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Characterizing and Quantifying Shear-Induced Hemolysis in a Hollow Fiber Membrane System

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Abstract

Clinical studies have shown that patients undergoing renal replacement therapy are more susceptible to developing hemolysis, or the rupturing of red blood cells. Rapid hemolysis can cause symptoms such as anorexia, vomiting, and even death in severe cases. The aim of this study is to identify how shear stress within a hollow fiber membrane impacts the level of hemolysis that occurs. This allows for the optimization of the ultrafiltration membranes that are typically used for hemofiltration treatments. The variables being studied are the radii of hollow fibers, number of fibers, and volumetric flow rate of blood being circulated. Here, we also use COMSOL software to simulate blood flow through a membrane, generating shear stress and velocity profiles. The extent of hemolysis is characterized by the concentration of free hemoglobin in the blood. The results of the calculations indicated that a smaller radius and a higher volumetric flow rate induced greater shear stress and therefore higher concentrations of free hemoglobin in the system, while increasing the number of fibers resulted in a smaller concentration. We concluded that the manipulation of these variables influences the total time a patient can undergo hemofiltration before experiencing adverse effects.

Introduction

Like hemodialysis, hemofiltration is a treatment that is routinely used in intensive care settings to treat patients experiencing renal dysfunction [1]. However, while hemodialysis relies on diffusion, hemofiltration is a convective therapy that utilizes pressure gradients to eliminate larger molecules in the blood [1]. Mechanically, blood enters the membrane of a dialyzer at one end and is then forced into a multitude of thin hollow fibers. Convective clearance is achieved by solute transportation across a semipermeable membrane in response to a positive transmembrane pressure gradient, removing solutes along with plasma water [1]. Before or after the filtration,

the purified blood is supplemented with a buffered electrolyte solution to maintain adequate volume before being passed back to the patient [1]. To be clinically effective, hemofiltration requires high ultrafiltration rates, resulting in a higher potential for adverse patient conditions such as electrolyte disturbances and depletion of nutrients [2]. However, unlike hemodialysis, hemofiltration requires no dialysate, making it more cost effective and allowing for increased middle molecule removal [2].

Chronic kidney disease, or CKD, affects more than 1 in 7 adults in the United States, furthering the need for research on advanced kidney therapies [3]. However, there continues to be complications with the treatments, several of which decrease the quality of life for the patient. As blood is forced through a narrow channel or orifice, it is subjected to an appreciable amount of shear stress [4] The fragmentation of cells that follows is termed red cell fragmentation syndrome, a phenomenon that makes cells more prone to lysis [4]. In a 1988 study, 30 patients in several different states were hospitalized due to stress-induced hemolysis [4]. The human body regularly destroys old or damaged erythrocytes, freeing space for healthy new red blood cells (RBCs) [5] However, when RBCs are lysed too soon or too often, the body is susceptible to more severe outcomes [5]. Hemolysis commonly presents as symptoms of anorexia, vomiting, nausea, and in some cases, death [4]. Artificial kidney devices that are portable or implantable and use hemofiltration or hemodialysis are expected to offer longer periods of use compared to the current 3-hour clinic visits that patients undergo. However, the operation of these devices may be limited by factors such as hemolysis. Reducing the frequency of stress-induced hemolysis during hemofiltration is crucial for improving quality of care in patients.

Shear stress induced hemolysis is a developing issue that rapidly gained the attention of the biomedical community following the Giersiepen et. Al proposed mathematical model in 1990 [6]

$$\frac{\Delta Hb}{Hb}(\%) = 3.62 \times 10^{-5} t^{0.785} \tau^{2.416} \quad (1)$$

Using equation (1), the severity of hemolysis is quantified by the amount of hemoglobin released in the blood; *t* represents exposure time, τ is shear stress, and $\frac{\Delta Hb}{Hb}$ corresponds to the change in hemoglobin as a result of RBCs lysing [6]. This equation serves as the basis for several other works and models, including the work done in this paper. Here, we implement computational fluid dynamics to simulate non-Newtonian flow through multi-channel hollow fiber simulations in COMSOL based on the Giersiepen model.

There are several acceptable metrics that are used to measure the extent of hemolysis. One of the most common, and the one used in this study, is the normalized index of hemolysis (NIH) [7]. NIH is normalized by hematocrit, H, and considers that the maximum amount of hemoglobin that can be released is proportional to the RBC concentration in the system [7]. This relationship is developed as equation (2).

$$NIH = \Delta PfHb \times \frac{100 - H}{100} \quad (2)$$

$\Delta PfHb$ represents the change in plasma-free hemoglobin, and hematocrit is the volume percentage of red blood cells in blood [7]. In this paper, $\Delta PfHb$ will be calculated and measured.

Methods

Calculations

A series of hand calculations were done to obtain results that could be compared with the computational model. Figures 1 and 2 are visual representations of the predicted shear stress and velocity profiles, respectively, from a radial view.

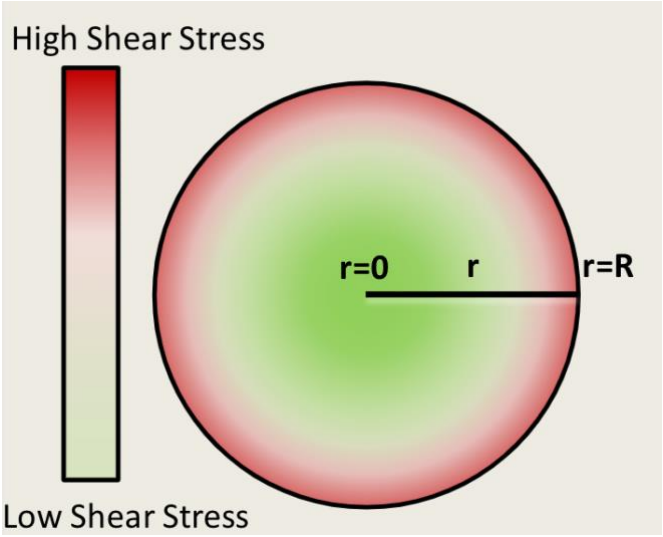

Figure 1. Radial view of shear stress profile

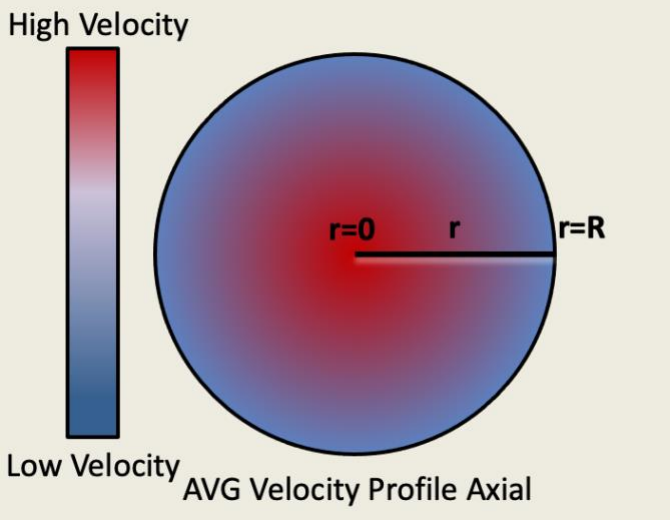

Figure 2. Radial view of velocity profile

If the hollow fibers in the membrane are considered to be straight, cylindrical tubes, the shear stress will be mainly distributed to the inner walls of the fiber, and the velocity will be greatest in the center of the fiber [8].

There were several assumptions that were made before beginning calculations:

1. No slip conditions
2. Identical conditions across all fibers
3. Radial movement does not affect the $Hb_{generated}$

To determine the shear stress of a non-Newtonian fluid such as blood, the power law for fluids was used. The viscosity is calculated by equation (3),

$$\mu = k\,(\dot{\gamma})^{n-1} \tag{3}$$

where μ is the viscosity, k is the flow consistency index, $\dot{\gamma}$ is the shear rate, and n is the power law index [9]. k and n are both determined experimentally and are dependent on characteristics of the blood such as hematocrit, cholesterol, etc. [9]. Using the definition for shear stress and equation (3), equation (4) is found and used to calculate shear stress (τ) for a non-Newtonian fluid:

$$\tau = k(\dot{\gamma})^{n} \tag{4}$$

For the purposes of this study, literature values of k and n from the Shibeshi et. Al [9] experiments will be used as shown in Table 1.

Table 1. Literature parameter values

Parameters	Values
Flow consistency index (k)	0.017 Pa^n
Power law index (n)	0.708

To determine how long the blood experiences a specific shear stress, it is imperative to also develop a velocity profile for the system. Assuming a parabolic velocity profile, equation (5) dictates the velocity as it changes in a tube as a function of the radius [10]

$$V(r) = v_{max} \times \frac{1 - r^2}{R^2} \tag{5}$$

R is the total tube radius, and v_{max} is the maximum velocity occurring in the center of the tube [10]. The max velocity is equal to $2 \times v_{average}$ [10]. Taking the volumetric flow rate, Q, into account, the maximum velocity can be written as equation (6):

$$v_{max} = 2 \times \frac{Q_{fiber}}{A_{total\ fiber}} \tag{6}$$

$A_{total\ fiber}$ is the total area of the fiber. The Q_{fiber} can simply be represented as the total volumetric flow of the pump divided by N, or number of fibers.

$$Q_{fiber} = \frac{Q_{pump}}{N} \tag{7}$$

Manipulating the equations above allows an equation for time, in minutes, to develop.

$$t(r) = \frac{dh \times A_{total\ fiber} \times N}{2 \times Q_{pump}} \times \left[\frac{1 - r^2}{R^2}\right]^{-1} \tag{8}$$

Equation (8) allows for the calculation of the amount of time the blood will take to pass through the fiber at each distance (r). *dh* is the change in the length of the fiber. Using the found residence time per blood cell, the total PfHb can be found per radius. The summation of the PfHb per radius allows for the total PfHb in a single fiber to be calculated. Assuming the Giersiepen model of Hb increase relates to mass percentage increase, equation (9) allows for the individual concentrations at each radius to be calculated.

$$C(r) = \frac{Hb_{Final}\,(r)}{2\pi r \ * dr \ * dh} \tag{9}$$

Figure 3 displays a visual representation of the progression of the blood traversing the total length of the fiber. For the purposes of the hand calculations, dh is assumed to be L, or the total fiber length.

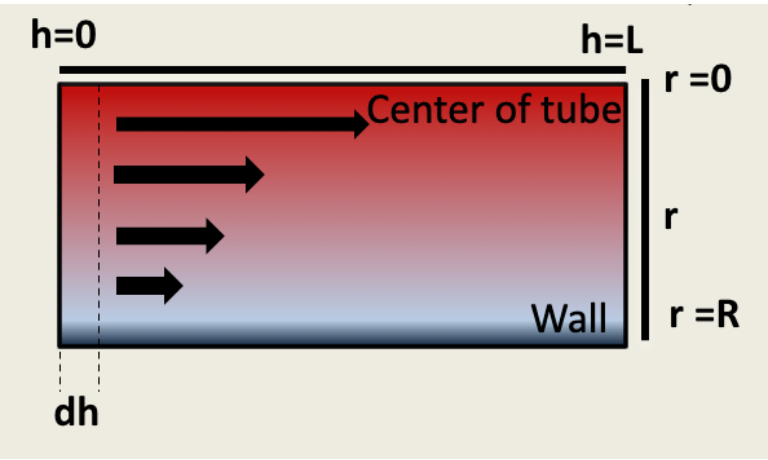

Figure 3. Velocity in the fiber as function of h

COMSOL Modeling

COMSOL version 6.0.0.405 was used in this study, with the Laminar Flow and Fluid Dynamics interfaces installed. Utilizing COMSOL allows for the visualization of fluid phenomena and has significant applications in the medical field.

Generally, running a simulation in COMSOL requires selecting the appropriate packages, defining known physical parameters and boundary conditions, inputting control equations, and collection of visual and quantitative results produced by the model [11]. The geometry of the

model was built in 2D for simplicity, and consists of an inlet, an outlet, and a multitude of rectangular “fibers” to mimic an actual hollowfiber membrane. For this simulation, 25 equidistant hollow fibers were chosen. Figure 4 displays the geometry of the simulation.

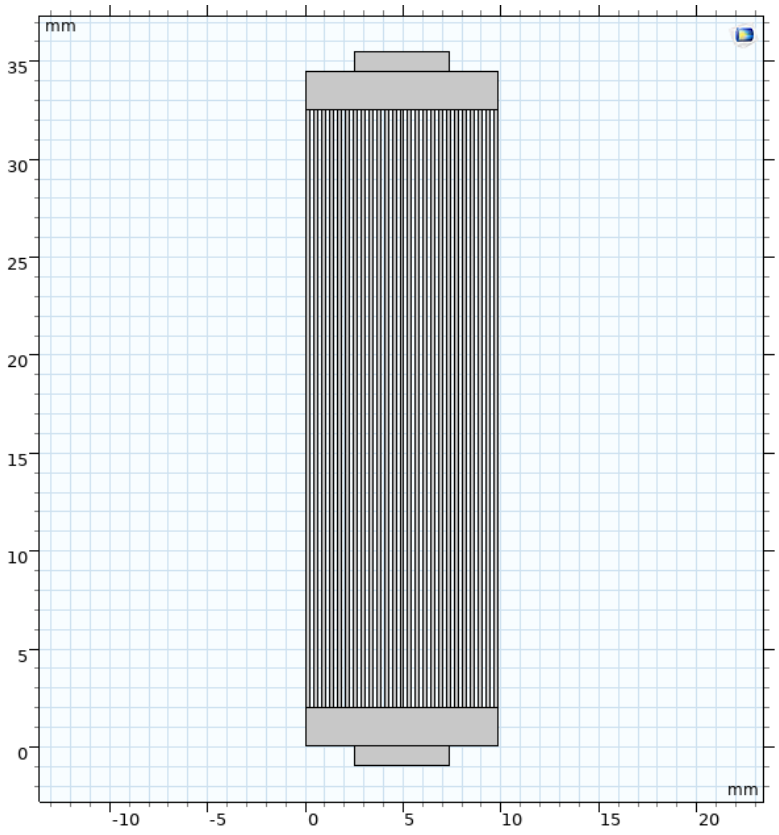

Figure 4. COMSOL geometry

The inlet and outlet measure to be 5 mm, and the length of each fiber is 12 in. After building the initial geometry, the parameters for this simulation and their corresponding values and units were put in. Table 2 contains the parameters utilized for the model.

Table 2. COMSOL Parameters

Name	Expression	Value	Description
Lm	.08 [mm]	8E-5 m	Thickness of membrane
L	304.8 [mm]	0.3048 m	Length of fiber
k	.017 [Pa]	.017 Pa	Flow consistency index
n	0.708	0.708	Power law index
Cmax	0.5 [g/dl]	5 kg/m^3	Max body concentration
Cin	.005 [g/dl]	0.05 kg/m^3	Inlet concentration of Hb
VolP	56.7 [dl]	.00567 m^3	Body blood volume
RL	.025 [mm]	2.5E-5 m	Smallest fiber radius
RM	.05 [mm]	5E-5 m	Average fiber radius
RH	0.1 [mm]	1E-4 m	Largest fiber radius
NL	50	50	Lowest fiber count
NH	1000	1000	Highest fiber count
QL	50 [cm^3/min]	8.3333E-7 m^3/s	Lowest pump volumetric flow rate
QM	150 [cm^3/min]	2.5E-6 m^3/s	Average pump volumetric flow rate
QH	300 [cm^3/min]	5E-6 m^3/s	Highest pump volumetric flow rate
LM	12 [in]	0.3048 m	Average fiber length
LH	24 [in]	0.6096 m	Longest fiber length
AL	3.14159 * RL^2	1.9635E-9 m^2	Area of smallest fiber
AM	3.14159 * RM^2	7.854E-9 m^2	Area of average fiber
AH	3.14159 * RH^2	3.1416E-8 m^2	Area of largest fiber
dh	0.001	0.001	Derivative
PresBody	120 [mmHg]	1.0132E5 Pa	Internal body pressure
RHouse	9.5 [mm]	0.0095 m	Housing radius
AHouse	3.14159 * RHouse^2	2.8353E-4 m^2	Housing area
EntWidthH	5 [mm]	0.005 m	Entrance width large
EntWidthL	2 [mm]	0.002 m	Entrance with short
FC	25	25	Fiber count
areainlet	4.9 [mm^2]	4.9E-6 m^2	

The fluid properties of blood are not readily available in COMSOL, so the viscosity was manually entered to be 3.5 cP, which is the typical dynamic viscosity of blood [12]. The simulation produced a velocity profile and a shear stress profile.

Results and Discussion

Calculations

The shear stress was calculated across three different volumetric flow rates (50 $\frac{ml}{min}$, 150 $\frac{ml}{min}$, 300$\frac{ml}{min}$) and three different fiber diameters (0.05 mm, 0.1 mm, 0.2 mm). These values were based on typical ranges for operating conditions of existing hollow fiber membranes. Figure 5 displays the shear stress for the varying diameters, with the volumetric flow rate held constant at 300 $\frac{ml}{min}$. Figure 6 shows the results of shear stress for different flow rates, with diameter being held constant at 0.2 mm.

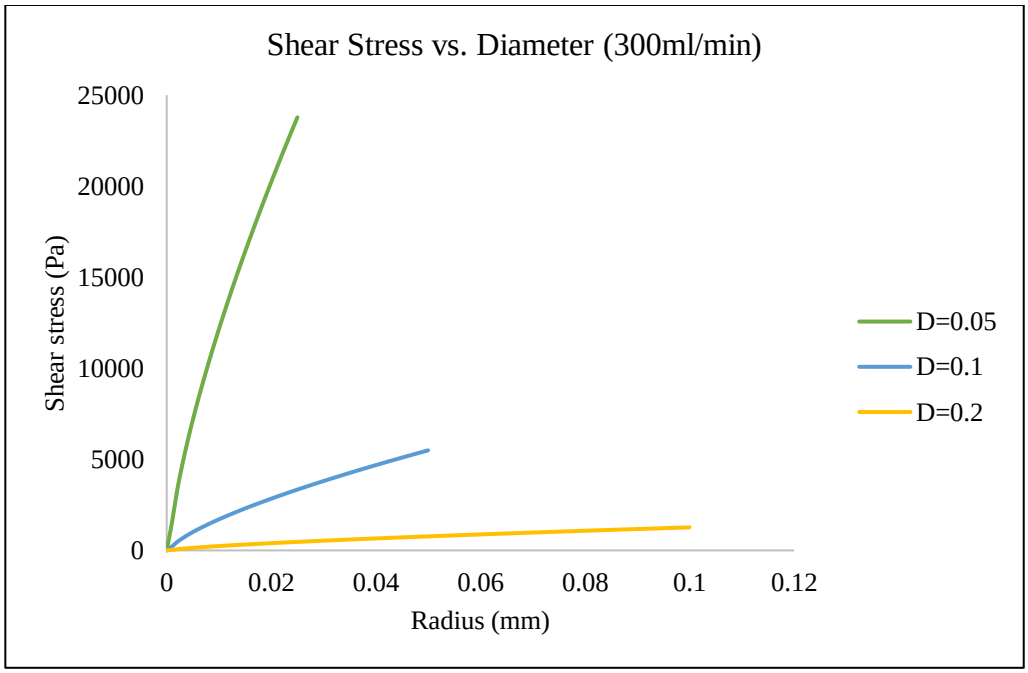

Figure 5. Shear stress at different diameters

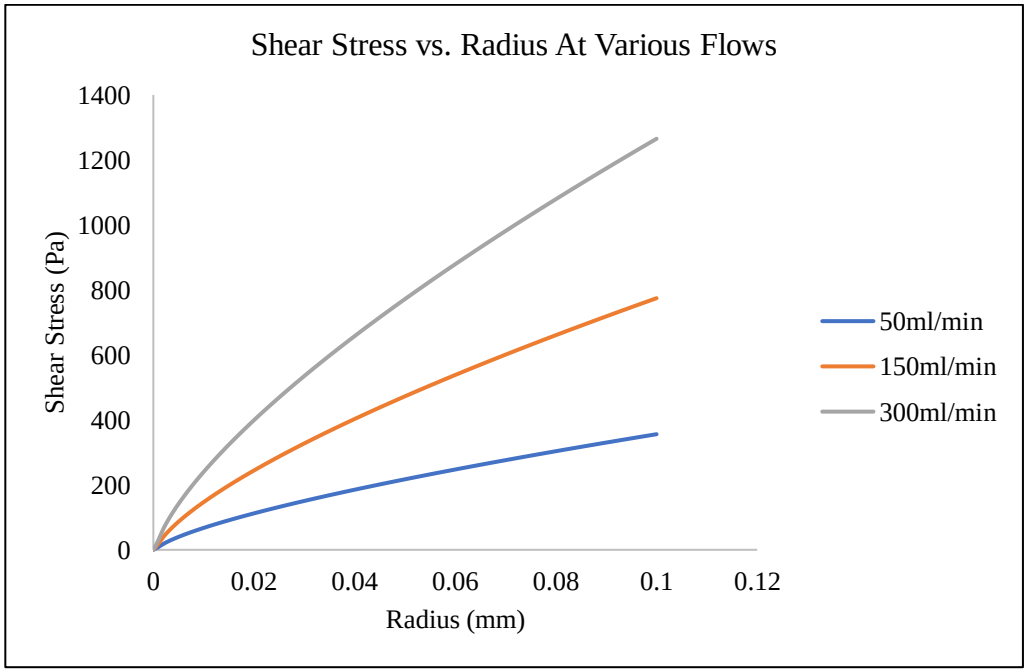

Figure 6. Shear stress at different volumetric flow rates

The shear stress values at each condition were then used to calculate the fractional increase in hemoglobin across the same range of diameters and flow rates, once again keeping the number of

fibers constant. Figure 7 displays the Hb increase across the three diameters at 300 $\frac{ml}{min}$. Figure 8 displays the linear relationship between hemoglobin increase and increasing flow rates at a constant diameter of 0.2 mm.

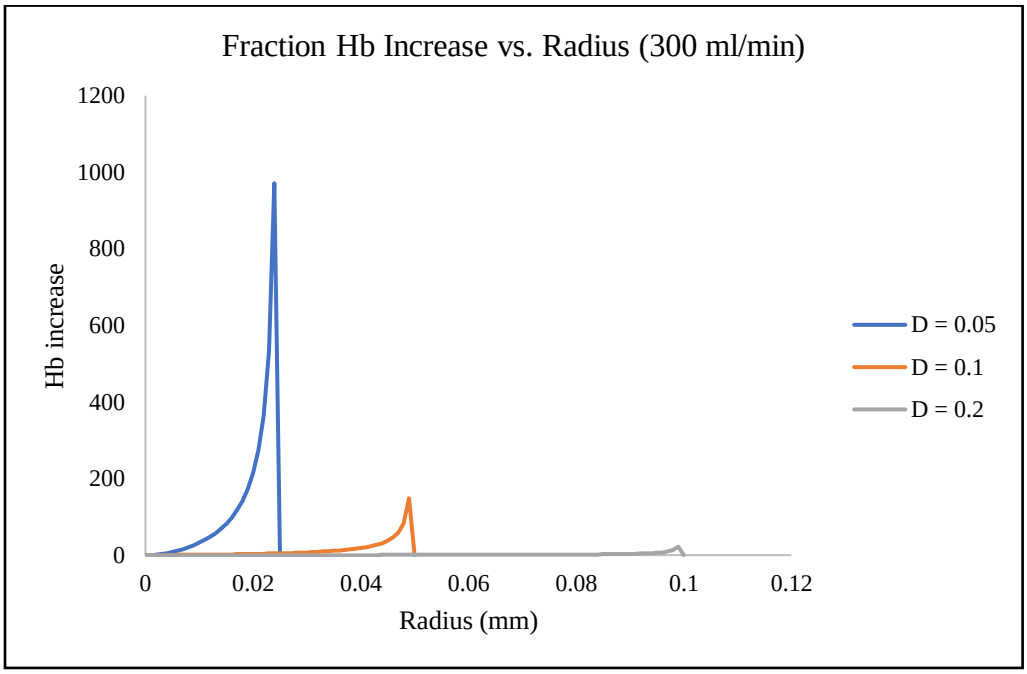

Figure 7. Fraction Hb at different diameters

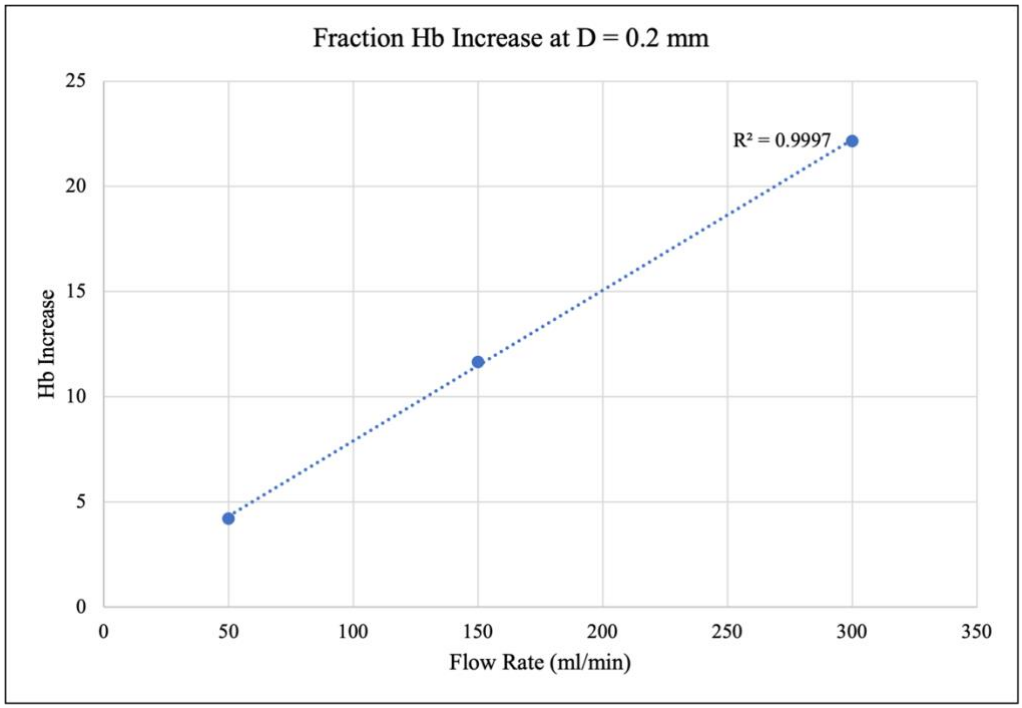

Figure 8. Fraction Hb increase at different flow rates

From these results, there are several conclusions that can be drawn regarding the effects of altering the flow rate and diameter of the fibers. Figures 5 and 6 indicate that as the diameter is reduced and the flow rate is increased, the amount of shear stress occurring increases. Similarly, figures 7 and 8 show that the smallest diameter and highest flow rate have the highest increase in hemoglobin. It can be concluded that higher volumetric flow rates result in higher levels of hemolysis, due to the increased level of free hemoglobin. This is likely due to the higher flow rate being rougher on the blood, forcing the cells through the channels at a greater velocity, and therefore damaging more cells. In addition, smaller diameters result in a greater level of hemolysis. As the diameter of the fiber channels is decreased, the blood cells are experiencing a greater flow and therefore a greater shear stress, resulting in increased hemolysis.

Medically, a hemoglobin value of 15.0 g/dL or above can lead to heart failure or even death [13]. This critical value of hemoglobin was referenced to obtain clinically valuable results that indicate how long a patient could undergo hemofiltration using different hollow fiber conditions. Figure 9 displays the time in hours until Hb concentration reaches 15.0 g/dl under different diameter and flow conditions. Figure 10 displays the time, but with the number of fibers increased from 50 to 10,000.

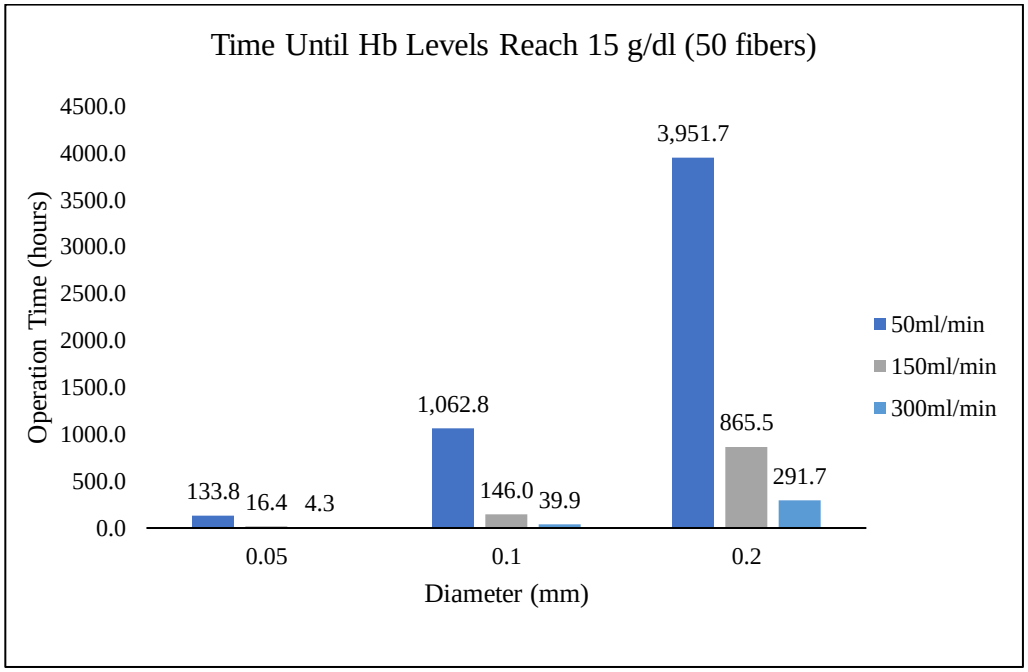

Figure 9. Maximum operation time until critical hemoglobin concentration (50 fibers)

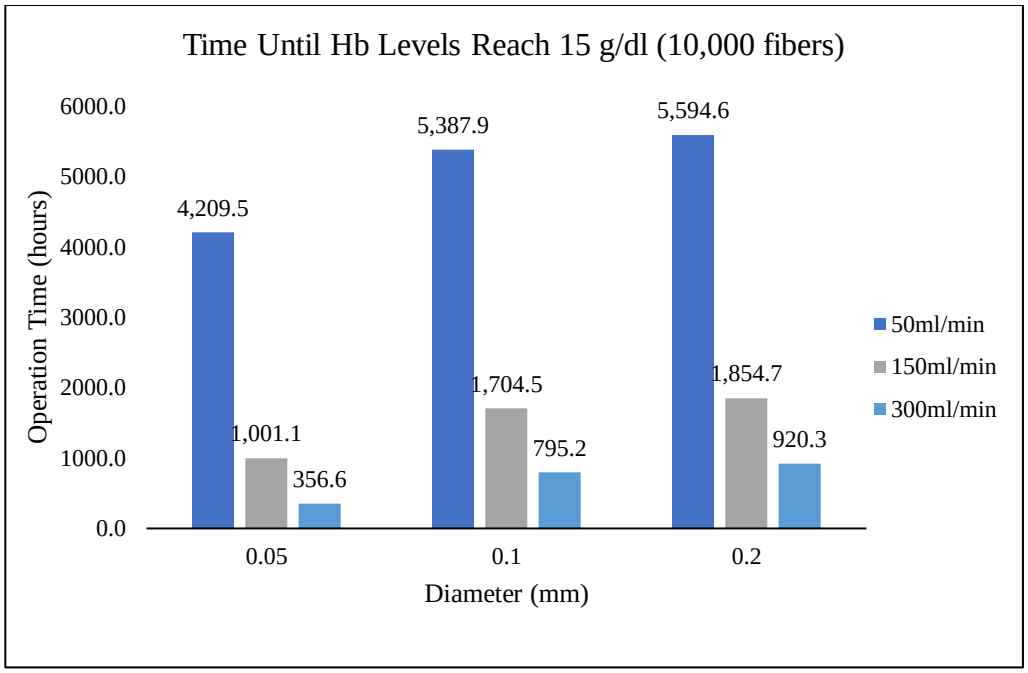

Figure 10. Maximum operation time until critical Hb is reached (10,000 fibers)

As described by the figures, when the number of fibers is increased, the time drastically increases for all conditions. Figure 9 shows that at 50 fibers, the shortest time that occurs at D = 0.05 mm and 300 $\frac{ml}{min}$ is only 4.3 hours. However, figure 10 displays that under these same conditions, the 10,000 fibers allow for a time of 356.6 hours. As the number of fibers is increased, there is a smaller volume of blood being forced through each fiber, and therefore a slower velocity in each fiber. This results in less shear stress and hemolysis throughout the fibers, allowing a patient to theoretically maintain hemofiltration for a longer period. These results help characterize the optimal conditions that could be used in a clinical setting, especially for an implantable filtration device that would require lengthy treatment times.

COMSOL

Figures 11 and 12 display the velocity and shear stress profiles, respectively, that were generated using COMSOL.

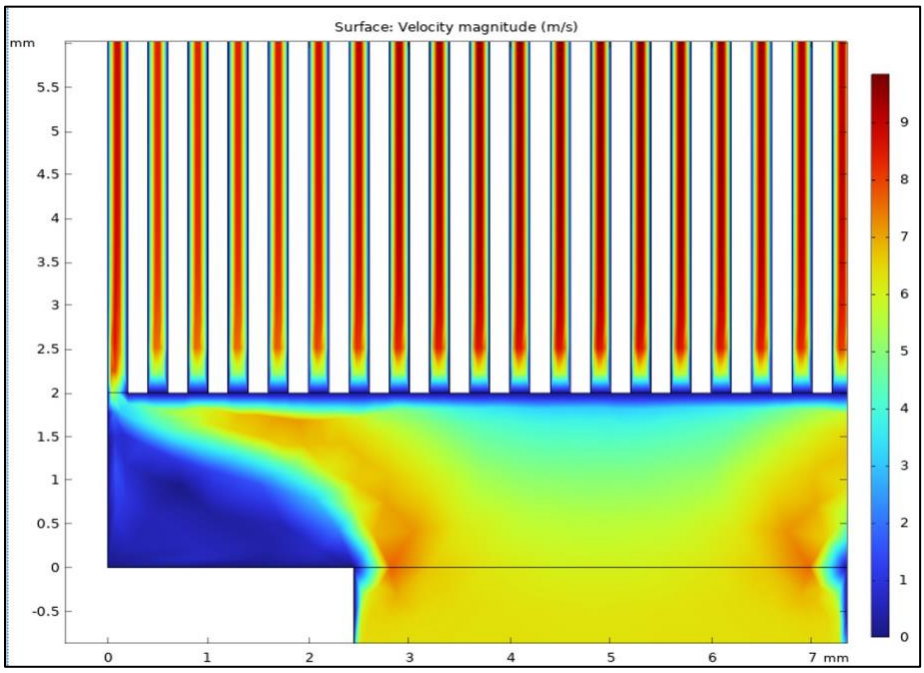

Figure 11. Velocity profile in COMSOL

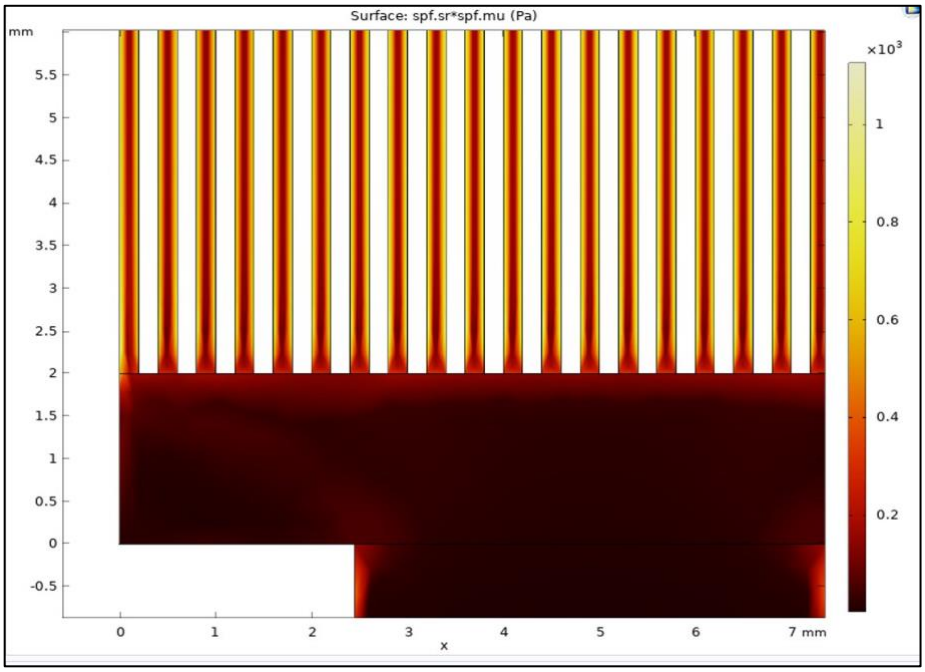

Figure 12. Shear stress profile in COMSOL

It can be observed that velocity is greatest in the center of the fibers, and shear stress is greatest along the walls of the fibers. These figures are consistent with the relationships used in the hand calculations.

Conclusion and Future Work Recommendations

Patients undergoing renal replacement therapy, specifically hemofiltration, are at a greater risk of experiencing hemolysis during their treatment. The objective of this study was to investigate how different conditions of the hollow fiber membrane in a hemofiltration device can affect the degree of hemolysis within the system. The study revealed that a smaller diameter and higher flowrate lead to increased shear stress, resulting in a higher level of hemolysis. Additionally, calculations were done to find the total duration of hemofiltration that a patient could undergo until they reach a critical hemoglobin concentration. It was discovered that increasing the number of fibers in the membrane can significantly prolong the treatment duration. These findings offer valuable insights into optimizing the membrane's characteristics for clinical use. The study also utilized COMSOL software to generate velocity and shear stress profiles, further confirming the identified relationships.

Incorporating COMSOL into the project has tremendous potential to improve our modeling capabilities. The subsequent step is to produce hemoglobin profiles for the system under various conditions. A major constraint of the study was the need to make simplifying assumptions to facilitate calculations. However, with COMSOL, it will be possible to simulate a real-world system, considering factors like membrane fouling and blood clotting.

Acknowledgments

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