation (considering the sticking process) will be in future research (next step), where the activated thrombus interaction will be analyzed. In Figure 1, a negative normal force corresponds to the attraction, and the positive corresponds to repulsion. Point S is the beginning of the approach, point L is the beginning of the load, point U is the beginning of unloading, point A is the beginning of the detachment (separation), point D is the end of the interaction with the surface during the detachment. If platelet cells do not have enough kinetic energy to overcome the effect of attraction and reach the initial point (Figure 1a, point D) of interaction, the cell will adhere to the blood vessel.

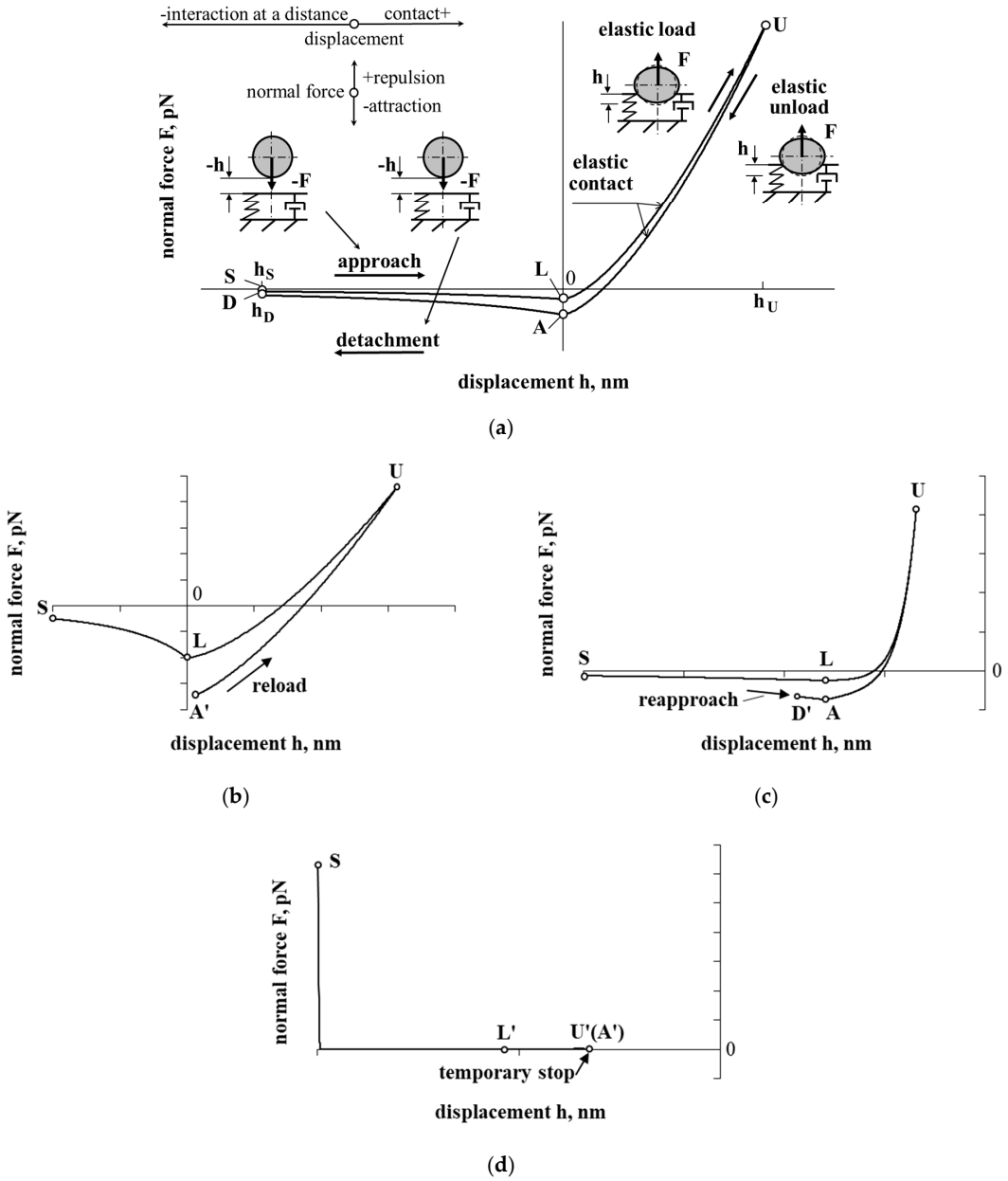

Figure 1. Force–displacement diagram of a normal adhesive–elastic dissipative interaction of a thrombocyte (platelet) for various situations of interaction: (**a**) the detachment of the cell from the interacting surface after reaching the initial position h_D at a point D; (**b**) the process of sticking begins during unloading at a point A′ or (**c**) during detachment at a point D′; (**d**) temporary stop (complete stop is possible, if there is no blood flow) at the point U′, due to the stop of the platelet, this point can also be considered as point A′.

The interaction of a platelet, when there is no contact, is described taking into account its approach (S-L), and the detachment/separation (A-D). Positive displacement at load (L-U) and unloading (U-A) correspond to contact and deformation with the interacting surface.

Since the interaction (in vivo) of the cell itself is a complex process that can cover various situations, the current study is limited by the fact that the initial data is selected from well-known physical experiments, that is, the initial data may change in physical experiments with various platelets (different cell size and/or various interacting surfaces, the cell is activated or inactivated). Using the initial data and the application of previous experience with modeling cells, in this work, the goal is to provide a universal theoretical model, which makes it possible to simulate the interaction of platelets with different initial data.

It should be noted that in this work the points L′, U′, A′, D′ are additionally indicated; they were chosen because the appearance of additional interaction effects, such as the possibility of the sticking process and deformation without physical contact, changes the model of classical mechanics (Figure 1a), which more closely replicates physical experiments with atomic force microscopy (AFM), where every cell movement (static) is controlled. In the case of dynamics and free movement of the cell, the classical model changes; the cell may not reach the points indicated in Figure 1a (L, U, A, D), but as the interaction process itself continues, additional points (L′, U′, A′, D′) are introduced, which are partially reflected by the model of classical mechanics (L—beginning of the load upon contact; U—beginning of unloading upon contact; A—beginning of separation/detachment and end of contact, D—end of interaction).

The discrete element method (DEM) is used to simulate the movement of the platelet. In the discrete element method, it is important to evaluate the forces acting on the interaction of the platelet. The interaction of the platelet (thrombocyte) is described using the total force that assesses the effect of various forces that act on the movement of thrombocyte. The influence of each force is different, it is important to analyze the history of the action in order to understand the effect of each force and dynamics of platelets, Jasevičius [15]. The net (total) force $F(t)$ acting on the cell:

$$F(t) = F_{adh}(t) + F_{el}(t) + F_{dl}(t) + F_{diss}(t) + F_{drag}(t) \quad (2)$$

Here, $F_{el}(t)$ is the elastic force; $F_{adh}(t)$ is the adhesion force; $F_{diss}(t)$ is the dissipation force (due to adhesion); $F_{drag}(t)$ is the drag force; $F_{dl}(t)$ is the electrostatic double-layer force. For modeling, the case was analyzed when the cell is located near the vessel wall and interaction can occur. During the simulation, the case was analyzed when the platelet is located near the surface of the vessel wall, and interaction may occur.

3.1. Approach

As the platelet approaches the surface of the blood vessel, an adhesion force, a double electrostatic layer, begins to act on it. At the initial moment of time, the cell is at some distance from the interacting surface. This distance is taken to be approximately 20 nm, at which the forces characteristic of interaction at a distance begin to act. In general, the forces acting on a platelet can be described as follows:

$$F(t) = F_{adh}(t) + F_{dl}(t) + F_{drag}(t) \quad (3)$$

When a cell moves in a fluid, adhesion is described by estimating the van der Waals force $F_{L,adh}$:

$$F_{adh}(t) = \frac{F_{L,adh} a_{F=0}^2}{(a_{F=0} + |h(t)|)^2} \quad (4)$$

Here $a_{F=0}$ is the initial interaction distance, at which the equilibrium of molecular attraction and repulsion potentials is assumed, and it is considered as the minimum molecular center separation; $h(t)$ is cell displacement. When the distance between the cell

and the interacting surface $|h| < |a_{F=0}|$, the force of attraction (van der Waals) becomes sufficient to attract/influence the cell at the interacting surface.

The force $F_{L,adh}$ can be calculated by assessing the interfacial energy γ (for interacting surfaces) and can be obtained using $F_{L,adh} = 4\pi R_{eff}\gamma$, where R_{eff} is an effective radius:

$$R_{eff} = \left(\frac{1}{R_i} + \frac{1}{R_j}\right)^{-1} \tag{5}$$

Here, R_i is platelet radius; R_j is the radius of the interacting surface. For the interaction of a cell with a flat surface, effective radius is $R_{eff} = R_i$.

The electrostatic double-layer force is described as follows:

$$F_{dl}(t) = 4\pi R_{eff}\varepsilon\varepsilon_0\psi_i\psi_j\lambda_D^{-1}\cdot e^{\frac{h(t)}{\lambda_D}} \tag{6}$$

Here, ε_0 is the permittivity of free space; ε is the dielectric constant of the medium, ψ_i, ψ_j are the surface potentials of the platelet i and the interacting surface j, λ_D is the Debye length:

$$\lambda_D = 0.304/\sqrt{c} \tag{7}$$

Here, the value of the electrolyte concentration c is taken equal to the ionic strength M. Considering the Stokes' drag force, the hydrodynamic force is described as follows:

$$F_{drag}(t) = 6 \cdot \pi \cdot \eta \cdot R_H \cdot v_{relative}(t) \tag{8}$$

Here, η is the dynamic viscosity of blood, R_H is the hydrodynamic radius of the thrombocyte, when $R_H = R_i$, $v_{relative}$ is the relative velocity in the normal direction:

$$v_{relative}(t) = v_i(t) - v_{blood}(t) \tag{9}$$

Here, v_i is the platelet velocity in the normal direction, and v_{blood} is the blood velocity in the normal direction.

3.2. Loading

Loading begins upon platelet contact. Compared to approaching the surface, the contact mainly evaluates not only the forces acting at a distance, but also the forces that evaluate the deformation

$$F(t) = F_{L,adh} + F_{dl}(t) + F_{drag}(t) + F_{el}(t) \tag{10}$$

When describing the deformation of a cell, the Hertz force is applied, which estimates the geometric nonlinearity of the cell, and the stiffness depends on the displacement, Jasevičius et al. [11–15]:

$$F_{el}(t) = \frac{4}{3}\cdot\frac{E_iE_j}{E_i\left(1-\nu_j^2\right) + E_j\left(1-\nu_i^2\right)}R_{eff}^{0.5}h^{1.5}(t) \tag{11}$$

Here, E_i, E_j is the modulus of elasticity of the cell and vessel, respectively; ν_i, ν_j is the Poisson's ratio of the cell and vessel, respectively. The deformation of the cell will affect the adhesion force describing the interaction, which will change during unloading. Unloading is described below.

3.3. Unloading

The force and displacement diagram has the nature of the hysteresis, and this hysteresis is related with the dissipation of kinetic energy due to changes in the influence of the attraction. In general, the unloading can be described as follows:

$$F(t) = F_{L,adh} + F_{adh,diss} + F_{dl}(t) + F_{drag}(t) + F_{el}(t) \quad (12)$$

An additional member that appears in the Equation (12) is $F_{adh,diss}$. This member theoretically evaluates the effect of adhesion upon cell deformation when the effect of adhesion changes both due to the deformation occurring in the contact zone and due to other factors associated with the effect of adhesion. The specified member is declared as follows:

$$F_{adh,diss}(t) = -\frac{2W_{adh,diss}}{h_U + a_{F=0}} \cdot \overline{h}(t) \quad (13)$$

Here, $\overline{h}(t)$ is the normal strain, $\overline{h}(t) = \frac{h_U - h(t)}{h_U}$ and depends on the overlap (displacement) h_U. The $W_{adh,diss}$ member evaluates the amount of energy dissipated during the interaction. The general expression can be described as follows:

$$W_{adh,diss} = k_H \cdot \left| F_{L,adh} \cdot a_{F=0} \right| \quad (14)$$

Here, $F_{L,adh}$ is the adhesion force at point L (Figure 1). $a_{F=0}$ is the initial distance of interaction, which is assumed to be the balance/equilibrium of molecular attraction and repulsion potentials, and it is considered a minimum molecular center separation.

Using the k_H coefficient (Equation (14)), it is possible to set/control (in accordance with the physical experiment) the amount of dissipated energy (due to a change in the influence of attraction during the interaction). This gives an advantage during modeling, when it is necessary to take into account the different amounts of dissipated energy associated with attraction (as an example, various sizes, activated and non-activated platelets are modeled).

It should be noted that in this work, the adhesion force is taken from a well-known physical experiment (Table 1) and the presented attractive force is not divided into separate parts associated with various influences acting on the cell. In the work presented here, the various chemical and molecular mechanisms are not analyzed, but the interaction is studied from a mechanical point of view and the overall attractive force is taken into account. Therefore, Equation (14) describes the overall effect of adhesion. This calculation method (Equation (14)) is useful for numerical modeling of a cell system because it does not complicate the entire calculation process, does not take into account the influence of each individual platelet attraction effect, and takes into account the overall attraction effect observed in known physical experiments.

Since the total work of adhesion is the result of the influence of various forces of attraction, it may be difficult to theoretically analyze each adhesive/cohesive mechanism acting on a cell separately, as well as its calculation. The presented model makes it possible to easily take into account the total work of adhesion, for example, if this amount of energy is known from a physical experiment with AFM. As a simplification, the presented adhesion-related energy dissipation mechanism can account for various adhesion-related effects. The amount of energy dissipation due to adhesion can be added to Equation (15), and after numerically simulating the interaction, the energy dissipation due to adhesion will be the same. Thus, as stated earlier:

$$W^N_{adh,diss} = W^N_{adh,diss,num} \quad (15)$$

In case of different calculation needs, i.e., when studying the influence of each of the adhesion mechanisms on activated platelets, the possibility of applying Equation (16) can be considered.

$$W^N_{adh,diss} = \sum_{i=1}^{n} W^N_{adh,\ diss,\ i} = W^N_{VdW,diss} + W^N_{GP-vWF} + \cdots \quad (16)$$

Here, $W^N_{VdW,diss}$ is energy dissipation due to van der Waals force, W^N_{GP-vWF} is energy dissipation due to molecular mechanisms regulation (glycoprotein, GP; von Willebrand factor, vWF). It should be noted that inactive and activated platelets have different surfaces

(with and without pseudopodia), as well as different influences of adhesion forces on the cell. When platelets are activated, the cell may be influenced by additional adhesion-related mechanisms.

This work models the normal interaction of non-activated platelets, but the molecular mechanism of an activated cell can also be mentioned. One of them is the molecular mechanisms regulating GPIbα-vWF bond formation and platelet adhesion under shear stress (tangential interaction), Ruggeri and Mendolicchio [7], Andrews et al. [16], Andrews and Berndt [17], Varga-Szabo et al. [18], Mori et al. [19], Hosseinzadegan and Tafti [20]. The initial capture of flowing platelets is mediated by the interaction of the glycoprotein (GP) Ib-V-IX complex with von Willebrand factor (vWF) immobilized on exposed collagens. The GPIbα-vWF interaction mediates platelet binding, thereby enabling the interaction of GPVI with collagen.

As noted in this work, a simplified expression of the effect of adhesion on platelets will be used, while leaving the possibility of also taking into account the additional dissipation effect caused by adhesion when it is obtained/found using physical experiments. If the amount of dissipation due to the additional influence of adhesion is known, it can be taken into account using the parameter $W^N_{adh,diss,i}$, Equation (16).

Table 1. Initial data.

Objects	Initial Parameters	Values	References, Source
Platelet (thrombocyte)	Diameter, d_i	2 μm	Paulus [21]
	Radius, R_i	1 μm	-
	Initial interaction distance, h_S	20 nm	Jasevičius [15]
	Initial velocity, v_0	-0.010783 cm/s	Jasevičius [15]
	Mass, m_i	≈1.9 pg (picograms)	Haley et al. [22]; Kim et al. [23]
	Density, ρ_i	≈1.067 g/cm^3	Corash et al. [24] Thompson et al. [25]
	Young's modulus, E_i	10 kPa	Radmacher et al. [26]
	Poisson's ratio, ν_i	0.5	Radmacher et al. [26]
	Surface potential, ψ_i	-14.2 mV	Tatsumi et al. [27]
	The adhesion force (point L), $F_{L,adh}$	-10 pN	Radmacher et al. [26]
	Adhesive dissipative energy, $W_{adh,diss}$	2.0×10^{-19} J	By Equation (14)
Vessel cell (endothelium)	Density, ρ_j	1.03 g/cm^3	Nees et al. [28]
	Young's modulus, E_j	5.0 kPa	Zeng et al. [29]
	Poisson ratio, ν_j	0.5	Jasevičius et al. [15]
	Surface potential, ψ_j	-48.3 mV	Nakashima et al. [30]
Blood	PH	7.4	Wilschut [31]
	Temperature, T_{temp}	36.8 °C	Jasevičius [15]
	The permittivity of the free space, ε_0	8.854×10^{-12} C^{2}J^{-1}m^{-1}	Jasevičius [15]
	Debye length, λ	0.785 nm	Jasevičius [15]
	A dielectric constant of water, ε	74.5	Butt et al. [32]
	Blood flow velocity, $v^T_{max,blood}$	-3.0 cm/s	Nagaoka and Yoshida [33]
	Blood flow velocity at $a_{F=0} = 20$ nm distance in normal direction, v_S	-0.010783 cm/s	Jasevičius [15]
	Dynamic viscosity, η_f	0.003 Pa·s	Nacev et al. [34]
Arteriole	Diameter, $d_{blood\ vessel}$	100 μm	Nagaoka and Yoshida [33]
Simulation	Time step	0.3 ps (picoseconds)	-

3.4. Detachment

Since separation/detachment occurs at a distance, the description of this process is similar to the description of the approach:

$$F(t) = F_{adh}(t) + F_{dl}(t) + F_{drag}(t) \tag{17}$$

Unlike the approach process, the increased effect of attraction acts on a platelet during a detachment/separation process. Additionally, as in unloading, the effect of the changed adhesion/attraction through the element $F_{adh}(t)$ is evaluated:

$$F_{adh}(t) = \frac{F_{A,adh} a_{F=0}^2}{(a_{F=0} + |h(t)|)^2} \tag{18}$$

Here, the force $F_{A,adh}$ is the adhesion force at point A (Figure 1). The force $F_{A,adh}$ can be described as:

$$F_{A,adh} = F_{L,adh} + F_{adh,diss} \tag{19}$$

The force $F_{adh,diss}$ (adhesive-dissipative) is considered to be obtained from the history of unloading and is described by the Equation (13).

4. Numerical Experiments

A numerical experiment of platelet interaction with the wall of a blood vessel is presented. The numerical experiment is designed to study the interaction of platelets. The results also reflect the ability to use the presented theoretical model, as well as give an insight into how the behavior of platelets is in the dynamics. Of course, different initial data can be used. In order to demonstrate this platelet behavior during interaction, and since it can be achieved in a numerical experimental study, the study is divided into three parts. This includes cases where the fluid drag force is considered, partially considered, or not considered. It should be noted that the dynamics (free movement/interaction of cells) and the statics (if cell deformation is controlled by an external force) will have different behaviors.

When conducting interaction studies in a blood vessel, the goal is to find out whether an inactivated, free-moving platelet can approach the wall of a blood vessel, and at the same time to determine if its contact will occur. This research path was chosen because the liquid strongly influences the dynamics of cellular interactions.

The study allows us to evaluate each effect separately. This is achieved by a numerical experiment; as already mentioned, this is its advantage. Unfortunately, when all the forces act together, it is difficult to assess the influence of each on the movement of the cell, it is difficult to notice which action is affected. The electrostatic force of a double layer is a typical force acting on a cell in a liquid. When evaluating the influence of liquid in a numerical experiment, it may be that the influence of elastic forces or even the influence of adhesion forces will be difficult to observe / or may not be observed at all, since the influence of the liquid becomes decisive. Basically, the movement of the platelet, which is a cell, is determined by the movement of the fluid. It should also be noted that the density of the cell is close to the density of the liquid and that the interior of the cell is separated from the blood fluid only by a thin cell wall. Since the movement of the cell is determined by the movement of the surrounding fluid, in order for the cell to approach the surface of the blood vessel, there must be a strong influence of the adhesion force in the fluid (blood). It should be noted that in a liquid adhesion is effective over a greater distance than a similar interaction in air (Jasevičius et al. [12,13]). In addition, this study considers the case when the platelet is not activated, in this situation the platelet itself has a weaker adhesive effect. The initial data of the experiment are presented in Table 1.

To achieve greater accuracy, a small-time step of 0.3 ps was selected. As can be seen in the following figures, one division corresponds to 0.01 piconewtons (or 10 femtonewtons). Greater precision is required: because an extremely small object is being considered; identify

cell movement/deformation in liquid and over time at a very small distance of 20 nm; identify various processes occurring with the cell (approach, load, unload, detachment). With a larger time-step, calculation inaccuracies are possible, which may prevent coverage of all processes presented in the work. Additionally, it should be noted that when modeling the interaction of a cellular system, due to the large number of calculations, the time step must be increased, but the accuracy of the interaction process may suffer.

The duration of the interaction in the work may include 10 microseconds, which is 100,000 times shorter than one heartbeat. It is accepted at work that the wall of the blood vessel remains motionless at this extremely short moment. The radius of the blood vessel is considered in Equation (8) by calculating hydrodynamic force. Below are the results of the numerical experiment in Figures 2–4 and in Table 2.

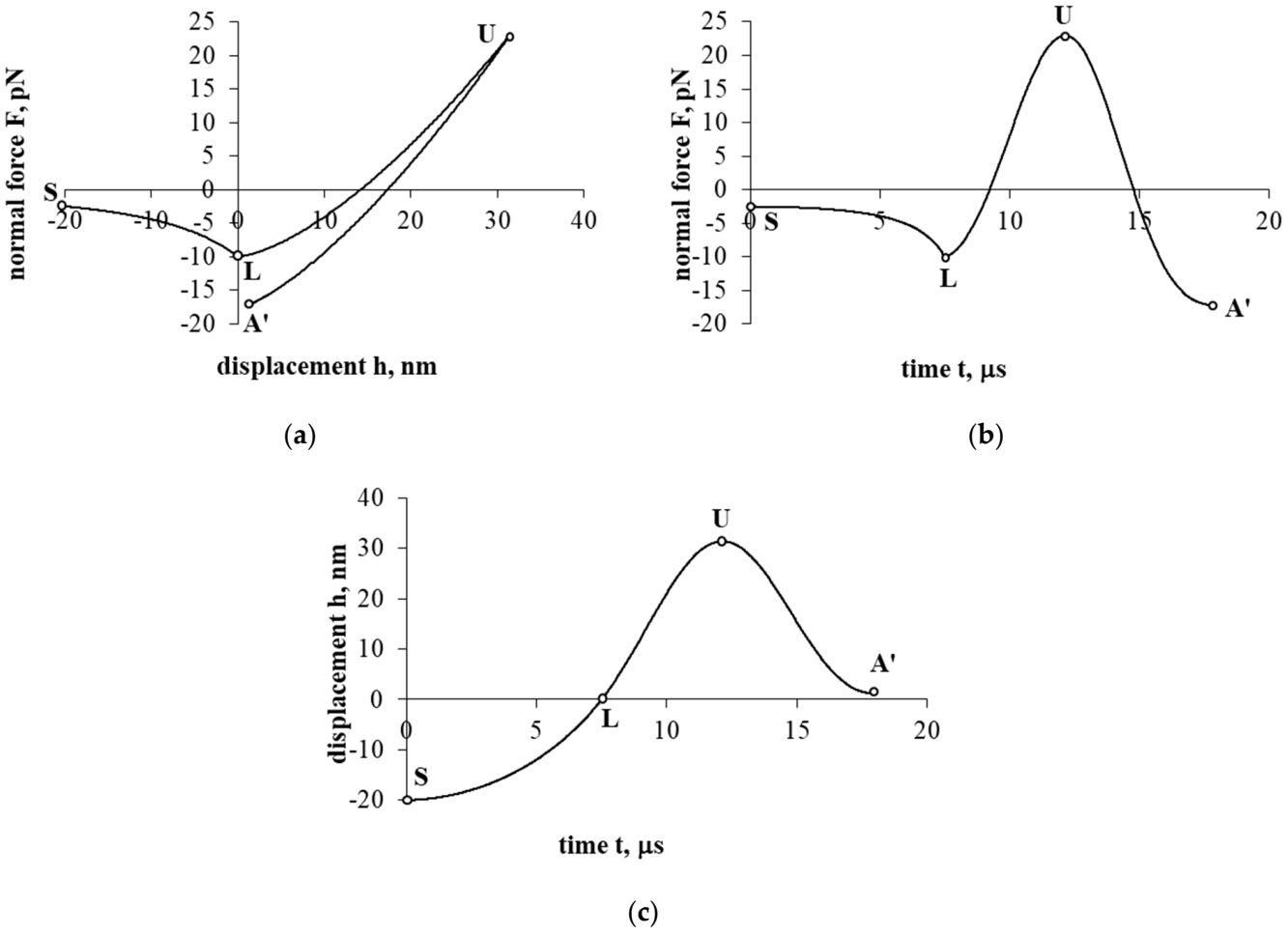

Figure 2. The first part of the investigation of the adhesive–elastic interaction. The electrostatic double layer force and the drag force are not considered. Dependence of force on displacement (**a**) and time (**b**); dependence of displacement on time (**c**).

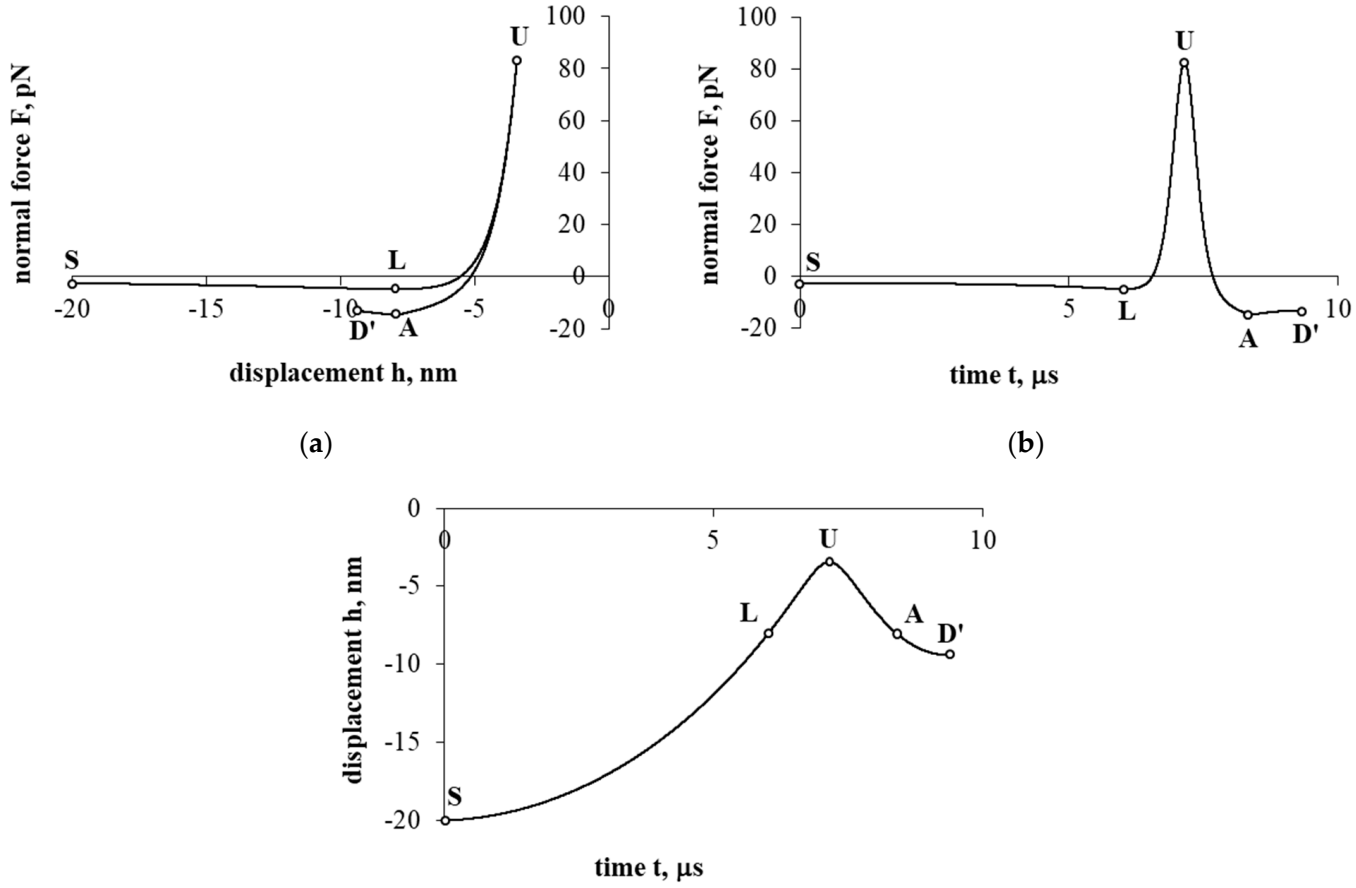

Figure 3. The second part of the investigation of the adhesive–elastic interaction. The electrostatic double layer force is considered (the drag force is not considered). Dependence of force on displacement (**a**) and time (**b**); dependence of displacement on time (**c**).

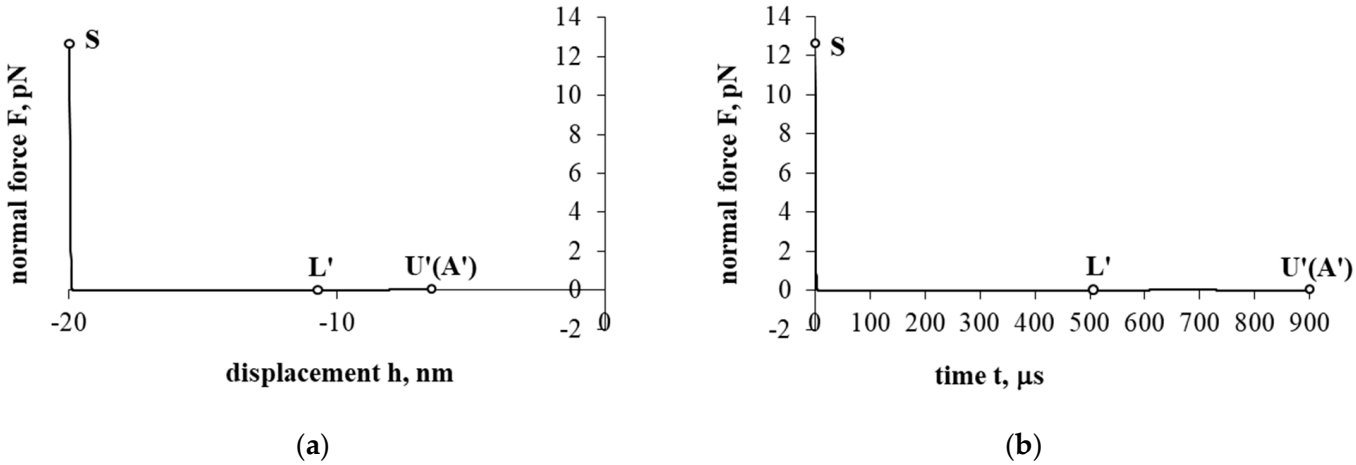

Figure 4. *Cont.*

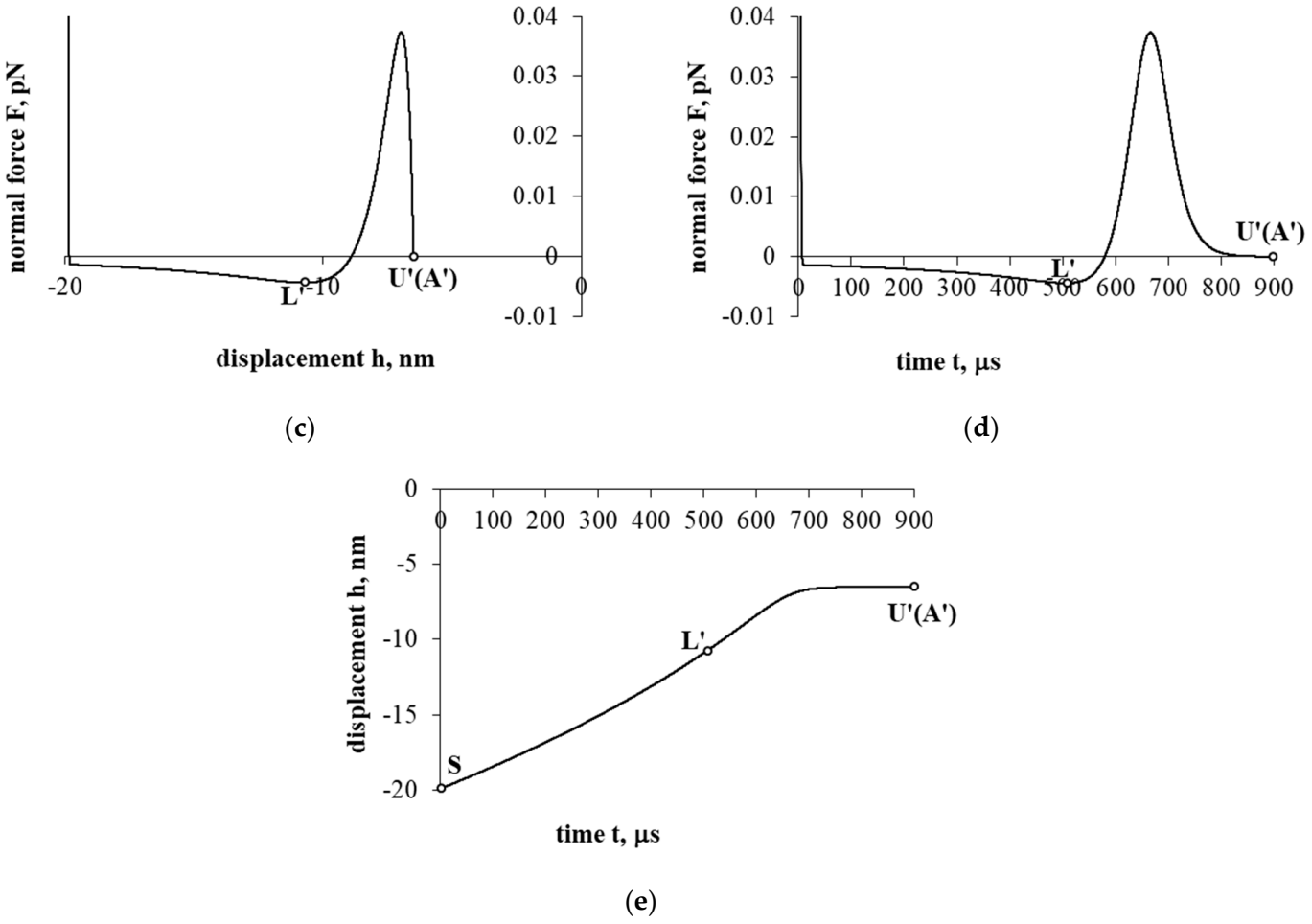

Figure 4. The third part of the investigation of the adhesive–elastic interaction. The electrostatic double layer force and the drag force are considered. Dependence of force on displacement (**a**) and time (**b**). An enlargement of (**a**) is shown in (**c**), and an enlargement of (**b**) is shown in (**d**); dependence of displacement on time (**e**).

Table 2. Platelet interaction properties during interaction at certain points: S-L/L′-U/U′-A/A′-D′.

Parameter		Values at Certain Points				
		S	**L/L′**	**U/U′**	**A′**	**D′**
First part	t, μs	0	7.49711	12.13904	17.88202	-
	F, pN	−2.5	−10	22.9651839	−17.203266	-
	h, nm	−20	0	31.395412	1.2637969	-
Second part	t, μs	0	6.028137	7.150608	8.378639	9.36514
	F, nN	−2.5	−4.830848	82.7117127	−14.830844	−13.090838
	h, nm	−20	−7.9555	−3.4445753	−7.9555	−9.4117088
Third part	t, μs	0	506.3692	≈900	-	≈900
	F, nN	−2.5	−0.004419826	≈0	-	≈0
	h, nm	−20	−10.736881	−6.5	-	−6.5

The results are given in Figure 2 and Table 2 (first part). Here, platelet behavior is represented by evaluating adhesion and elastic forces, while electrostatic double layer forces and fluid drag forces are not taken into account. This study is close to the case when a cell interacts in an air environment. In research, it has been observed that interactions involve both approach and contact. The duration of the interaction is about 18 μs (Table 2, first part, point A′). When approaching, the maximum adhesive force is 10 pN (Table 2,

part one, point L). According to well-known studies with platelets (Rana et al. [35]; Kim et al. [36]), there is a high-affinity state engaging ~10 pN with around 20-fold longer bond lifetime and greater ability to withstand strong hemodynamic forces. Deformation occurred only when the platelet came into contact with the surface of the blood vessel. The maximum achieved total repulsion force is about 23 pN, and the displacement is about 31 nm (Table 2, first part, point U). During the deformation process, when the platelet is unloaded, the platelet does not have enough kinetic energy to separate from the surface. At point A′, the attractive force achieved is about ≈17.2 pN, the magnitude of which is in the range from 4.7 to 19.3 pN, which is observed in known physical experiments with platelet tension (Zhang et al. [37]).

After reaching point A′ (Figure 2), further movement is a return process, which is considered the beginning of the process of sticking or aggregation of platelets. After conducting the study, in the case where fluid forces are not assessed, it can be initially concluded that non-activated platelets tend to stick to the surface of the blood vessel if fluid effects are not assessed. If we take into account that the heartbeat covers 1 s, then this duration (Figure 2b,c) of cell interaction is approximately 56,000 times shorter.

Further results are presented in Figure 3. This shows the behavior of the platelet when additionally taking into account the electrostatic double layer force. As in the previous case, the adhesive and elastic forces are taken into account, but the fluid resistance force is not taken into account.

Compared to Figure 2, in the results of Figure 3, the platelet interaction did not include contact, the interaction occurred only at the appropriate distance between the interacting surfaces, when the platelet was far from the surface of the vessel. This is due to the premature action of the repulsion force on the soft structure of the cell. In addition, due to the action of the force of the electrostatic double layer, the adhesion force achieved during the approach was several times less (about 2.1 times).

Compared to Figure 2, the maximum repulsion force achieved in Figure 3, is 3.6 times higher (Figure 3, point U). The achieved adhesion force decreased and became lower by 1.16 times, which is associated with the action of the force of the electrostatic double layer. At point A, an attractive force of about 14.83 pN is achieved, the magnitude of which ranges from 4.7 to 19.3 pN, which is observed in well-known physical experiments with platelet tension, Zhang et al. [37]. The duration of the interaction also became shorter, it was halved (about 1.9 times). When detached from the surface of the blood vessel, the cell stopped at point D′. Further cell movement is considered as a sticking process, which is not analyzed in this work. If we take into account that the heartbeat covers 1 s, then this duration (Figure 3b,c) of cell interaction is approximately 107,000 times shorter.

The following numerical experiment results in Figure 4 evaluate the effect of all the forces mentioned in this article on platelet interaction, including the effect of the fluid drag force. Assessing the influence of the fluid, in the presence of free movement of the cell, its dynamics, at the beginning of the interaction, due to the strong effect of the fluid, the repulsive force strongly increases, and then the resulting interaction force is suppressed just as quickly, and the further movement of the cell is determined by the influence of a small cumulative force. An enlargement of Figure 4a is shown in (c), and an enlargement of Figure 4b is shown in (d). Compared with the previous cases (Figures 2 and 3), even in the case of a very small cumulative force, certain interaction tendencies can be seen (Figure 4c,d). Here, an increase in adhesion forces is observed, the achievement of a greater adhesion force at the point L′, then a transition to an increase in the repulsion force, after which the platelet stops at the point U′ and the sticking process should begin. However, unlike the previous cases, the platelet simply stops at an appropriate distance from the surface of the blood vessel. Additionally, the displacement history is presented (Figure 4e), where it can be seen that until the end cell comes to a complete stop, it remains almost in the same position ($t > 700$ μs) until the normal force decreases to zero (Figure 4d). Of course, such a case can be assumed, since the duration of this interaction itself is short; if we take into account that the heartbeat covers 1 s, then this duration (Figure 4b,d,e) is

approximately 1100 times shorter. Ideally, this can be viewed as the behavior of a cell over a very short period of time.

Therefore, it remains interesting how the problem is solved in a living organism, so that the platelet effectively adheres to the surface of the blood vessel when the vessel is damaged. This study clearly shows that fluid influence is the determining factor in platelet movement. In addition, for effective sticking to the surface, the platelet must have different surface properties, moreover, its surface geometry must also be different. The geometry must be different, because when it is inactive and has a sphere-like surface; it will not reach the inner surface of the blood vessel. Therefore, subsequent studies focused on the case where the platelet is activated and will have a slightly changed surface geometry as well as changed surface adhesive properties. Further investigation will be concentrated on sticking (Jasevičius and Kruggel-Emden [11]; Feghhi and Sniadecki [38]) of the thrombocyte to a certain surface.

Key Findings That Have Not Been Observed before for Platelet Mechanical Interaction

- The platelet tends to deform even in the absence of contact (at an appropriate distance from the interacting surface), this has not been observed before.
- The paper considers the interaction of one platelet with the wall of a blood vessel. It has been observed that non-activated platelets in the fluid do not tend to approach/adhere to the surface of the blood vessel. This (numerical experiment results) confirms the known fact that the human body itself thus protects itself from accidental platelet agglomeration (possible/spontaneous formation of emboli).
- If we consider the idealistic case—interaction in the air, then at a small nanoscale distance, when influence of adhesion is already significant, the cell itself tends to stick to the surface. However, such an interaction (in air) does not occur under natural conditions. Since a numerical experiment makes it possible (to study the interaction of cells in air), this study is also presented in addition.
- It is known that after damage to a vessel, in order to restore it, the platelet must adhere to the damaged surface. The present study shows that without any additional surface changes, platelets are unable, or it is too difficult to reach the surface. That is, there must be an additional change in the surface geometry that could help overcome the repulsion forces acting on the platelet. To do this, the activated platelet changes its geometry, and has additional extensions in the form of spikes on the surface, which are called pseudopodia. Pseudopods have a smaller surface area, so it is easier for them to overcome the electrostatic double layer force, drag force and reach the interacting surface (while studying how activated platelets interact with the surface will be the next step for future research).

5. Concluding Remarks

This work investigated the platelet interaction with the surface of the blood vessel. The idea of the study was to look at the behavior of a platelet under normal conditions, when it has not yet been activated. Since a platelet is primarily supposed to adhere to a surface when it is activated, there is a concern in this work to see if it tends to adhere even when it is not yet activated, when it is not necessary. Based on the initial data of well-known physical experiments describing the mechanical behavior of a platelet, a numerical study of the platelet dynamics during the interaction of a platelet with the surface of a blood vessel was carried out. The results of the study confirmed what was assumed before the study, that under normal conditions, in liquid, it is quite difficult for platelets to reach the surface of the blood vessel. The fluid must be completely eliminated for this interaction (the process of sticking to the surface of the vessel) to occur. Although the result of the study revealed the behavior of a platelet under normal conditions (the blood vessel is not damaged and not pathological), the question remains how the platelet sticking process occurs/is realized by implementing a numerical experiment, taking into account the case of platelet activation. This will be the subject of further research. Finally, it can be said that

the main task has been achieved: a theoretical model has been presented to study platelet dynamics by applying a numerical experiment using the discrete element method.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Data are contained within the article.

Conflicts of Interest: The author declares no conflict of interest.

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