Simulated Effects of Curvature on Thrombus Formation

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Abstract

Thrombosis is a pathological condition of thrombus formation, as a blood clot or thrombus is formed inside the blood vessel and obstructing the blood flow. Simulation models are helpful at studying the formation of thrombus and predicting the future growth of thrombus inside a blood vessel. After a review of literature, a gap was found in the field of thrombus simulation. Despite the importance of incorporating the effects of blood vessel's curvature during thrombus formation, none of the current simulation studies explicitly addressed it. In order to fill this gap, an experimental study with simulation models at the mesoscopic scale using curved vessel geometries were carried out. The DPD (Dissipative Particle Dynamics) method was used as the primary interactive force model and the simulation data was analyzed with statistical trendlines. It was shown that curvature does have a significant effect on the average rate of thrombus growth and physical experiments should be done in the future to verify or reject the simulation results.

Introduction

Purpose

This paper investigated the effects of blood vessel's curvature on the formation of a thrombus. After reviewing literature on thrombosis, particularly the computer simulation models for thrombus formation, a gap is found in regard to how the blood vessel's curvature affects the rate of thrombus development. An explicit model summarizing the effects of blood vessel's curvature during thrombus formation is important for future pathological thrombus research that study at the mesoscopic level. Therefore, this research aimed to determine the effects of the blood vessel's curvature on the average rate of thrombus formation in an ideal situation.

Problem Statement

Thrombosis is a pathological condition of thrombus formation, where a blood clot or thrombus is formed inside the blood vessel and obstructing the blood flow. The thrombus is a blood clot that is made of aggregated platelets, red blood cells, and a mesh of cross-linked fibrin protein. There is a problem with the current mathematical modelling of thrombosis. Despite the importance of incorporating the effects of blood vessel's curvature during thrombus formation, none of the current studies on the computer modelling of thrombus growth explicitly addressed it. A lot of them used linear blood vessel models to simulate what happens during the formation of a thrombus at the mesoscopic level (Filipovic et al., 2008; Tosenberger et al., 2012, 2013, 2014, 2015; Yazdani et al., 2017), and some of them simulated thrombosis within a complex blood vessel geometry at the macroscopic level (Assemat et al., 2014; Menichini et al., 2016; Polanczyk et al., 2015; Saveljic et al., 2018; Silva et al., 2013).

The Importance of Modelling Thrombosis

Thrombosis as a blood disease is classified into two main categories, venous thrombosis and arterial thrombosis. Venous thrombosis refers to the condition where thrombosis occurs in veins, and it can lead to pain and swelling as the blood flow returning to the heart is obstructed. Deep Vein Thrombosis (DVT) is a type of venous thrombosis where the blood clot is formed in major veins such as arms and legs. As estimated, 900,000 people in the United States are affected by venous thromboembolism every year, which is about 1 to 2 per 1000 people (MG et al., 2009). Arterial thrombosis, where the blood clot occurs in arteries, is usually associated with Atherosclerosis. Atherosclerosis occurs when plaque builds up inside the artery and narrows the blood vessel. As the high blood pressure inside the narrow artery leads to rupture, a blood clot will form inside and could lead to a heart attack or stroke.

Simulation models are usually used to study the formation of thrombus and help to predict the growth of thrombus inside a blood vessel (Menichini et al., 2016; Polanczyk et al., 2015; Silva et al., 2013). Therefore, modelling thrombus formation can lead to more effective medical treatments for the patients. A well-developed model could also be used in further research projects on thrombosis.

Various Methods of Simulation

Tosenberger et al. categorized thrombus simulation models into three groups (Tosenberger et al., 2015). The first group includes all the continuous simulation models, which models blood flow by using partial differential equations within a numerical scheme at the macroscopic level. Partial differential equations in the first group are either used to describe blood as homogeneous

fluid with non-Newtonian properties (Polanczyk et al., 2015; Silva et al., 2013), or are used to describe Newtonian blood plasma's blood cell concentrations (Assemat et al., 2014; Saveljic et al., 2018). Continuous models of thrombus formation often include the complicated geometry of blood vessels, as they require relatively less computational power at the same scale(Assemat et al., 2014; Menichini et al., 2016; Polanczyk et al., 2015; Saveljic et al., 2018; Silva et al., 2013).

The second group refers to discrete models and they simulate blood cells as individual particles at the mesoscopic level. Simulation methods include Smoothed-Particle Hydrodynamics (SPH), Lattice Gas Automata (LGA), Lattice Boltzmann (LB), and Dissipative Particle Dynamics (DPD) (Tosenberger et al., 2015). As compared to continuous models, discrete models include the dynamic behaviors of individual blood cells and their specific interaction. However, due to the requirement of great computational power, discrete models are usually at the local level and ignore the complicated blood vessel geometry (Filipovic et al., 2008).

The third group of simulation model are hybrid models. This model combines the previous two models together. It models certain blood cells as individual particles using DPD method and uses partial differential equations to describe the concentrations of other important blood plasma components (Filipovic et al., 2008; Tosenberger et al., 2015).

Hypothesis

From the standpoint of Newtonian Dynamics, a particle will follow a straight path if no force is exerted on it, and such a particle will more likely hit the outer side of the vessel wall within a curved blood vessel. Although the blood as a biological fluid is much more complex and the mesoscale models tend to focus on a small linear section of the curved blood vessel, the effects of curvature will likely remain even within a small linear region of a curved blood vessel. At the same time, the velocity profile of a fluid travelling through a curved pipe will be skewed and some turbulence may be initiated too (Koutsiaris, 2009), implying that the platelets, cells that initiate thrombus formation, are more likely to aggregate. It is hypothesized that as the curvature of the blood vessel increases, the average rate of thrombus formation initiated on the outer side of the vessel will also increase while exhibiting similar growth trends.

Methods

To investigate the effects of curvature during thrombus formation, an experimental method using real blood sample within physical glassware is certainly possible, as Costa et al. successfully mimicked arterial thrombosis and collected data from their physical experiment (Costa et al., 2017). However, due to the lack of equipment and guidance, a physical experiment could not be performed for this research, and computer simulations will be run instead to collect necessary quantitative data with using the experimental method. Tosenberger et al. qualitatively analyzed the shape of the formed blood clot to suggest the effects of some biological conditions on the geometry of the clot (Tosenberger et al., 2013). However, since the dependent variable of this research is the average rate of blood clot formation as a numerical value, quantitative approach was chosen over qualitative approach.

Thrombus formation is a complicated biological process. Not only is it difficult to form a detailed description about the mechanical interactions among different blood cells and the vessel

wall, but the numerous chemical reactions for thrombus initiation and formation pose even greater challenges for computer simulation. For example, blood coagulation by itself includes some fifty proteins within approximately two hundred reactions in the presence of flow and diffusion (Tosenberger et al., 2013).

In order to collect data from simulated thrombus formation within different curved geometries, the simulation model must be simplified and efficient. Modelling thrombus formation with including every chemical molecule and reaction will require too much computational power, and a model that represents the whole blood plasma as a continuous fluid will oversimplify the process; DPD method therefore fills the gap between microscopic simulation and macroscopic simulation methods (Moeendarbary et al., 2009).

Simulation Model

In the simulation model, DPD method is used to govern the interactions among the fluid particles and platelets, which have the same mass and radius.

The DPD method simulates complex biological molecules as simple soft spheres and are governed by three interactive forces, a conservative force (F^C), a dissipative force (F^D), and a random force (F^R).

$$\begin{aligned} \vec{f} &= (F^C + F^D + F^R)\hat{r_{ij}} \qquad r < r_c \\ F^C &= Aw(r) \\ F^D &= -\gamma w^2(r)(\hat{r_{ij}} \bullet \vec{v_{ij}}) \\ F^R &= \sigma w(r)\alpha(\Delta t)^{-1/2} \\ w(r) &= 1 - r/r_c \end{aligned}$$

where r_{ij} is a unit vector in the direction between two neighboring atoms, v_{ij} is the velocity vector difference between two neighboring atoms, alpha (σ) is a Gaussian random number with zero mean and unit variance, Δt is the timestep size, and w(r) is a weighting factor that varies between 0 and 1 with r_c as the cut-off distance. The cut-off distances for other forces will use the same notation. The equations also satisfy the relation $\sigma^2 = 2\gamma k_B T$, where k_B is the Boltzmann constant, T is the temperature, and γ is the parameter associated with dissipative force (Groot et al., 1997).

Platelet aggregation is an extremely important step for thrombus formation. The aggregation or adhesion process as a complex multi-step process involves adhesion receptors and subsequent platelet activation (Kulkarni et al., 2000). The platelet is first weakly connected to the clot through GP1b bonding, and a stronger connection through integrin bonding may be initiated after a certain time interval (Tosenberger et al., 2012).

Due to the blood clot's elastic properties (Brown et al., 2009; Weisel, 2008), the platelet adhesion force is modelled as

$$F_{ij}^{\ A} = f^A \cdot (1 - \frac{r_{ij}}{d_c}) \cdot \hat{r}_{ij}$$

where d_c is the force relaxation distance and is equal to twice the radius of the platelet particle

and f^A is the force strength coefficient. This force also has its own cut-off distance.

Modelling platelet adhesion with a linear spring function was proposed by Filipovic et al. as a time-independent attractive force, in agreement with the experimental result of the number of adhered platelets on collagen wall (Filipovic et al., 2008).

In addition to the adhesion force, a soft repulsive force written in potential energy form was also added to the platelets to prevent significant particle overlapping during the aggregation

$$E = S[1+\cos(\frac{\pi r}{r_c})]$$

where S is a pre-factor that determines the force strength and r is the distance between the centers of two particles. Note that the cut-off distance is set to twice the particle radius to ensure proper repulsive force. An advantage of this soft force is that the force will not approach infinity as two particles overlap significantly, which avoids unwanted particle motions.

Finally, the ideal vessel wall was modelled with a harmonic spring potential

$$E = \varepsilon(r - r_c)^2$$

where ε is the strength coefficient corresponding to the wall potential energy, and the cut-off distance is equal to the particle radius.

See table 2 for all simulation parameters.

Data and Variables

In order to objectively obtain the effects of curvature on the average rate of thrombus growth, quantitative data was collected. The nature of this experiment as simulation models also helps to obtain more accurate data directly from computations. Qualitative data such as the simulation snapshots were mostly used for parameter calibration.

The independent variable in this experiment is the curvature of the cylindrical blood vessel, and the dependent variable is the average rate of platelet particles' aggregation. The curvature of the blood vessel is quantified as the mathematical curvature of a semi-circle, and the rate of blood clot formation is measured as the average rate of platelets aggregation over the entire simulation time domain.

Procedure

All necessary software was downloaded including Lammps simulator and the visualization tool Ovito. A new pairwise force and a new geometric wall source code file were written and added to create an executable file for running all simulations. More specifically, each time after the new source code files were added, the whole simulator had to be re-compiled in order to incorporate the added new functions. The source code was tested with simple simulations to ensure its functionality.

An input script that includes all the necessary parameters was written and run with Lammps. Two kinds of particles were created for each simulation run, platelets and fluid particles. Both were governed by DPD pairwise forces and two other forces were added to the platelets. To initiate clotting, nine platelet particles were placed on the outer side of the vessel wall and

assigned infinite mass. Thus, the platelet particles were essentially frozen and would attract other platelets to form a blood clot.

Seven simulation groups were established, where six of them had curved cylindrical vessel walls as the experimental groups and one had straight cylindrical wall as the control group. See table 1 for the geometric parameters of the vessel wall, figure 1 for a snapshot of straight vessel wall, and figure 2 for a snapshot of curved vessel wall.

The simulation parameters were then tested and chosen to match closely with both the physical scales and the qualitative aspect of thrombus formation. The seven simulation groups were assigned the same simulation parameters except the geometric curvature. For each simulation group, five trials each with a different set of random number seeds were run for 10000 timesteps. The random number seeds were used to generate "random" coordinates for inserted particles and the random force of DPD, thus imitating real-life experiment. Ovito was used after the simulation to collect data about thrombus growth and generate visualizations.

After all the data was obtained, Excel and Desmos were used to carry on the statistical analysis. The growth curves of three simulations were plotted and compared. The independent variable and dependent variable, on the other hand, were analyzed with regression to investigate the effects of blood vessel's curvature on the average rate of blood clot formation. A bar graph was also built to visualize the differences in the final thrombus size among the seven groups.

Results

Three different simulation snapshots are presented below to help visualize the simulations. The necessary simulation parameters are organized into two tables, where Table 1 includes the vessel curvature data of each group and Table 2 includes the simulation model parameters applied to every group. Three analysis graphs on curvature's effects on the average rate of platelet adhesion and platelet growth curve are presented at the end.

Simulation Snapshots

Figures 1-3 are all simulation snapshots. The green spheres are fluid particles, the white spheres are mobile platelet particles, and the blue spheres are frozen platelet particles. Figure 3 has fluid particles erased to better visualize the platelet particles. As shown by the snapshots, the fluid particles and mobile platelet particles enter the vessel at one end and exit at the other end.

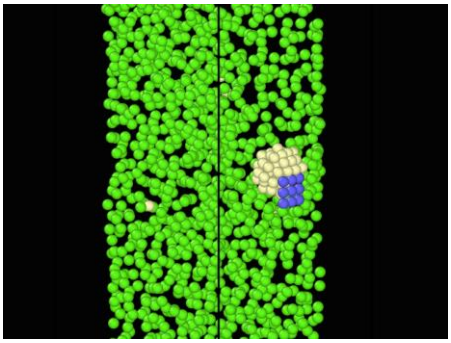

Figure 1. Snapshot of the final stage of the control group

It should be noted that the green fluid particles in figure 1 move vertically up, and the white thrombus made up of individual platelets are still under the influence of the fluid flow even in the final stage. One piece of evidence is that the final thrombus is attached to the upper part of the nine stationary platelets, as the fluid particles constantly hit the thrombus during the flow.

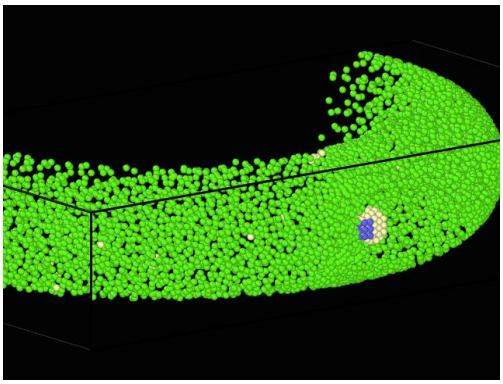

Figure 2. Snapshot of the final stage of the experimental group with 40 as the radius of curvature

The fluid particles flow from left to right in figure 2. Notice that the green fluid particles on the left side of the thrombus has a greater density, as the final thrombus partially blocks the fluid flow. And the fluid particles have a smaller density on the right side on the thrombus, as blocked fluid particles could not easily pass through and occupy that region.

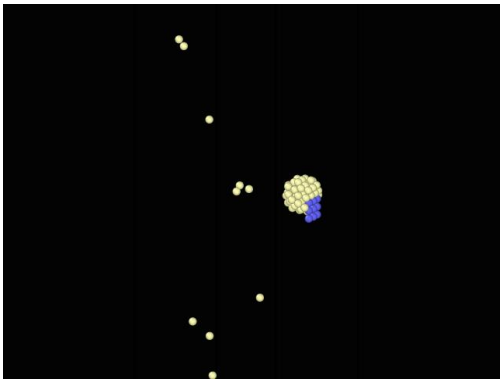

Figure 3. Snapshot of the final stage of thrombus in the control group with fluid particles excluded

Note that in figure 3, although the formed thrombus on the right side will exert a fairly strong attractive force to nearby mobile platelet particles, not all platelets in the force range would join the thrombus, as they might be swapped by fast-moving fluid particles.

Simulation Parameters

Table 1. Geometric parameters of the vessel wall

Simulation Group	Curvature (reduced unit)
1	0
2	1/40

3	1/27
4	1/24
5	1/21
6	1/18
7	1/15

Table 1's curvature values are obtained from the radius of curvature of the torus. The radius of curvature is defined as the distance from the torus's center to its cylindrical central axis. Every torus geometry covers 180 degrees, so the length of the torus increases as the radius of curvature increases.

Table 2. Simulation model parameters

Variable	Simulation	Physical	Description
L	20	20 μm	Vessel diameter
d	1	1 μm	Particle diameter
m	0.523599	10 pg	Particle mass
dt	0.001	1 s	Timestep size
v	100	100 μm/s	Particle initial velocity
c		6.37×10^{11}/L	Platelet concentration
ρ		1 pg/ μm^3	Blood vessel density
A	30		DPD coefficient
γ	1		DPD coefficient
r_c (DPD)	5	5 μm	DPD cut-off distance
T	1		DPD temperature
f^A (adhesion)	30		Adhesion force coefficient
r_c (adhesion)	7	7 μm	Adhesive force cut-off distance
d_c	1	1 μm	Adhesive force coefficient
S	3000		Soft potential coefficient

r_c (soft)	1	1 μm	Soft potential cut-off distance
ε	100000		Wall force coefficient
r_c (wall)	0.5	0.5 μm	Wall force cut-off distance

Table 2 shows the model parameters in both physical and reduced units used in the simulation. Notice that the table contains some blanks, which will be explained in the discussion section.

Analysis Graphs

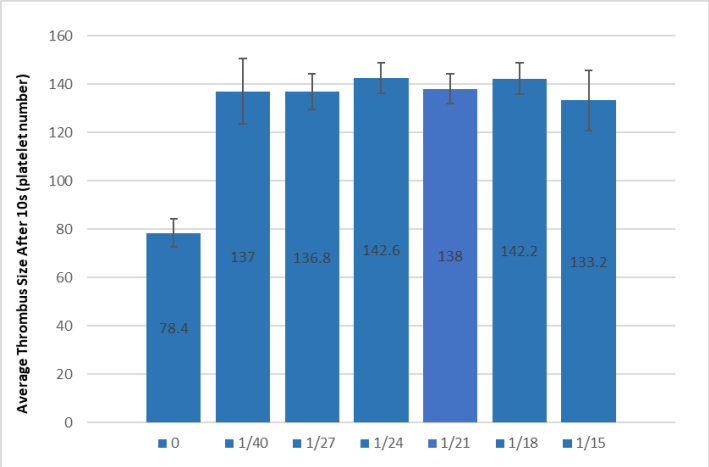

Figure 4. Bar graph of all seven groups' average thrombus size after 10s with error bars for each five trials

In figure 4, the average final thrombus size of the seven groups were plotted. The error bars correspond to 95% confidence interval or about 1.96 standard error up and down.

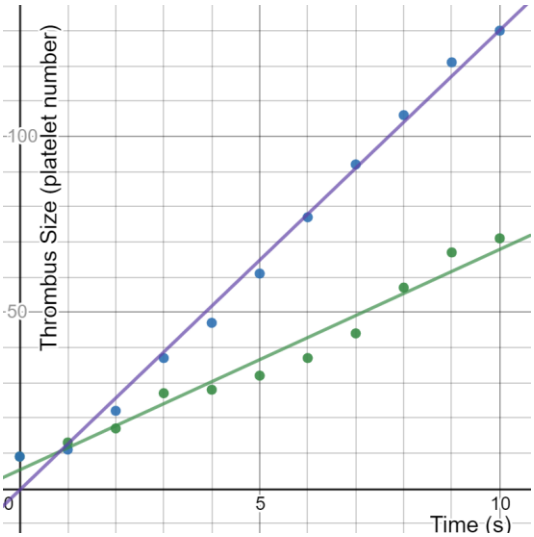

Figure 5. Growth curve of two trials from different groups

In figure 5, the steeper growth curve corresponds to one trial of the experimental group with radius of curvature 40, and the less steep curve corresponds to one trial of the control group. The steeper line has a slope of 13.0636 and a r value of 0.9956, whereas the less steep line has a slope of 6.26364 and a r value of 0.9827.

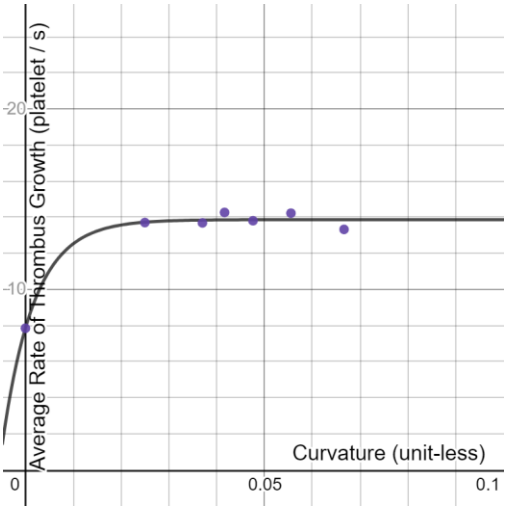

Figure 6. Regression analysis of curvature's effects on the average rate of platelet adhesion with average growth rate values plotted.

As shown in figure 6, the effect of curvature on the average rate of platelet adhesion was modelled with an exponential trendline with a R^2 of 0.9803. The model is $a \cdot e^{bx} + c$, where a is -6.02056, b is -150.273, and c is 13.8603.

Discussion and Conclusion

An important question of simulation models is whether their simulated phenomenon will actually happen in real life, or to what degree do they represent an aspect of reality. This question

will be addressed throughout the discussion to support the validity of the results.

Justification for Parameters

As shown by table 1, each simulation group had a unique curvature value, which is also the independent variable of this experiment. The definition of curvature was chosen to be the inverse of the torus's radius of curvature, similar to circles. Zero curvature means the vessel is straight. For convenience, all curvature values were presented as unitless and could be converted into physical unit as $1/\mu m$.

Table 2 shows all the simulation model parameters, corresponding to the simulation models from the method. Two types of values were presented, simulation values and physical values. The simulation values were directly used as inputs of the simulation, and they were converted into physical values through some conversion factors. For example, the length measurement has a 1:1 ratio. The simulation value for the particle mass was the default value, and to ensure the physical significance of the blood vessel density, the mass's physical value was chosen to be 10 pg, quite larger than the actual mass of a platelet, which is around 2 pg (Haley et al., 2011). The platelet concentration value is also slightly higher than the normal range as $1.5\text{-}4\times10^{11}$/L and is justified by the phenomenon that the presence of red blood cells would push the platelets to the outer sides of the blood vessel (Tosenberger et al., 2015), so the platelet concentration near the thrombus is higher.

As shown by table 2, not all simulation parameters have both simulation and physical values because they are not needed. For example, the blood vessel density's physical value was carefully chosen to be 1 pg/μm through manipulations of the particle mass, particle insertion, and vessel geometry. Converting it to simulation value is definitely doable, but the extra work is useless. On the other hand, the force or force potential parameters were manipulated during the simulation tests in order to yield good qualitative result. These force models are, after all, bold approximations of complicated real-life chemical processes. Therefore, their strength parameters have little physical significance and physical values are not shown.

Another important parameter is T from the DPD model. This parameter was originally used to represent temperature in a molecular system and is connected with energy through the equipartition theorem. However, since the simulation model in this study is at the mesoscale, the parameter T and the calculated energy values through standard Molecular Dynamics algorithms no longer have the same physical significance. The value T is merely a parameter that controls how the particles exhibit certain movements like the dissipative force.

Graphical Analysis

Figure 1 and 2 as simulation snapshots show the simulations' boundary conditions. For all 7 groups, fixed boundary conditions were used, meaning that new particles will be inserted at one end and exit at the other end. Unlike the periodic boundary condition where exited particles re-enter the simulation box at the opposite end, all exited particles were destroyed in the memory. Fixed boundary conditions were used because the periodic boundary conditions in Lammps require the two ends to be facing each other, which was doable in the straight vessel but not curved ones. Extra coding could be implemented to make periodic boundary work in torus, but it was not considered due to the time constraint of this research.

An advantage of fixed boundary conditions is that new particles entering the simulation box were not influenced by the curvature. Since the curvature could lead to skews in velocity profile (Koutsiaris, 2009), the re-entering particles could lead to unwanted result. The disadvantage, on the other hand, is that the regions near the two ends do not have particles to interact with, which in real life the long blood vessel is continuous. After all, the final thrombus shape as shown by figure 3, is qualitatively similar to the experimental result of thrombus shape (Begent & Born, 1970).

Figure 4 shows the differences in the final thrombus size among the seven groups. The final thrombus size is directly proportional to the rate of thrombus growth and the error bars indicate significant differences between straight vessel group and curved vessel groups. For example, between group "0" and group "1/40", their error bars do not overlap at all, suggesting that their final thrombus sizes are significantly different. As shown in figure 5, the growth curve within a straight blood vessel is significantly different from the growth curve within a curved blood vessel. The thrombus in the curved vessel had consistent higher rate of growth throughout the simulation. However, from figure 4 and 6, thrombus growths in the experimental groups do not show significant differences. This may due to the small variation of blood vessel curvature, especially when the blood vessel's diameter is comparable to the radius of curvature.

Conclusion

Overall, the simulation results of this research strongly suggest that blood vessel's curvature has a significant effect on thrombus growth, that the presence of curvature will increase the thrombus growth rate. Although the simulation results may not exactly match with thrombus growth in reality, this research provides a plausible argument about the possible effects of blood vessel's curvature on thrombus growth. At the same time, the research results do not support the hypothesis about the effects of increasing the curvature's magnitude as the trendline in its limited domain does not show an increase in growth rate.

Limitations and Future Directions

DPD is a simulation method that models complex fluid as equal-size simple spherical particles. The real biological fluid is much more complex and each DPD particle represents a small mesoscopic component of the blood fluid. Although DPD method simplifies the biological condition in real life, it still yields close results with adjusted parameters (Moeendarbary et al., 2009). In the future, well-designed physical experiments should be carried on to confirm or reject the results from simulation models.

Another assumption for this research is the absence of red blood cells. Red blood cells occupy the space near the blood vessel's primary axis and push platelets towards the vessel wall (Tosenberger et al., 2015). At the same time, red blood cells also exhibit significant deformation and make the interaction even more complex (Dao et al., 2005). To improve the simulation model, correctly shaped and deformable red blood cells should be included along with platelets and fluid particles.

Thirdly, platelets go through complex biological interactions in order to become activated and change into a "sticky" mesh shape (Byrnes & Wolberg, 2017). This simulation model instead

used a simplified attractive force to mimic platelet aggregation and skips the activation process. Despite this simplification, qualitative analysis of the simulation still shows that the platelets are still affected by the fluid flow, and not all platelets within the adhesion force range join he thrombus. The platelet adhesion model also assumes that the platelet aggregation precedes platelet activation. This assumption is supported by some biological observations (Kulkarni et al., 2000; Jen et al., 1990; Tosenberger et al., 2015) and justifies the platelet pairwise function. Thus, this assumption has not yet been disproved by any physical observations.

Fourthly, the blood's velocity profile was also simplified with a uniform velocity profile, where in reality the velocity profile should be more parabolic depending on the viscosity. A power-law velocity profile model for blood could significantly improve this (Sequeira & Janela, 2007).

Discrete mesoscale simulation models are important tools for investigating thrombosis mechanisms, and the effects of curvature should be considered in future studies. Experimental studies on the effects of blood vessel curvature in a biomedical lab should be carried out to verify or reject the simulation results.

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