Computational Modelling of Device-induced Thrombosis

Undergraduate Thesis Mid-semester Report

Submitted in partial fulfillment of the requirements of

BITS F422T Thesis

By

Saurav Shenoy P.

ID No. 2016B4A40493P

Under the supervision of:

Dr. Bhupendra Kumar Sharma

BIRLA INSTITUTE OF TECHNOLOGY AND SCIENCE PILANI,

PILANI CAMPUS

April 2021

Declaration of Authorship

I, Saurav Shenoy P., declare that this Undergraduate Thesis Mid-semester Report titled, 'Computational Modelling of Device-induced Thrombosis' and the work presented in it are my own. I confirm that:

- This work was done wholly or mainly while in candidature for a research degree at this University.
- Where any part of this thesis has previously been submitted for a degree or any other qualification at this University or any other institution, this has been clearly stated.
- Where I have consulted the published work of others, this is always clearly attributed.
- Where I have quoted from the work of others, the source is always given. With the exception of such quotations, this thesis is entirely my own work.
- I have acknowledged all main sources of help.
- Where the thesis is based on work done by myself jointly with others, I have made clear exactly what was done by others and what I have contributed myself.

Signed: _____

Date: _____

Certificate

This is to certify that the thesis entitled, "*Computational Modelling of Device-induced Thrombosis*" and submitted by Saurav Shenoy P. ID No. 2016B4A40493P in partial fulfillment of the requirements of BITS F422T Thesis embodies the work done by him under my supervision.

Supervisor

Dr. Bhupendra Kumar Sharma

Associate Professor,

BITS-Pilani Pilani Campus

Date:

BIRLA INSTITUTE OF TECHNOLOGY AND SCIENCE PILANI, PILANI CAMPUS

Abstract

Master of Science (Hons.)

Computational Modelling of Device-induced Thrombosis

by Saurav Shenoy P.

Device-induced thrombosis is a major risk factor in blood-contacting medical devices. This mode of thrombosis occurs through a pathway that is distinct from the thrombosis caused by vascular injury, and hence has only risen as an issue after the last few decades have seen brisk progress in device development. Since device development and testing can be an expensive process, computer simulations have seen heavy use in a bid to reduce costs. To improve simulations, better mathematical models of thrombosis must be formulated, keeping in mind the computational costs and the accuracy of the outcomes. In this thesis, a model proposed by Taylor et al. is chosen and validated. Since this model is only valid for laminar flow and low shear rates, it is modified to handle turbulent flows and high shear rates, which are commonly seen in arterial flows and flow in stenosed vessels.

Acknowledgements

I would like to thank Dr. Sharma for guiding me in my thesis and providing a foundation for me to study and conduct research in a nascent field of science.

I would like to thank Mr. Umesh Khanduri for the regular discussions and feedback, and for helping me conduct simulations.

I would like to thank Dr. Aneesh A. M., and Dr. Anirudh Singh Rana for introducing me to CFD and helping me understand the concepts and good practices in the field.

I would like to thank Dr. Abhik Choudhury for getting me started with OpenFOAM, a skill without which I would not have been able to conduct the research in my thesis.

Lastly, I would like to thank my friends and family who have been by my side during tough times, pushing me on to not give up.

Contents

List of Figures

List of Tables

Chapter 1

Introduction

1.1 Motivation & Background

Advances in medical technology in the past few decades have empowered the use of blood-contacting devices to aid blood circulation in individuals with cardiovascular conditions. Such devices have been used to augment heart function as in the case of Ventricular Assist Devices (VADs, for short), or to serve as replacements for heart valves, or in the form of stents to reduce the effects of occluded blood vessels.

These devices need to be biocompatible in order to reduce the risk of biofouling of blood[5]. This involves the adsorption of blood proteins onto the surface of the medical device, which then leads to the adhesion of platelets onto the surface. These platelets can then get activated under the effect of shear stress or agonists, starting a feedback loop that results in the aggregation of platelets at the surface. This aggregate is called a clot or thrombus. The process of thrombus formation is termed thrombosis, and is a serious condition that must be treated swiftly.

The growing thrombus can eventually occlude, or block vessels, reducing the blood flow. This condition is called occlusion. It can also break under the influence of the flow, and create blockages at other parts of the vascular system. One such condition, that is a leading cause of deaths globally, is pulmonary embolism. Here, embolism refers to the

embolus, which is the medical term for a thrombus that has been mobilised in the blood stream.

Mitigating the risk of thrombosis is therefore a major design factor for medical devices. This can be done either by conducting experimental in-vivo or in-vitro tests, or by conducting in-silico simulations. Since the process of experimentation is expensive, time-consuming, and subject to bioethical standards, there is a need for a computational model of thrombosis. Such a computational model must balance computational costs with biological complexity, since for most practical purposes only a macroscopic prediction of thrombosis is necessary.

All computational models must satisfy Virchow's triad, which states that any of three key conditions — hypercoaguability of blood, haemodynamic factors like high shear rates or stasis, and material surface interactions — must be present for thrombosis to occur[17]. A good mathematical model must account for the effects of all the three conditions.

1.2 Literature Survey

The biological pathway of thrombosis is dependant on the mode of activation of platelets. The two most common pathways are one that is initiated by endothelial damage, and the other that is initiated by the presence of a medical device in the system. A thorough review of the former pathway can be found in an article by Furie & Furie[2]. For a thorough review on the medical device case, a series of review articles by leading experts is referred[22,6,16,26].

The modelling of thrombosis kicked off when Fogelson published a method to model platelet aggregation in 1992. He treated the platelets on a continuum rather than discretely, enabling them to be described by a convection-diffusion-reaction type equation[12]. Building on this work, Sorenson et al. came out with a model that could simulate thrombosis in the presence of ADP, prothrombin, thrombin, anti-thrombin, and thromboxane A2 in 1999[33]. This work was the first to give a complete model of the coagulation processes and the platelet interactions.

Goodman et al. in 2005 built what is believed to be the first model for device-induced thrombosis specifically. This model had a validated approach for the embolization process, but it was only at a molecular level. The primary activator of platelets were agonists, but mechanical activation of surface adherent platelets was included as well[15]. The solid thrombus was treated as a highly viscous liquid, in order to address the effect of a growing thrombus on the fluid flow.

Building on the work of Fogelson, Sorenson, and Goodman, models were published independently by Taylor et al. and Wu et al. in the mid-2010s[36,42]. The Taylor model focussed on simplifying the thrombosis model, in order to increase the utility for rapid testing and prototyping of medical devices, while the Wu model built directly on the Sorenson model to include capabilities of fluid-solid interaction[41], which was done by treating the thrombus as a packed spherical bed, and to add shear-induced platelet activation (SIPA). They then followed this model up with a stenosis/arterial thrombosis model that is designed to handle high shear flows and the effects of the von Willebrand factor[43].

The Taylor model treats the thrombus as a porous medium, modelled using a Brinkman term in the Navier-Stokes equations. The porosity is indirectly determined using a novel aggregation intensity function, building on the work of Leiderman and Fogelson[24]. The model also relies heavily on the shear activation of platelets rather than through ADP, unlike other models. This model only uses ADP as a chemical species, while the Wu model uses 5. It also has only two states for the platelets while the Wu model classifies platelets into 5 categories.

A third contemporary model was given by Rojano et al.[27], but it is based on the factor XII activation system, which is still unexplored largely. The Rojano model is a novel model that builds on the work of Chatterjee et al.[7]. In his thesis, Rojano has coupled the factor XII contact system with the Taylor model to present a complete model of thrombosis, but the results are not too different from the Taylor results, suggesting there is more here than meets the eye.

1.3 Objectives

- To implement and validate a state-of-the-art computational model of device-induced thrombosis
- To extend the thrombosis model to include von Willebrand factor and turbulence, thus enabling its application to arterial devices and stenotic models
- To evaluate the thrombotic potential of real-world medical devices like stents or catheters using the extended model

Chapter 2

Thrombosis Modelling

2.1 Biological Background

Virchow's triad provides guidelines to determine the factors needed to describe a mathematical model for thrombosis. The three conditions, namely haemodynamic factors, biomaterial surface interactions, and hypercoagubility, need to be addressed. The biology of the thrombosis process is dependant on which conditions are satisfied in the system. In the case of device-induced thrombosis, only the former two conditions are present. Before detailing the mathematical model of thrombosis, a brief biological background is presented. A flowchart of the cascade can be seen in 2.1.

2.1.1 Protein Adsorption and Platelet Adhesion

In the case of deviced-induced thrombosis, the adsorption of proteins onto the device surface initiates thrombosis. This phenomenon, in which a thin layer of proteins is formed on the surface, is known as the Vroman effect[40]. This protein layer, which consists of factor XII, fibrinogen, and von Willebrand factor among other proteins, can then capture platelets from the blood stream and create platelet aggregates. Depending on the participating protein, and the shear stress of the blood flow, the pathway can then vary, but all of them require the presence of a Vroman protein layer[17,22].

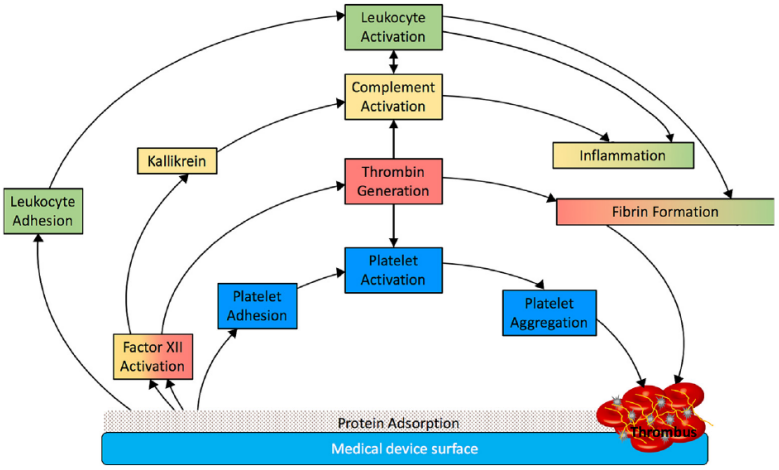


FIGURE 2.1: Flowchart of device-induced thrombosis. Figure reproduced from a review article by Jaffer et al.[22]

Human blood contains hundreds of different species of proteins[1], all of which are believed to be capable of adsorbing onto surfaces[18]. This layer of proteins covers the entire surface and is a single molecule thick. Not all of these proteins have thrombogenic potential. Some proteins, like factor XII (FXII), high molecular weight kininogen (HMWK), and prekallikrein (PKK) can initiate the coagulation of plasma. The intrinsic pathway involving these proteins is largely not understood, but a handful of mathematical models have been formulated based on it[27,7]. In fact, the significance of this pathway was discovered only in 2005 by Renne et al[29]. For a detailed description, the PhD thesis of Rojano can be referred[27]. In simple terms, FXII is the most important protein in this pathway, as it triggers the conversion of thrombin from prothrombin, which is found on the surface of platelets, and also induces complement activation. This starts a feedback loop that amplifies the production of thrombin, which is a major coagulant of blood[19]. Thrombin converts surface-adherent fibrinogen to fibrin, which along with platelets form clots[2].

The other major protein that triggers thrombosis is the von Willebrand factor (vWF). This protein changes its receptivity to platelets under the influence of high shear rates ($> 3000s^{-1}$)[30]. This causes platelets to adhere to the surface through the captured vWF. While some studies have been conducted on the effects of varying vWF concentration, its specific role and the concentration required to play a major role in clotting is still unstudied[6]. Together, the pathways introduced in this subsection satisfy the surface interaction condition of Virchow's triad.

2.1.2 Platelet Activation

Platelet activation can take place either through chemical reactions or through mechanical activation. Once the platelets are captured on the surface, the probability of activation vastly increases. The process of activation is an important driver of a feedback loop that activates more platelets, amplifying the adhesion and aggregation of platelets into a thrombus.

Activated platelets release and synthesise agonist biomolecules like adenosine diphosphate (ADP) and thromboxane A2 (TxA2), which further activate platelets from the bloodstream. vWF has also been found to release ADP molecules upon activation[8]. The other important activator of platelets is shear accumulation. This mode can occur over time because of the shear stress that acts on a platelet. It is believed that platelets that have not been inactivated but have adhered to a surface or another platelet can be activated via this mode. In the case of vWF, since it is usually found in regions of high shear, the activation of platelets is rapid once captured[11]. This satisfies the haemodynamic factor condition of Virchow's triad.

2.1.3 Platelet Aggregation

At lower shear rates, the aggregation of platelets is driven by the conversion of fibrinogen to fibrin, which stabilises the activated platelets. Three key elements are required for the establishment of platelet-platelet bridges, namely a plasma protein (mostly fibrinogen), a platelet surface receptor, and an agonist (thrombin in the case of fibrinogen)[21]. The feedback amplification processes mentioned in the preceding subsections drive the aggregation through the production of thrombin and activation of platelets.

At higher shear rates, vWF plays a big role, making it critical to all three stages of the platelet transformation. Along with fibronectin, which is also sensitive to mechanical shear, vWF is believed to provide a large surface area with an array of platelet receptors binding site that greatly increases the rate of platelet-platelet interactions. The activity of fibrinogen is seen to decrease under such conditions[21].

2.1.4 Embolization

Once the platelets have aggregated and a thrombus is formed, it is susceptible to breakdown under the effect of shear stress due to the blood flow. While it mostly occurs at a cellular level with only a few platelets breaking away at any instant, the risk of a large fraction of the thrombus breaking off is significant. This breakaway thrombus, called an embolus, can cause infarctions if it lodges itself downstream. Beyond the rupture of platelet-platelet bridges due to the effect of shear, not much is known about the mechanism of embolization, requiring a lot of further research. It has been observed that clots with a higher percentage of fibrin can withstand vastly higher shear rates than clots with no fibrin ($83,000s^{-1}$ vs. $5,300s^{-1}$)[9]. Such clots, with high fibrin concentration, are known as white clots and are known to form in flow with higher shear rates and Reynolds numbers, where embolization is certain for red clots, which are rich in RBCs but not in fibrin[10]

2.2 Taylor's Mathematical Model

For the purpose of analysis and simulation, it is necessary to translate the biological mechanisms of thrombosis into the language of mathematical equations. Depending on the scale of space and time required for the study, the approach required for modelling can vary.

For instance, a multi-scale model, which would most likely aim to couple the macroscopic effects of blood flow with microscopic scale interactions between cells and molecules, would need to take a mixed Eulerian-Lagrangian approach. Such models would require the use of convection-diffusion-reaction (or CDR, for short) equations to determine the concentration of some species like for example, thrombin, and lattice models for calculating the energy interactions between individual cells[44]. Multi-scale models offer superior accuracy and can resolve concentration fields for various species, but are computationally expensive. In the context of medical device development, where the composition of the thrombus is not as important as the information about the location and growth of the thrombus as a whole, keeping computational complexity down is critical.

Hence, in this section, only the development of a single-scale model, specifically the model published by Taylor, et al. is described.[36]

The Taylor model is one the few state-of-the-art models in the field of device thrombosis. The main features of the model are the mathematical simplicity and the accuracy of macroscopic thrombus predictions. It builds on the works of Fogelson and Leiderman[12,24] to mainly address the fluid-solid interaction between the blood flow and the thrombus in a novel manner, and the effect of mechanical shear in a device-induced setting.

Most validated single-scale models in the literature employ CDR equations for the modelling of reacting species. These equations account for all the possible modes of scalar transport in haemodynamic flow, and are coupled with it via the velocity in the convection term. These equations are of the form

$$\frac{\partial Q}{\partial t} + (\boldsymbol{u} \cdot \nabla) Q = D \nabla^2 Q + R \tag{2.1}$$

where Q is the unit concentration of the reacting species, $\boldsymbol{u}$ is the velocity of the flow, D is the diffusivity of species Q, and R is a reaction term for Q.

The boundary conditions for these equations describe the platelet-platelet and platelet-surface adhesion by making use of reactive wall flux conditions. These can sufficiently describe the formation of the protein monolayer at the surface, and also serve as the initiator of the thrombosis in simulations[33]. Since the Taylor model simplifies these boundary conditions by treating the cells neighbouring the walls specially, further description of these equations are skipped.

The reaction term for the activated platelet equation accounts for the activation of platelets from inactivated platelets, and is hence equal in magnitude but opposite in sign to the reaction term for the inactivated platelet equation. The only agonist included in this model is ADP as it is thought to be the most important activator of platelets[13]. Each platelet releases $\lambda = 2.4 - 3.0 \times 10^{-8}$ nmol of ADP, which means that the reaction

term for the ADP transport equation can be obtained by multiplying this factor with the activated platelet reaction term.

Since the activation of platelets is reliant on chemical factors and mechanical factors, the effects of both must be quantified. The chemical activation is solely regulated by ADP, and is activated only after a threshold concentration ADP_t of $2\mu M$ is reached[14,33]. The time characteristic time for activation must also be included to account for the rate of the activation. The chemical activation term is thus given as

$$A_C(ADP) = \begin{cases} 0 & \text{for } \frac{ADP}{ADP_t} < 1 \\ \frac{ADP}{(ADP_t)(t_{ADP})} & \text{for } \frac{ADP}{ADP_t} \geq 1 \end{cases} \tag{2.2}$$

The mechanical activation of platelets is dependant on the shear stress history of the individual platelets, which is obviously a problem for a Lagrangian framework. Since the model is fully Eulerian, the shear accumulation on the platelets must be quantified using an Eulerian approach. Soares et al. gave a power law approximation for this, which requires only the scalar shear stress at any instant, thus neglecting the accumulated shear and the characteristic time required for the activation[32]. The scalar shear stress τ is calculated using the shear stress tensor σ as follows

$$\sigma = -\nu\rho(\nabla \boldsymbol{u} + \nabla \boldsymbol{u}^T) \tag{2.3}$$

where nu is the kinematic viscosity of blood, and rho is the density of blood.

$$\tau = \frac{1}{\sqrt{3}}\sqrt{\sigma_{xx}^2 + \sigma_{yy}^2 + \sigma_{zz}^2 - \sigma_{xx}\sigma_{yy} - \sigma_{xx}\sigma_{zz} - \sigma_{yy}\sigma_{zz} + 3(\sigma_{xy}^2 + \sigma_{xz}^2 + \sigma_{yz}^2)} \tag{2.4}$$

The obtained scalar shear stress is then plugged into the Soares power law equation that is given by

$$A_M(\phi_f, \tau) = (1 - \phi_f)C^{\frac{1}{\beta}}\beta\phi_f^{\frac{\beta-1}{\beta}}\tau^{\frac{\alpha}{\beta}} \tag{2.5}$$

where ϕ_f is the fraction of activated platelets, and C, α and β are empirical constants that are determined from experimental data. This gives the reaction term for the activated platelet equation as follows

$$R_{phi_a} = [A_C(ADP)]\phi_n + [A_M(\phi_f, \tau)](\phi_a + \phi n)$$

Since $\phi_f = \phi_a/(\phi_a + \phi_n)$, this can be manipulated to simplify the reaction terms to require only the concentration of non-activaed platelets, reducing the number of mathematical operations required. The reaction terms can then be given as

$$\begin{aligned} R_{\phi_a} &= \phi_n[A_C(ADP) + c^{\frac{1}{\beta}}\beta\phi_f^{\frac{\beta-1}{\beta}}\tau^{\frac{\alpha}{\beta}}] \\ &= -R_{\phi_n} \\ &= \lambda R_{ADP} \end{aligned} \tag{2.6}$$

The novel feature of the Taylor model is the aggregation intensity ϵ, which is a non-physical parameter that is used to quantify the growth of the thrombus. This parameter is coupled to the flow equations, serving as a measure of the porosity of the thrombus. It also determines the likelihood of thrombus breakdown, though this feature not been validated in any study. The evolution equation for ϵ is given by

$$\frac{\partial \epsilon}{\partial t} = \alpha_\epsilon P_{TSP}(\tau_w)\phi_a^2 - \beta_\epsilon(\tau_w)\epsilon \tag{2.7}$$

where α_ϵ is a constant that controls the formation and growth of the thrombus. The two functions $P_TSP(\tau_w)$ and $\beta_\epsilon(\tau_w)$ are functions that quantify the likelihood of deposition and breakdown under shear, respectively. The former funtion is called the thrombus susceptibility equation, and was first described my Medvitz et al.[38]. It is a probability function that gives the likelihood of deposition under shear stress. The latter function is a thrombus breakdown rate, and is taken to be constant in the current model. As mentioned earlier, it has not been validated due to the lack of embolization data in the literature. Here, the wall shear stress is calculated as the product of the dynamic viscosity and the norm of the gradient of the velocity.

$$P_{TSP}(\tau_w) = \begin{cases} 1 & \text{for } |\tau_w| \leq \tau_{low} \\ 1 - \frac{|\tau_w|}{\tau_{high}} \cdot \frac{e^{\frac{|\tau_w| - \tau_{low}}{\tau_{high} - \tau_{low}}} - 1}{e-1} & \text{for } \tau_{low} < |\tau_w| < \tau_{high} \\ 0 & \text{for } |\tau_w| \geq \tau_{high} \end{cases} \tag{2.8}$$

$$\beta_\epsilon(\tau_w) = \begin{cases} 0 & \text{for } |\tau_w < \tau_{breakdown} \\ B & \text{for } |\tau_w \geq \tau_{breakdown} \end{cases} \tag{2.9}$$

The simplification mentioned earlier about the reactive wall-flux boundary condition can be seen in the evaluation of the TSP. For thrombus deposition, it is only evaluated in cells which share a computational face with a wall. This means that deposition occurs only if the wall shear stress at a point is less than the threshold shear stress. Similarly, the function is only evaluated at cells that are inside the thrombus.That is, they have an aggregation intensity ϵ above a threshold aggregation intensity ϵ_t. It is also evaluated at cells which do not satisfy this condition but are neighbours with a cell that does, thus allowing for the growth of the thrombus.

With the reactions and the aggregation intensity defined, we can give the modified laminar Navier-Stokes equations as

$$\nabla \cdot \boldsymbol{u} = 0 \tag{2.10}$$

$$\frac{\partial \boldsymbol{u}}{\partial t} + (\boldsymbol{u} \cdot \nabla)\boldsymbol{u} = -\frac{1}{\rho}\nabla p + \nu \nabla^2 \boldsymbol{u} - \nu F(\epsilon)\boldsymbol{u} \tag{2.11}$$

The extra term in the momentum equation is a modified Brinkman term. This term couples the aggregation intensity with the velocity and pressure fields, and it behaves as a resistive force. Since the aggregation intensity is unbounded, as can be seen in its evolution equation, it needs to be transformed to mimic porosity and to bound it to a maximum value of 1. This is done using the function $F(\epsilon)$, which is given as

$$F(\epsilon) = \begin{cases} 0 & \text{if } \epsilon < \epsilon_t \\ \frac{1}{k} \frac{\frac{\epsilon}{\epsilon_t}}{\frac{\epsilon}{\epsilon_t} + 1} & \text{if } \epsilon > \epsilon_t \end{cases} \tag{2.12}$$

The step-by-step procedure for the model is as follows[27]

1. The shear stress field triggers the mechanical activation of platelets, and the growth of the aggregation intensity at the walls. ADP production also begins as a result of the activation.

2. The aggregation intensity grows in regions of low shear until it crosses the aggregation threshold, at which point all neighbouring cells are also eligible to be evaluated using TSP.

3. The growing thrombus is mapped by the aggregation intensity, and its effects can be seen in the velocity field and the shear stress field.

4. Once the ADP threshold is crossed, the chemical activation term also adds to the reaction equations. Since this is large in compared to mechanical activation, the concentration of activated platelets increases rapidly, and thus also the aggregation intensity, which is squarely proportional to the concentration of activated platelets.

2.3 Modifications to the Taylor Model

While the Taylor model has shown good agreement with in-vitro data collected by Taylor et al.[37], it does not address some thrombus growth that is seen in the simulations but not in the in-vitro data. Rojano[27], in his thesis corrects this by using an arbitrary pulsatile inlet, suggesting that the model needs some modifications. Also, the model currently can not be used in a high shear flow, since it does not include the effects of von Willebrand factor, or that of turbulence. To account for these effects, and to thereby extend this model to simulate thrombosis in arterial and stenotic flows, some modifications are made.

There is a lack of experimental data for thrombus growth in the case of arterial devices, but the availability of stenosis clot growth means that models can still be developed for it. This is because both cases see the same two important clotting factors as an addition when compared to venous device flows - turbulence and von Willebrand factor.

2.3.1 Turbulence

Shear activation of platelets has been seen to be higher and quicker in turbulent flow, and is thought to be a result of the eddies that platelets flow through. While the instantaneous shear stress on the platelets may not be much higher than in laminar flow, the increased exposure time to the shear results in higher levels of activation[28].

Very few publications in the literature have compared the thrombotic results between laminar flow and turbulent flow. Some early results published by Stein et al. have shown over 5 times more volume of clotting as a result of turbulent flow[34,31]. While no computational models for thrombosis have included turbulence in their models thus far, the increase of research and experimentation in models of stenosis means that results can be validated against stenosis data instead.

Studies have been conducted on the shear stress maps of turbulent flow by Bozzi et al. recently, in which they investigated the effects of different turbulence models on platelet activation[4]. Their work can directly be adapted into the Taylor model, since the activation is calculated using the power law model of Soares[32] et al., which needs the scalar shear stress to quantify the Lagrangian shear accumulation in an Eulerian form.

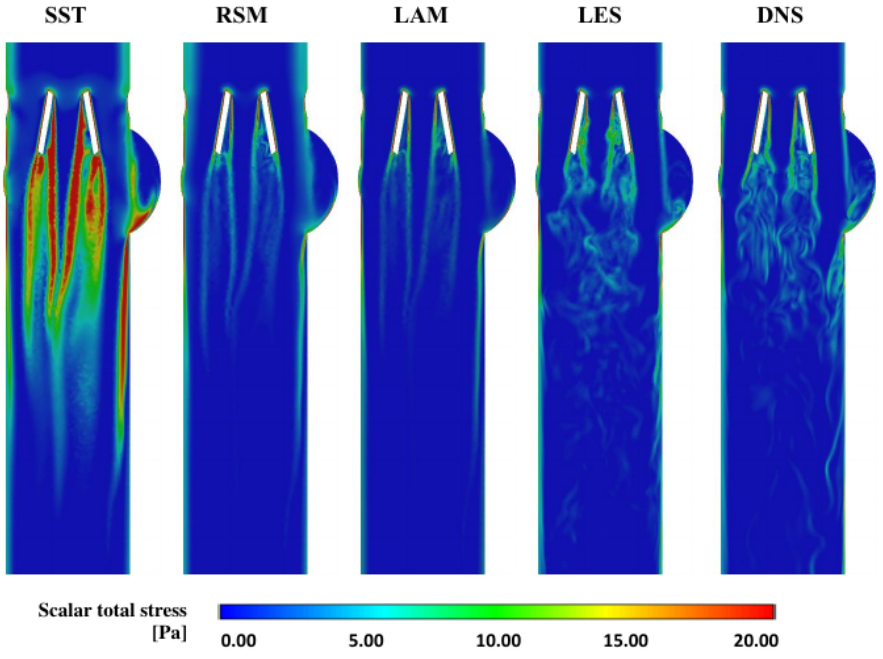


FIGURE 2.2: Comparison of scalar shear stress contours in various turbulence models[4]

Because of the computational cost involved, the choice of turbulence model is very important. Direct numerical simulation (DNS), is the most computational expensive model, but it produces excellent results because it resolves the domain to a fine scale, and then simulates the complete NS equations. Various models have been formulated to statistically approximate the effects of turbulence by averaging the velocity and viscosity fluctuations ($k-\omega$), or by using filters (LES). As can be seen in 2.2, the choice of model can make a significant difference. While the SST (same as $k-\omega$) model can introduce the effects of turbulence at a low computational cost, it's accuracy leaves a lot to be desired, with the shear stress results off by an order of magnitude. Since platelets and agonists are sensitive to shear stress, accuracy must take precedence. Clearly, the large eddy simulation model predicts the turbulent effects with highest accuracy, when compared to the DNS results.

It is proposed that the only necessary changes to the Taylor model to account for turbulence are the inclusion of turbulence in the momentum equation, which will depend on the model being used, and a change to the calculation of the stress tensor σ (Eq. 2.3). The modified stress tensor for the SST model and the LES model are given as

$$\sigma = (\mu + \mu_t)(\nabla \boldsymbol{u} + \nabla \boldsymbol{u}^T) \tag{2.13}$$

where μ_t is the turbulent viscosity, and $\boldsymbol{u}$ is the time-average velocity in the case of SST, and filtered velocity in the case of LES. Since the model is implemented numerically using OpenFOAM, the modification of the Navier-Stokes equations can be done by merely specifying the model required.

The effect of turbulence on the porous thrombus must also be evaluated. It can be assumed that the turbulence is restricted to the fluid domain, and need not be evaluated in the porous phase[23]. This assumption is valid at the macroscopic level, and while pore-scale turbulent structures can form, it is believed that these structures can not generate sufficient shear to cause the breakage of platelet-platelet interactions since the shear rate required for breaking fibrin is large. Thus it can be assumed that embolization will only occur at the surface. Since there are no studies or experiments on such cases of embolization, the validation of these features is difficult.

2.3.2 von Willebrand Factor

The von Willebrand factor is activated at shear rates above 3000 s^{-1}, and when activated, it rapidly increases the thrombosis rates in its vicinity. The platelet activation occurs via shear accumulation over a period of time, the period of time is dependant on the maximum shear stress to which the platelet is exposed.

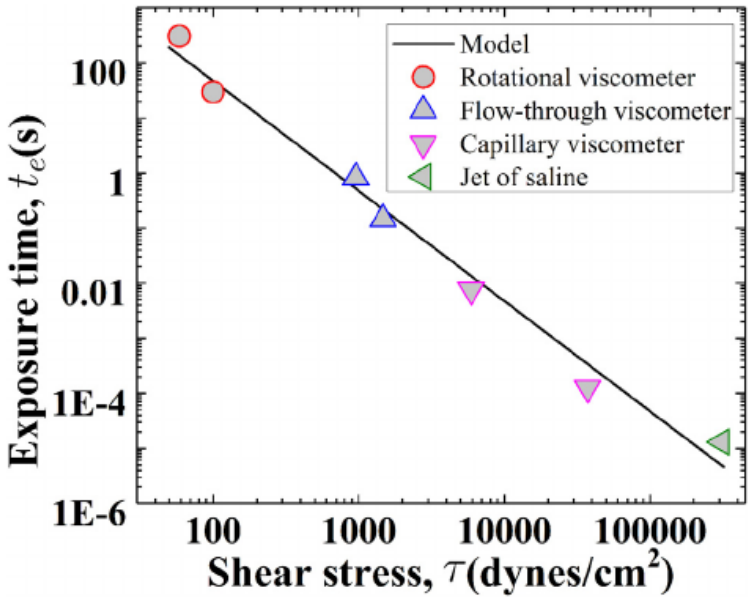


FIGURE 2.3: Exposure time vs shear stress for platelet activation[43]

So far, only the work by Wu et al. has devised a method to include the effects of von Willebrand factor in thrombosis simulations. Their model gives uses a shear accumulation model to determine the local stress accumulation of platelets, assuming it can be modelled on a continuum and can be transported via convection. A vWF concentration equation, which is dependent on the shear exposure as given by 2.3, is used to accelerate the increase of shear accumulation. This effect is quantified using an amplification function which varies a independent source term in the shear accumulation equation.

$$\frac{\partial SA}{\partial t} + div(\boldsymbol{u}SA) = f_{sa} - k_{pa}SA \tag{2.14}$$

The Wu formulation, can of course be directly implemented in the Taylor model, but the Taylor model uses a variable rate of shear activation, while the Wu model uses a constant rate. So, the factor $A_M(\phi_f, \tau_w)$ can be used at every time step. The shear accumulation field must then be coupled with the aggregation intensity equation. This is not a direct process and will require further study.

Chapter 3

Results and Conclusions

3.1 Methodology

The simulation of the mathematical thrombosis model is conducted using OpenFOAM[25]. A custom solver titled clotFoam, and based on pisoFoam[20], a packaged PISO-based solver for turbulent single-phase flow, is written to incorporate the necessary equations. PISO, which stands for Pressure-Implicit with Splitting of Operators, solves the momentum equation using a predictor-corrector method, and is designed to maintain continuity. It is based on the finite-volume method, just like the SIMPLE family of algorithms. For the case of steady-state flows, the SIMPLE algorithm is stable and quick, but this is not the case for transient problems as it requires multiple iterations every timestep[39]. The PISO method was designed specifically for transient problems, so it is more suitable for the thrombosis model. It is used to solve all the partial differential equations that the model employs.

3.1.1 The Backward-facing Step Case Validation

Before the solver is used, it must be validated to guarantee the reproducibility of the Taylor model, which does not have any open-source code published. To achieve this, the geometry that is used in the original validation is used. A backward facing step geometry

produces a region of re-circulation downstream of the step, which results in sufficiently low shear stresses for the thrombosis to initiate. 3.1 only contains a section of the geometry, as the entrance region has not been illustrated. A entrance region in accordance with the type of flow must be factored. Since the flow is laminar in this case, the length of the region can be calculated as[3]

$$L = 0.05 R_e \boldsymbol{D} \tag{3.1}$$

where R_e is the Reynolds number of the flow and D is the diameter of the pipe. In this case, the entrance length will be 183.75mm since the Reynolds number is 490 and the diameter is 7.5mm.

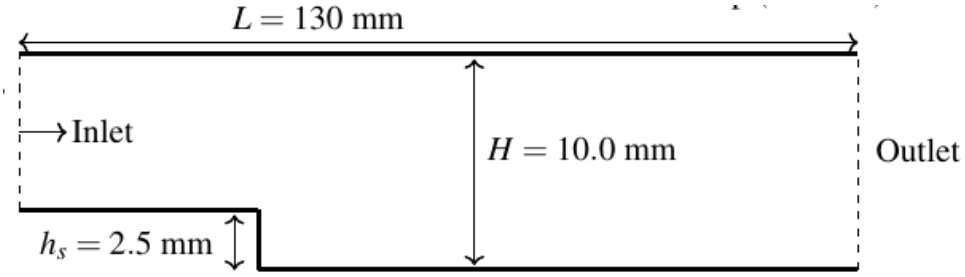


FIGURE 3.1: The backward-facing step geometry

The mesh for the geometry is created using blockMesh, which is an inbuilt text-based meshing tool in OpenFOAM. Since the computations had to be conducted on a system with a quad-core AMD processor, the mesh had to be kept coarse in order to reduce simulation time. According to the mesh independence study conducted by Taylor, a coarse mesh of roughly 6,000 cells will have an error in thrombus area of about 10% when compared to a fine mesh with 70,000 cells[35]. A nonuniform structured cartesian mesh is used, with higher cell density around the step. The boundary conditions are as follows

- The inlet is taken to be at a constant velocity of 0.229m/s. This gives a maximum velocity of 0.343m/s once the boundary layer has formed, in accordance with the in-vitro data.
- All the scalar quantities are taken to be fixed as 0, except for the two forms of platelets, which are fixed according to the percent activation assumed. In the case

of activated platelets, the entire domain and inlet are set to 25×10^{12}platelets per m^3. Similarly, inactivated platelets are set to $475 \times 10^{12} platelets per m^3$

- All walls are no-slip for velocity, and zero-gradient (zero flux) for scalars.
- The outlet pressure is set to 0 Pa, and the outlet velocity condition is zero gradient. The outlet condition for all the other scalar quantities is zero gradient.

Parameter	Value	Units
ν	3.5×10^{-6}	$m^2 s^{-1}$
D_{ϕ_n}	1.58×10^{-11}	$m^2 s^{-1}$
D_{ϕ_a}	1.58×10^{-11}	$m^2 s^{-1}$
D_{ADP}	2.37×10^{-10}	$m^2 s^{-1}$
C	1.4854×10^{-07}	-
α	1.4854	-
β	1.4401	-
k	9.56×10^{-16}	m^2
λ	3×10^{-17}	mol
α_ϵ	3.7×10^{-11}	$m^3 s^{-1}$
B	2000	s^{-1}
ADP_t	1.2×10^{18}	mol m^{-3}
t_{ADP}	1	s
$\tau_{low,wall}$	0.02	Pa
$\tau_{high,wall}$	0.15	Pa
$\tau_{breakdown,wall}$	0.8	Pa
$\tau_{low,thrombus}$	0.1	Pa
$\tau_{high,thrombus}$	0.3	Pa
$\tau_{breakdown,thrombus}$	0.9	Pa
ϵ_t	5.25×10^{18}	m^{-3}
ρ	1.060×10^3	kgm^{-3}

TABLE 3.1: List of parameters

Operator	Scheme
Time derivative	Crank-Nicholson ($\psi = 0.9$)
Gradient	Gauss Linear
Divergence	Gauss Upwind
Laplacian	Gauss Linear Corrected
Interpolation	Linear

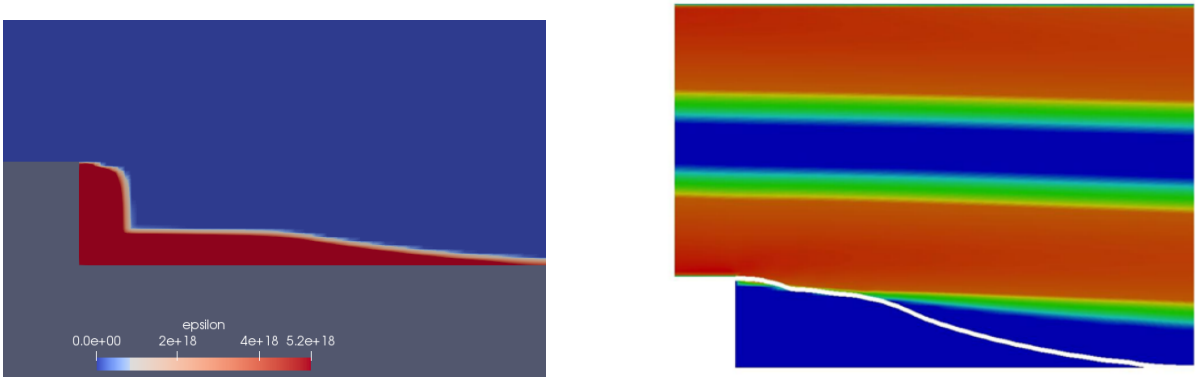
TABLE 3.2: List of numerical schemes

The timestep for the simulation must satisfy the Courant-Friedrich-Lewy criterion for stability, and since upwind schemes are being used, the calculated value must be smaller

than 1. OpenFOAM automatically chooses an appropriate timestep based on the mesh quality, and it was found that the maximum timestep for obtaining a stable solution is 1 ms. With this timestep, it took 30 hours of simulation time to obtain 30 minutes of thrombosis data.

3.2 Validation Results

For validation, the thrombus height and thrombus length are compared. The velocity and shear stress graphs are also verified.



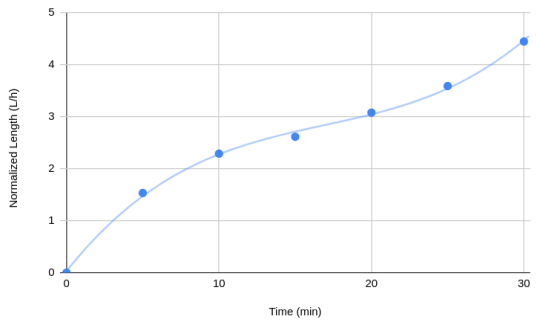
(A) clotFoam (B) Taylor simulation

FIGURE 3.2: Visual comparison of thrombus at t = 30 min

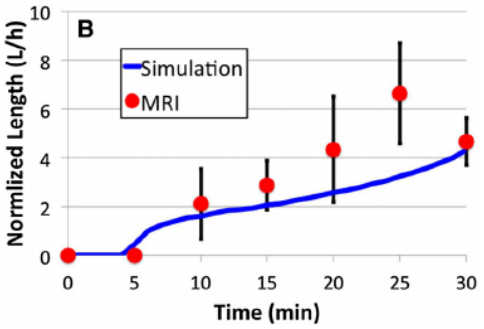
From 3.2, it can be seen that while the thrombus length and height are roughly equal, the area of the thrombus is not equal. This can be attributed to the coarseness of the mesh, which results in the neglecting of lower shear stresses at finer scales.

The length and height of the thrombus, measured along the wall of the geometry, is compared to the Taylor data after normalization in 3.4 and 3.3. This is done by using the thrombus step height 25mm as the scale. The length graphs show good agreement with the simulation, but the height in the clotFoam simulation increases very quickly. This can again be attributed to the coarse mesh, which doesn't resolve the wall shear stress well.

The effect of the porous thrombus can be seen in the velocity and shear stress graphs, where the quantity goes down to near zero, in 3.5.

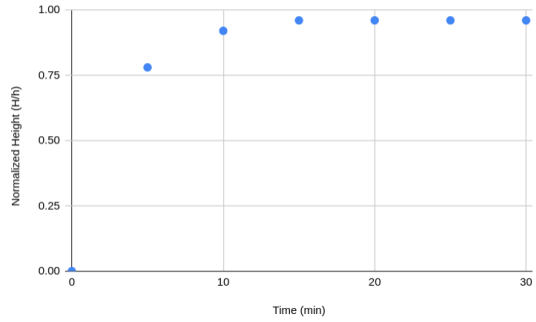


(A) clotFoam

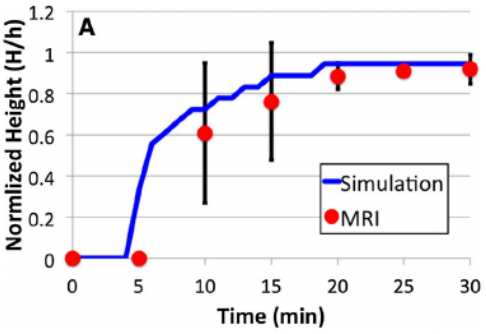


(B) Taylor simulation

FIGURE 3.3: Comparison of normalized length of the thrombus. Note: the range on the y-axis for the clotFoam simulation is shortened

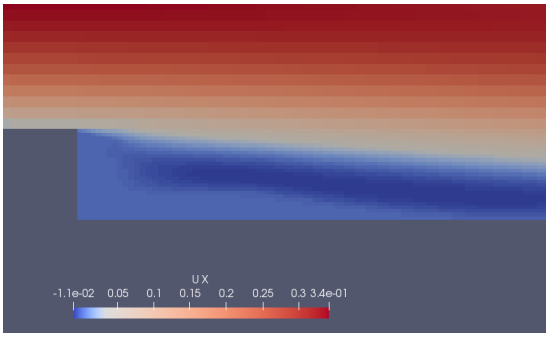


(A) clotFoam

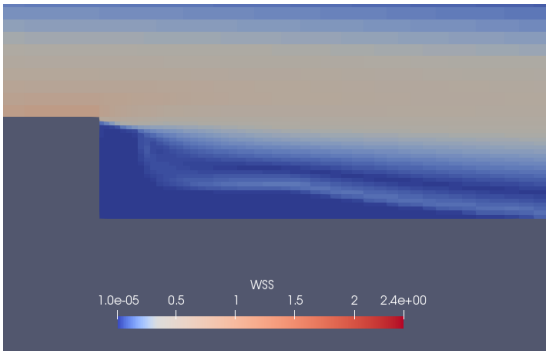


(B) Taylor simulation

FIGURE 3.4: Comparison of normalized height of the thrombus



(A) Axial velocity



(B) Scalar shear stress

FIGURE 3.5: Field values at t = 30 min

3.3 Conclusions & Future Work

The Taylor model of device-induced thrombosis has provided a good tool for engineers and scientists for use in the development and testing of medical devices. While it is not as accurate or complete as its contemporary models, it perhaps has the most utility owing

to its computational simplicity. While it is sensitive to mesh quality and Courant number restrictions on stability, the competing models in the literature require mesh cell counts an order of magnitude higher, only to produce similar results. It certainly can not be used for compositional studies on thrombi, but its ability to predict the macroscopic growth of thrombi is valuable nonetheless. Since code for the model is not available openly, the work conducted during this thesis can be published online for researchers without CFD expertise to use. The inclusion of turbulent effects and von Willebrand factor were also explored, but the findings were not incorporated fully into the model.

Future work can focus on the inclusion and validation of these factors. While experimental data is not available for turbulence's effect on thrombosis, the effects of vWF have been well-studied, and data for stenosis can be found in the literature for the purpose of validation. The inability to address embolization remains a major drawback of this model, and it can be revisited in the future if a valid model for embolization is published in the literature.

Bibliography

[1] N. Leigh Anderson et al. "The Human Plasma Proteome: A Nonredundant List Developed by Combination of Four Separate Sources*". In: *Molecular & Cellular Proteomics* 3.4 (2004), pp. 311–326. ISSN: 1535-9476. DOI: https://doi.org/10.1074/mcp.M300127-MCP200. URL: https://www.sciencedirect.com/science/article/pii/S1535947620348994.

[2] Furie B and Furie BC. "Mechanisms of Thrombus Formation". In: *N Engl J Med* 359 (Aug. 2008), pp. 938–49. DOI: 10.1056/NEJMra0801082.

[3] Theodore L. Bergman et al. *Fundamentals of Heat and Mass Transfer, 8th Edition.*

[4] Silvia Bozzi et al. "The Effect of Turbulence Modelling on the Assessment of Platelet Activation". In: (Dec. 2020). DOI: 10.21203/rs.3.rs-129700/v1.

[5] John L. Brash et al. "The blood compatibility challenge. Part 2: Protein adsorption phenomena governing blood reactivity". In: *Acta Biomaterialia* 94 (2019), pp. 11–24. ISSN: 1742-7061. DOI: https://doi.org/10.1016/j.actbio.2019.06.022. URL: https://www.sciencedirect.com/science/article/pii/S1742706119304337.

[6] John L. Brash et al. "The blood compatibility challenge. Part 2: Protein adsorption phenomena governing blood reactivity". In: *Acta Biomaterialia* 94 (2019), pp. 11–24. ISSN: 1742-7061. DOI: https://doi.org/10.1016/j.actbio.2019.06.022. URL: https://www.sciencedirect.com/science/article/pii/S1742706119304337.

[7] Kaushik Chatterjee et al. "Contributions of contact activation pathways of coagulation factor XII in plasma". English (US). In: *Journal of Biomedical Materials Research - Part A* 90.1 (July 2009). Copyright: Copyright 2009 Elsevier B.V., All rights reserved., pp. 27–34. ISSN: 1549-3296. DOI: 10.1002/jbm.a.32076.

[8] Thomas W. Chow et al. "Shear Stress-Induced von Willebrand Factor Binding to Platelet Glycoprotein lb Initiates Calcium Influx Associated With Aggregation". In: *Blood* 80.1 (1992), pp. 113–120. ISSN: 0006-4971. DOI: https://doi.org/10.1182/blood.V80.1.113.113. URL: https://www.sciencedirect.com/science/article/pii/S0006497120706622.

[9] Thomas V. Colace, Ryan W. Muthard, and Scott L. Diamond. "Thrombus Growth and Embolism on Tissue Factor-Bearing Collagen Surfaces Under Flow". In: *Arteriosclerosis, Thrombosis, and Vascular Biology* 32.6 (2012), pp. 1466–1476. DOI: 10.1161/ATVBAHA.112.249789. eprint: https://www.ahajournals.org/doi/pdf/10.1161/ATVBAHA.112.249789. URL: https://www.ahajournals.org/doi/abs/10.1161/ATVBAHA.112.249789.

[10] Scott L. Diamond. "Systems Analysis of Thrombus Formation". In: *Circulation Research* 118.9 (2016), pp. 1348–1362. DOI: 10.1161/CIRCRESAHA.115.306824. eprint: https://www.ahajournals.org/doi/pdf/10.1161/CIRCRESAHA.115.306824. URL: https://www.ahajournals.org/doi/abs/10.1161/CIRCRESAHA.115.306824.

[11] Jun Ding et al. "Quantification of Shear-Induced Platelet Activation: High Shear Stresses for Short Exposure Time". In: *Artificial Organs* 39.7 (2015), pp. 576–583. DOI: https://doi.org/10.1111/aor.12438. eprint: https://onlinelibrary.wiley.com/doi/pdf/10.1111/aor.12438. URL: https://onlinelibrary.wiley.com/doi/abs/10.1111/aor.12438.

[12] Aaron L. Fogelson. "Continuum Models of Platelet Aggregation: Formulation and Mechanical Properties". In: *SIAM Journal on Applied Mathematics* 52.4 (1992), pp. 1089–1110. DOI: 10.1137/0152064. eprint: https://doi.org/10.1137/0152064. URL: https://doi.org/10.1137/0152064.

[13] Aaron L. Fogelson and Robert D. Guy. "Immersed-boundary-type models of intravascular platelet aggregation". In: *Computer Methods in Applied Mechanics and Engineering* 197.25 (2008). Immersed Boundary Method and Its Extensions, pp. 2087–2104. ISSN: 0045-7825. DOI: https://doi.org/10.1016/j.cma.2007.06.030. URL: https://www.sciencedirect.com/science/article/pii/S0045782507002976.

[14] M Frojmovic and Truman Wong. "Dynamic measurements of the platelet membrane glycoprotein IIb-IIIa receptor for fibrinogen by flow cytometry. II. Platelet size-dependent subpopulations". In: *Biophysical journal* 59 (May 1991), pp. 828–37. DOI: 10.1016/S0006-3495(91)82295-0.

[15] Paul D. Goodman et al. "Computational Model of Device-Induced Thrombosis and Thromboembolism". In: *Annals of Biomedical Engineering* 33.6 (Jan. 2005), pp. 780–797. DOI: 10.1007/s10439-005-2951-z. URL: https://doi.org/10.1007/s10439-005-2951-z.

[16] Maud Gorbet et al. "The blood compatibility challenge. Part 3: Material associated activation of blood cascades and cells". In: *Acta Biomaterialia* 94 (2019), pp. 25–32. ISSN: 1742-7061. DOI: https://doi.org/10.1016/j.actbio.2019.06.020. URL: https://www.sciencedirect.com/science/article/pii/S1742706119304313.

[17] Jun Ki Hong et al. "Evaluating medical device and material thrombosis under flow: current and emerging technologies". In: *Biomater. Sci.* 8 (21 2020), pp. 5824–5845. DOI: 10.1039/D0BM01284J. URL: http://dx.doi.org/10.1039/D0BM01284J.

[18] Thomas A. Horbett and John L. Brash. "Proteins at Interfaces: Current Issues and Future Prospects". In: *American Chemical Society* 343 (1987). DOI: doi:10.1021/bk-1987-0343.ch001. URL: https://doi.org/10.1021/bk-1987-0343.ch001.

[19] Jaffer IH et al. "Medical Device-induced Thrombosis: What Causes It and How Can We Prevent It?" In: *J Thromb Haemost* 13 (Suppl. 1) (Jan. 2015), S72–S81.

[20] R.I Issa. "Solution of the implicitly discretised fluid flow equations by operator-splitting". In: *Journal of Computational Physics* 62.1 (1986), pp. 40–65. ISSN: 0021-9991. DOI: https://doi.org/10.1016/0021-9991(86)90099-9. URL: https://www.sciencedirect.com/science/article/pii/0021999186900999.

[21] Shaun P. Jackson. "The growing complexity of platelet aggregation". In: *Blood* 109.12 (June 2007), pp. 5087–5095. ISSN: 0006-4971. DOI: 10.1182/blood-2006-12-027698. eprint: https://ashpublications.org/blood/article-pdf/109/12/5087/1480063/zh801207005087.pdf. URL: https://doi.org/10.1182/blood-2006-12-027698.

[22] Iqbal H. Jaffer and Jeffrey I. Weitz. "The blood compatibility challenge. Part 1: Blood-contacting medical devices: The scope of the problem". In: *Acta Biomaterialia* 94 (2019), pp. 2–10. ISSN: 1742-7061. DOI: https://doi.org/10.1016/j.actbio.2019.06.021. URL: https://www.sciencedirect.com/science/article/pii/S1742706119304325.

[23] Y. Jin and A. V. Kuznetsov. "Turbulence modeling for flows in wall bounded porous media: An analysis based on direct numerical simulations". In: *Physics of Fluids* 29.4 (2017), p. 045102. DOI: 10.1063/1.4979062. eprint: https://doi.org/10.1063/1.4979062. URL: https://doi.org/10.1063/1.4979062.

[24] Karin Leiderman and Aaron L. Fogelson. "Grow with the flow: a spatial–temporal model of platelet deposition and blood coagulation under flow". In: *Mathematical Medicine and Biology: A Journal of the IMA* 28.1 (2011), pp. 47–84. DOI: 10.1093/imammb/dqq005.

[25] The OpenFOAM Foundation Ltd. *OpenFOAM*. URL: openfoam.org.

[26] Manfred F. Maitz et al. "The blood compatibility challenge. Part 4: Surface modification for hemocompatible materials: Passive and active approaches to guide blood-material interactions". In: *Acta Biomaterialia* 94 (2019), pp. 33–43. ISSN: 1742-7061. DOI: https://doi.org/10.1016/j.actbio.2019.06.019. URL: https://www.sciencedirect.com/science/article/pii/S1742706119304301.

[27] Rodrigo Mendez Rojano. "Thrombosis modeling in blood coated medical devices". 2018MONTS088. PhD thesis. 2018. URL: http://www.theses.fr/2018MONTS088/document.

[28] Khandakar Morshed et al. "Theory to Predict Shear Stress on Cells in Turbulent Blood Flow". In: *PloS one* 9 (Aug. 2014), e105357. DOI: 10.1371/journal.pone.0105357.

[29] Thomas Renné et al. "Defective thrombus formation in mice lacking coagulation factor XII ". In: *Journal of Experimental Medicine* 202.2 (July 2005), pp. 271–281. ISSN: 0022-1007. DOI: 10.1084/jem.20050664. eprint: https://rupress.org/jem/article-pdf/202/2/271/1154025/jem2022271.pdf. URL: https://doi.org/10.1084/jem.20050664.

[30] Minoo Shahidi. "Thrombosis and von Willebrand Factor". In: *Thrombosis and Embolism: from Research to Clinical Practice: Volume 1*. Ed. by Md. Shahidul Islam. Cham: Springer International Publishing, 2017, pp. 285–306. ISBN: 978-3-319-22108-3. DOI: 10.1007/5584_2016_122. URL: https://doi.org/10.1007/5584_2016_122.

[31] R. L. Smith et al. "Thrombus production by turbulence". In: *Journal of Applied Physiology* 32.2 (1972). PMID: 5007881, pp. 261–264. DOI: 10.1152/jappl.1972.32.2.261.

[32] João Soares, Jawaad Sheriff, and Danny Bluestein. "A novel mathematical model of activation and sensitization of platelets subjected to dynamic stress histories". In: *Biomechanics and modeling in mechanobiology* 12 (Jan. 2013). DOI: 10.1007/s10237-013-0469-0.

[33] Erik N. Sorensen et al. "Computational Simulation of Platelet Deposition and Activation: I. Model Development and Properties". In: *Annals of Biomedical Engineering* 27.4 (July 1999), pp. 436–448. DOI: 10.1114/1.200. URL: https://doi.org/10.1114/1.200.

[34] Paul D. Stein and Hani N. Sabbah. "Measured Turbulence and Its Effect on Thrombus Formation". In: *Circulation Research* 35.4 (1974), pp. 608–614. DOI: 10.1161/01.RES.35.4.608.

[35] Joshua O. Taylor. "Toward a Computational Model for Macroscopic Predictions of Device-induced Thrombosis". PhD thesis. 2015.

[36] Joshua O. Taylor et al. "Development of a computational model for macroscopic predictions of device-induced thrombosis". In: *Biomechanics and Modeling in Mechanobiology* 15.6 (Jan. 2016), pp. 1713–1731. DOI: 10.1007/s10237-016-0793-2. URL: https://doi.org/10.1007/s10237-016-0793-2.

[37] Joshua O. Taylor et al. "In Vitro Quantification of Time Dependent Thrombus Size Using Magnetic Resonance Imaging and Computational Simulations of Thrombus Surface Shear Stresses". In: *Journal of Biomedical Engineering* 136 (2014). ISSN: 7. DOI: https://doi.org/10.1115/1.40276132.

[38] Stephen Topper et al. "The Use of Fluid Mechanics to Predict Regions of Microscopic Thrombus Formation in Pulsatile VADs". In: *Cardiovascular engineering and technology* 5 (Mar. 2014), pp. 54–69. DOI: 10.1007/s13239-014-0174-x.

[39] H.K. Versteeg. *An Introduction to Computational Fluid Dynamics : the Finite Volume Method*.

[40] L Vroman et al. "Interaction of high molecular weight kininogen, factor XII, and fibrinogen in plasma at interfaces". In: *Blood* 55.1 (Jan. 1980), pp. 156–159.

[41] Wei-Tao Wu, Nadine Aubry, and Mehrdad Massoudi. "On the coefficients of the interaction forces in a two-phase flow of a fluid infused with particles". In: *International Journal of Non-Linear Mechanics* 59 (2014), pp. 76–82. ISSN: 0020-7462. DOI: https://doi.org/10.1016/j.ijnonlinmec.2013.11.006. URL: https://www.sciencedirect.com/science/article/pii/S0020746213002114.

[42] Wei-Tao Wu et al. "Multi-Constituent Simulation of Thrombus Deposition". In: *Scientific Reports* 7.1 (Feb. 2017). DOI: 0.1038/srep42720. URL: https://doi.org/10.1038/srep42720.

[43] Wei-Tao Wu et al. "Simulation of thrombosis in a stenotic microchannel: The effects of vWF-enhanced shear activation of platelets". In: *International Journal of Engineering Science* 147 (2020), p. 103206. ISSN: 0020-7225. DOI: https://doi.org/10.1016/j.ijengsci.2019.103206. URL: https://www.sciencedirect.com/science/article/pii/S0020722519322803.

[44] Zhiliang Xu et al. "A multiscale model of thrombus development". In: *Journal of The Royal Society Interface* 5.24 (2008), pp. 705–722. DOI: 10.1098/rsif.2007.1202.