EVALUATION OF A NUMERICAL THROMBOSIS MODEL FOR A HIGH SHEAR ROTATING FLOW

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ABSTRACT

Blood clotting, or thrombosis, is an interesting biological application for computational fluid dynamics. Existing numerical thrombosis models have previously been shown to be effective for low shear rates and simple geometries. For these models to be used in biomedical applications such as the design of rotary blood pumps, however, they must first be experimentally validated for high shear rates and complex geometries. In this study, we test the ability of a numerical thrombosis model to predict thrombosis related phenomena in a high shear flow by creating a geometry similar to that of a rotary blood pump. We have applied an existing numerical thrombosis model to an annular gap between rotating concentric cylinders, a geometry that is closely related to rotary blood pumps. Additionally, we created a physical model of the same geometry and exposed blood to a range of shear rates in both the empirical and numerical model. The empirical and numerical results are compared in order to evaluate the ability of the numerical model to predict thrombosis in similar geometries, such as high shear blood handling pumps.

Fluent was used to solve the coupled convective-diffusion equations along with user defined equations that include production and consumption of 7 species critical to thrombosis. These equations, along with equations of fluid motion, were solved iteratively within the Fluent solver. All reaction constants were from previously published work. At each of the shear rates and exposure times tested, the numerical model calculated platelet deposition, platelet-platelet aggregation and the two-dimensional distribution of three primary agonists (ADP, thromboxane and thrombin) in addition to the standard fluid variables (velocity, pressure, shear rate, etc.).

A physical model was designed and constructed to control the shear rate that to which blood is exposed. An annular gap of 360µm was chosen in order to induce a shear rate of up to 10,000 s⁻¹ while maintaining laminar flow. In a series of experiments, fresh, heparinized, bovine blood was exposed to a constant shear rate ranging from 1,000 to 10,000 s⁻¹ for 120 seconds. Prothrombin time (PT) and activated partial thromboplastin time (APTT) of the blood was then measured for each stress level.

While the observed changes in thromboembolic potential (as measured by PT and APTT) of the whole blood test samples qualitatively correspond to platelet activation and agonist concentration predicted by the numerical model, further work is needed to quantitatively verify the numerical model. Thrombosis models based on coupled convective-diffusion equations show promise, but need further refinement and validation before they can be trusted to authoritatively predict thromboembolic potential.

INTRODUCTION

Thrombosis, the formation of blood clots, remains one of the most significant challenges in the design of blood contacting medical devices such as implantable blood pumps, hemodialysis, and oxygenators [7]. An attached clot can grow until it obstructs the natural flow and a detached or suspended embolus may travel through the blood stream until it eventually obstructs a vessel. The design methodology of blood handling devices has progressed remarkably in the past years, largely because of the use of finite element analysis and computational fluid dynamics [3]. Nonetheless, the prediction of thrombosis in devices is unsatisfactory because there is not a validated model that can be used for the predictions.

Thrombosis is principally due to three factors: platelet transport, coagulation cascade, and haemodynamics. While considerable research has gone into studying the underlying mechanisms of thrombosis [2, 4, 5] these models are generally not quantitative enough to decidedly predict the occurrence of
thrombosis. While many studies of thrombosis focus on one of the three mechanisms in order to gain insight into specific area of the larger problem, the design process needs a single comprehensive model that includes effects of platelets, surface chemistry and haemodynamics. One of the more promising models was developed by Sorensen (1999) [15] and included platelets and 5 agonists, chemical species that are part of the biochemical cascade of thrombogenesis. The model accounts for the agonist induced activation of platelets, enhanced species diffusion, attachment of platelets to the solid surfaces, and convective and diffusive transport of platelets by the flow. Goodman (2005) [8] implemented the Sorensen model using Fluent, a commercially available CFD package and determined reaction rate constants of platelet deposition and embolization from his own experiments.

To date, this coagulation model has been applied to relatively simple geometries and flow regimes such as an abrupt cylindrical contraction or expansion [8], or physiological conditions of shear rate and material [15]. The model was compared to empirical data and was shown to be effective for these cases [8, 16]. However, the experimental data has been case dependent and more research is needed to determine how robust this numerical model is. Unlike physiological flows, the flow within blood prostheses is often characterized by high shear rates, bio-reactive materials, and turbulence. While the implementation of the model in Fluent make it feasible to apply the model to complex geometries such as mechanical blood pumps, the validity of the model in these applications is questionable because of both high shear rates and non-biological materials.

The objective of this study is to test the validity of applying these numerical models to a geometry that more closely resembles rotary blood pumps. Specifically, we use the annular flow between rotating cylinders to create a shear flow with controllable shear rate. We have implemented the thrombosis model on this geometry and conducted numerical experiments by varying the shear rate. Additionally, we have designed and constructed a mechanical apparatus to expose whole blood to the same conditions. We compare the numerical and empirical results in an effort to determine under what, if any, conditions the model is valid.

METHODS

Geometry.

An annular gap between rotating concentric-cylinders was chosen for its machinability and similarity to an axial flow blood pump (shown in Figure 1). The shear rate within the annular gap is varied by controlling the rotational speed. The maximum shear rate is 10,000 s^{-1}, which is typical of axial flow blood pump and higher than previously tested with this numerical model. The radial dimensions, angular velocity, and Reynolds number at this shear rate are listed in Table 1. The annular gap is 0.014 in (0.36 mm) in order to maintain laminar flow (Re < 1,500) over the range of rotational speeds. The outer cylinder is rotated in order to avoid any Taylor instabilities [11].

![Figure 1: Flow geometry](image)

Test Rig Design and Construction

A device (Figure 2) was designed and constructed for the purpose of exposing the blood to a known, constant and controlled shear rate. Natural polycarbonate was chosen for the blood contacting test section because of its optical clarity and its common usage in blood handling devices.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inner radius (mm)</td>
<td>16.3</td>
</tr>
<tr>
<td>Gap (mm)</td>
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</tr>
<tr>
<td>Angular velocity (rad/s)</td>
<td>445</td>
</tr>
<tr>
<td>Reynolds number</td>
<td>459</td>
</tr>
</tbody>
</table>

Based on blood viscosity of 3 cp and density of 1.06 g cm^{-3}

Blood Collection

Fresh, whole bovine blood was collected by relieving the hide and puncturing the carotid artery. The freely flowing blood was then collected in polyvinyl chloride (PVC) container containing enough heparin (porcine intestinal mucosa, EMD Chemicals INC (Biosciences), Darmstadt, Germany) to reach a final concentration of 1.5 U/ml. The blood was then transferred to a sterile Polyethylene Terephthalate Glycol (PETG) container (VWR International) for storage. The process was done at a local slaughterhouse in accordance with all USDA regulations.

Exposing Blood to Shear

Because of the instability of blood, great care was taken to replicate the method for each individual trial. 2 mL of blood was pipetted from the PETG storage container using a variable volume pipettor (VWR International). The blood was then placed in the annular gap test section. The test rig was then turned on and speed adjusted to the desired rpm. The time from when the blood is placed in the test section until the desired rpm was reached was 30 seconds for all trials. The blood was exposed to the desired shear rate for an additional 120 seconds. The blood was pipetted from the test section and placed in a sterile, borosilicate glass test tube.

Three different shear rates, 2200, 6600, and 9500s^{-1}, were tested in this experiment and compared to a control of 0 shear (simply exposing the blood to the section). This control was chosen in order to isolate the effects of shear stress on the...
Figure 2: Test rig assembly, 1: DC motor; 2: Inner cylinder held static; 3: Outer cylinder mounted in bearings

whole blood, while including any effect of exposure to the material. Two or three trials were run at each shear rate. One outlying data point was omitted from the results because the BBL Fibro System malfunctioned.

Coagulation Measurement

Each whole blood sample was centrifuged for 10 minutes and approximately 1mL of plasma was collected for each trial. The BBL Fibro System (Becton Dickinson Microbiology Systems, NJ) was used to measure coagulation by conducting the prothrombin time (PT) and activated partial thromboplastin time (APTT) tests. PT and APTT are medical standards for measuring coagulation and detailed methods have been well documented [13]. PT measures the extrinsic pathway, which is activated by exposure to damaged endothelial cells, and APTT measures the intrinsic pathway, which is activated by exposure to any negatively charged surface. Both pathways test levels of prothrombin which is one of the agonists in the numerical model. Prothrombin leads directly to thrombin which is the final and most important factor for fibrin clot formation. PT and APTT of the blood were then measured for each stress level.

After the trials at the highest shear rate, the polycarbonate inner cylinder was inspected for platelet attachment with microscopy. Directly after each trial, the inner cylinder was rinsed with a 0.9% NaCl solution. The surface was then stained with Wright stain in order to visualize the platelets. A Keyence VHX-500 (Keyence Corporation of America, NJ) digital microscope was used to inspect the surface.

COMPUTATIONAL METHODS

Thrombosis Model

The species included in the numerical model consist of unactivated platelets, activated platelets and 5 agonists of thrombogenesis (ADP, TxA2, prothrombin, thrombin and antithrombin). The interactions of these species are briefly described here and shown schematically in Figure 3. Details of the model can be found in the literature [8, 15]. Platelet activation is dependent upon a weighted summation of the concentrations of ADP, TxA2, and thrombin. When this summation reaches a critical threshold, platelets begin to activate based upon a first order source term. This rate continues to increase without bound in proportion to the concentration of the agonists. Upon activation, platelets release ADP, TxA2, prothrombin, and thrombin, which creates a positive feedback loop because these species further encourage platelet activation. Activated platelets adhere to the biomaterial surface at a higher rate than unactivated platelets. The current model takes into account rate constants for the attachment of each in addition to available surface area, so that platelets are less likely to adhere to a surface that is already occupied by a large number of platelets. Once a platelet is attached, it encourages further platelet activation in the bulk flow. The current model allows for a grid element that contains a high enough concentration of attached platelets to be converted to a solid. This solid represents a thrombus and does not allow fluid to flow through the grid element. In this way, a clot can “grow” by converting adjacent numerical elements to thrombus. Additionally, attached thrombus can also embolize and attached platelets may return to the bulk flow as unactivated platelets.

The kinetic constant of platelet adhesion is a constant that determines the rate at which platelets adhere to the surface. Unfortunately, this constant is not widely used and there is little available empirical data. The previous research used SEM to measure platelet adhesion to polyethylene and fit the numerical data to the experimental data by changing the constant. In addition, the previous research conducted experiments with polyethylene and silicon rubber and concluded that “thrombus growth rate was independent of material.” [8] Therefore, this research used the published value of 2.5e-6 for the kinetic constant of platelet adhesion.

The motion of red blood cells (RBC) in flowing whole blood has been observed to enhance the diffusivity of other particles in the blood [17]. The enhanced diffusivities for unactivated platelets, activated platelets, prothrombin, thrombin and antithrombin III were accounted for. The other species (ADP and TxA2) are too small to be affected by the RBC motion; therefore, the Brownian diffusivity was used for these species. The diffusion coefficient for each species (enhanced and Brownian) was taken from the literature. [15]

Numerical Methods

The continuity, momentum, and convection-diffusion equations were solved using a commercially available CFD package, Fluent 6.3 (Fluent Inc., Lebanon, NH). A control-
A volume approach was used and the geometry was represented by a structured mesh. Blood was modeled as a Newtonian fluid with a viscosity of 3 cp. The Navier-Stokes equations used for continuity and momentum are not shown here, but the governing equation for the species transport solver in Fluent is given as

$$\frac{\partial c_i}{\partial t} + \frac{\partial}{\partial x_j} \left( u_j c_i \right) = -\frac{\partial}{\partial x_j} \left( D_i \frac{\partial c_i}{\partial x_j} \right) + S_i$$

where $c_i$ is the concentration of the $i$th species, $x_j$ is the $j$th direction, $u_j$ is the velocity component in the $j$th direction, $D_i$ is the diffusion coefficient of the $i$th species, $S_i$ is the source term of the $i$th species. The species transport solver in Fluent was used to model the convection and diffusion of the coagulation species according to Equation 1. Each species has a unique source term, $S_i$, that governs how that species is generated or consumed. The interactions described above and shown in Figure 3 are included in the numerical model through calculation of these source terms. The equations to calculate source terms were implemented as a User Defined Function (UDF) written in C and solved in Fluent. Fluent solves the Navier-Stokes and convection-diffusion equations iteratively. At each physical time step, the UDF calculates the source term of each species to generate a time dependent solution that represents the physiological phenomena of thrombosis.

**Validation of Model by Comparing with Previously Published Results**

The previously published results of flow through an axisymmetric stenosis from Goodman [8] were reproduced to ensure that our numerical model was working and implemented correctly. All of the simulation parameters were exactly replicated with the exception of mesh size, due to computational expense. We used a mesh size of 2 microns whereas Goodman used 0.5 micron. The geometry of an abrupt contraction and expansion was modeled with a two-dimensional, axi-symmetric mesh.

**Numerical Model Applied to Annular Gap**

The cylindrical annular gap was solved using a two-dimensional, laminar solver in Fluent. Rotational periodic boundary conditions were used to simulate a 0.048 radian portion of the geometry (Figure 4). A structured mesh with a grid size of 5.14 microns was used to represent this characteristic volume, resulting in 70 elements across the annular gap. The outer wall was set as a rotating boundary condition and the inner wall is a fixed wall. The bulk fluid is initially at rest, but develops as it is driven by the outer wall rotating at a constant angular velocity.

![Figure 4: Schematic of complete flow geometry compared to computational domain with labeled boundary conditions 1: Rotational periodic; 2: Stationary wall; 3: Rotating wall](image)
The following modifications of the implementation of Goodman were made in order to produce a well posed problem. First, periodic boundary conditions were used. Periodic boundaries must come in pairs and the paired boundaries are treated as neighbors, so whatever is the output of one boundary is the input to the other. Secondly, as there was no flow rate or pressure difference specified for this simulation, the rotating outer boundary is the only cause for convection. Because there is no inlet boundary condition, a method of inputting initial species concentration was determined. A user defined function was written that added a second source term to the diffusion equation. This source term was turned on only for the first time step of the simulation at which time the species reached the necessary concentration. The source was then turned off and only the original source terms remain.

The simulation was run to a convergence criteria of 1e-5 for residuals of continuity, 1e-4 for velocity and convection-diffusion of each species. An adaptive time step was used to efficiently balance the instability of the simulation with the computational expense. A time step of 1e-5 was necessary for stability at the beginning of the simulation, but the simulation eventually was stable with a larger time step. A QUICK discretization scheme was used for the unactivated platelets to aid in the stability of the simulation [12].

RESULTS

Experimental

Figure 5 shows the results from the PT and APTT tests as a function of shear rate. Although regression showed the data to be statistically insignificant, a trend of decreasing time is seen from the linear fit line. The variance “R” was found by linear regression on the data points in the Figure 5 and solved in Microsoft Excel. An area representing approximately 10% of the total surface area was inspected and no platelets were observed attached to the surface.

\[ y = -0.01x + 211.67 \]
\[ R^2 = 0.356 \]
\[ y = -0.0031x + 78.794 \]
\[ R^2 = 0.1879 \]

Figure 5: Measured PT and APTT

Comparison of Numerical Model with Previous Results

The result of the simulation of flow through the stenosis compared very well with the published results [8]. Figure 6 illustrates the thrombus growth that is similar in size, shape and location to that published by Goodman [8 Fig #13]. The time when the thrombus reaches this size is about 30% faster in the current model than calculated in the prior study due to the larger mesh size.

Annular Gap

The annular gap geometry generated expected flow properties. The steady-state velocity profile was linear, which resulted in a uniform shear across the entire domain. While most of the species maintained nearly uniform concentration throughout the solution, activated platelets diffused towards the center of the domain after approximately 60 sec.

Because the fluid is initially at rest, there is a transitional period in the fluid before it reaches a steady state velocity profile (Figure 7). The development time (~0.025 seconds) is short compared to the total solution time (>60 seconds) and any shear stresses imparted by this transitional period have minimal impact on the final solution.

The mass fraction of resting and activated platelets in the bulk flow decreases over time due to platelet deposition. Figure 8 illustrates the higher rate of deposition for activated platelets compared to resting platelets.

Over the three shear rates tested, the mass fraction of thrombin was observed to increase with increasing shear (Figure 9).
Figure 7: CFD velocity profile development

Figure 8: The mass fraction of activated and resting platelets decrease over time in the CFD simulations.

CONCLUSION AND DISCUSSION

The trend seen in the experimental results of PT and APTT decreasing with increasing shear indicate that higher levels of coagulation factors are present. The numerical model demonstrated a similar trend in that the concentration of agonists, including thrombin, and activated platelets increased as a function of shear. While this comparison does not quantitatively validate the numerical model, the qualitative agreement between numerical model and experiment does demonstrate the numerical model’s potential to simulate high shear flow regimes. This initial evaluation of the numerical coagulation model is necessary to guide future research with the ultimate goal of applying this model to a mechanical blood pump.

One area of possible improvement to this computational model is the threshold nature of platelet activation. It has been shown that weak agonists (ADP, epinephrine, etc.) and strong agonists (thrombin, etc.) act synergistically, and that different concentration combinations of each have varying effects [6].

The experiment and the numerical model both showed no signs of clot formation. This is likely due to the high shear washing the surface. This type of flow, while uniform and controllable, does not promote thrombogenesis. This numerical model is best suited for comparing with experiments that encourage platelet deposition and clot formation. In the future, a similar comparison of numerical and physical models should be made for a high shear rotating flow that also includes regions of stagnation or recirculation.

The current numerical model only contains two factors of the coagulation cascade (prothrombin and thrombin). These two factors are part of the common pathway (coagulation factors that are in the extrinsic and intrinsic pathways). While these two factors are subsequent to thrombus formation, the model would benefit from the inclusion of other coagulation factors from the individual pathways. Lastly, the validation of the numerical model would benefit from experimentation that directly measured values of the individual agonists that are included in the numerical model.

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REFERENCES


