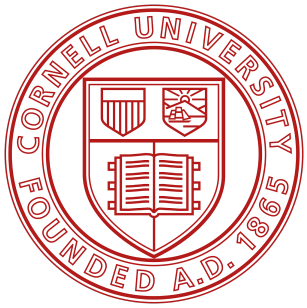
Shear Stress-Induced Nanoparticle Drug Delivery in the Right Coronary Artery

Nash Allan-Rahill, Sushruta Iruvanti, Nick Miller, Jerry Sarubbe

Keywords: Atherosclerosis, Plaque, Nanoparticles, Coronary Artery Disease, Shear Stress

In partial fulfillment of the requirements for BEE 4530
Computer Aided Engineering: Applications to Biological Systems



Department of Biological and Environmental Engineering
Cornell University

Table of Contents

1. Executive Summary

Shear stress-sensitive nanoparticles are a promising new field for drug delivery. This novel method may allow the targeted release of drugs such as statins or vasodilators to areas of high shear in the bloodstream, as occurs near a stenosis. Previous work claims that shear stress-sensitive nanoparticles may deliver a targeted release of clot-busting or cholesterol-fighting drugs to arterial plaque [1]. However, these studies have only examined *flow* characteristics near plaques and have not considered the movement of nanoparticles within these flows or the complex process of drug diffusion from the particle's shear location into the plaque. The study outlined here considers the entire process from nanoparticle entry upstream of the plaque through drug diffusion into the tissue.

A right coronary artery with a Type I plaque morphology was designed using the 3D CAD design software SolidWorks®. COMSOL Multiphysics®, a commercially available modeling software, was used to model blood flow past this plaque with a varying inlet velocity to simulate pulsatile flow. Particle diffusion through the blood and subsequent drug diffusion into the tissue were simulated. Average dimensional values and flow velocities for men were used since they are more at risk for developing atherosclerosis.

The results of these simulations showed that the plaque buildup at 35% stenosis causes sufficient shear stress to break the nanoparticles, releasing the drug into the blood. Most drug, once it was released from the nanoparticles, was found to diffuse into the downstream half of the plaque. Moreover, it was found that the optimal breaking shear stress of the nanoparticles for targeted drug delivery to the stenosis was nearly the maximum shear stress achieved in the flow at 75 Pa, while the optimal infusion concentration is close to the maximum clinically allowable at 0.045 mol/m^3 [2].

This computational study has filled an important void in the body of research on this novel drug delivery method. It has verified the rupture of nanoparticles under 35% stenotic conditions while showing subsequent drug diffusion patterns, which suggests that this method may not be suited for targeting drug delivery to arterial plaques. Further research should examine the effects of arterial wall compliance, consider non-Newtonian blood flow, and test realistic plaque geometries obtained, for example, via intravascular ultrasound (IVUS). Though shear stress-sensitive nanoparticle drug delivery may not ideally target drug to arterial stenoses, this novel method may prove useful for modeling tumorigenic systems, where fluid shear stress has been shown to affect cancer cell motility.

Keywords: Atherosclerosis, Plaque, Nanoparticles, Coronary Artery Disease, Shear Stress

2. Introduction

Coronary artery disease (CAD) is the most common type of heart disease with more than 3 million cases and over 370,000 deaths annually [3]. The main cause of CAD is atherosclerosis, or plaque buildup along the walls of the artery [4]. If caught in time, atherosclerosis can be treated by percutaneous revascularization (stent placement) to reopen arteries, beta blockers to lower blood pressure, nitroglycerin to dilate vessels, and a class of drugs called statins to lower blood cholesterol levels [5]. However, all these treatments have risks and side effects. Nitroglycerin can cause headaches, sweating, and dizziness, while statins can cause various and significant side effects such as muscle pain, liver damage, increased risk of type II diabetes mellitus, memory loss, and confusion [5-6]. In an attempt to mitigate these side-effects, various targeted treatments are being developed that aim to minimize drug diffusion to non-affected areas.

Nanoparticles have become an increasingly popular tool in multiple disciplines because of their versatility, size, and uniformity, and recent research focus has yielded an abundance of new methods and uses [7]. A few recent studies have investigated nanoparticle use in cardiovascular disease, specifically in delivering targeted drug treatment to plaque-prone areas [1,7,8]. The results seem promising but as in any study, there is a need for future research and validation. The proposed technique involves fabricating nanoparticles that are sensitive to the higher-than-normal shear stresses in blood flow around arterial plaques as shown in Figure 1. Given the diversity of the human vascular system and the complex interplay between blood flow and drug diffusion, it has yet to be determined whether this technique is as robust as it seems. Specifically, high flow velocities in arteries could cause rapid washout of drug after release from the nanoparticles, causing statins or other drugs to diffuse into downstream tissue where they may elicit some combination of the side effects listed above.

As noted above, there are many drugs used to treat coronary artery disease. Each of the three main types listed above (beta blockers, statins, nitroglycerin) has a different target. In particular, beta blockers and statins are most effective when delivered to the entire circulatory system while nitroglycerin need only be delivered to the affected areas. To understand why, it is important to know how nitroglycerin operates. In the blood, nitroglycerin is rapidly converted to nitric oxide which acts as a non-selective vasodilator, diffusing into the vessel wall and causing relaxation of the arterial smooth muscle layer found in the tunica media, resulting in vessel widening (see Figure 2). The vessel-widening action of nitroglycerin is, in effect, the reverse process of coronary artery disease where plaque buildup causes vessel narrowing and limits blood flow downstream. Therefore, it need only target areas where vessels have become constricted due to plaque buildup. In fact, nitroglycerin would *ideally* only target those vessels, as its non-selective vasodilatory effects are the cause of many of the side effects associated with the drug.

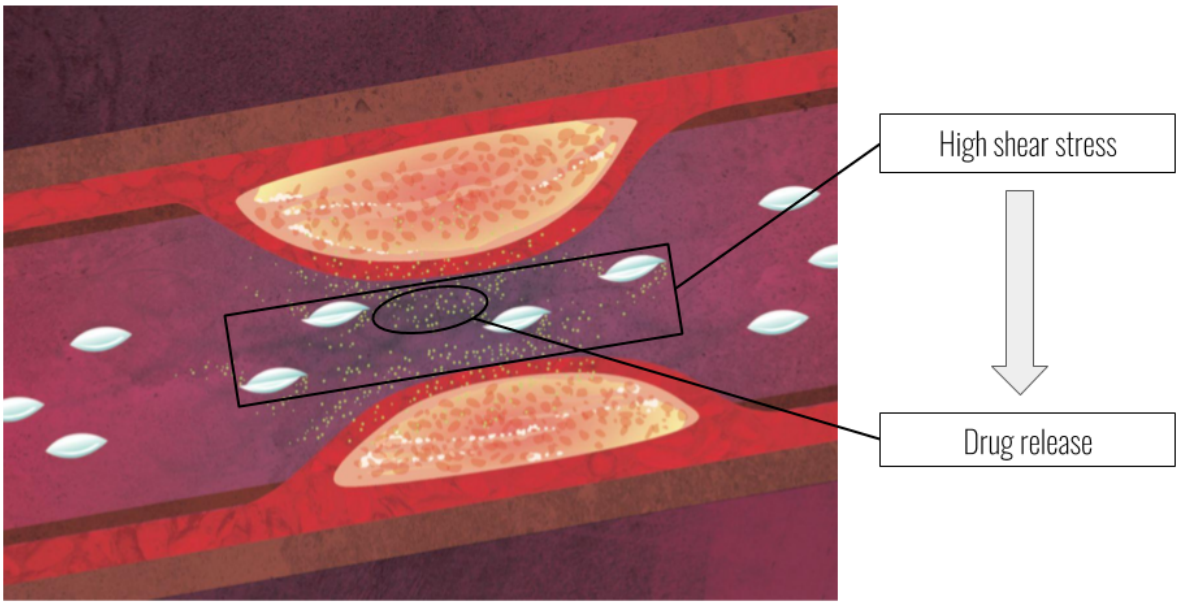


Figure 1: Proposed method for targeted drug delivery to arterial stenoses using shear stress-sensitive nanoparticles. Shown is an axial cross-section of a vessel with plaque buildup, colored tan, nanoparticles as white capsules, and drug as yellow dots. Darker red-purple blood signifies high shear stress and nanoparticles in this region have ruptured, releasing drug.

Computational studies are playing an increasing role in the research process for a variety of reasons. The time and cost-effectiveness of simulated studies is significant compared to physical prototyping and experimentation. This allows broader access to the engineering process given the ubiquity of sufficient computing power. Furthermore, computational studies are inherently more adaptable and iterable than their counterparts, and testing or examining different sets of parameters does not require buying a whole new suite of testing or imaging equipment. Compared to analytical solutions of modeled systems, numerical solutions are more flexible and nuanced than often oversimplified analytical methods. COMSOL Multiphysics®, is a widely-used general-purpose modeling software that can simulate a variety of physical systems including but not limited to: fluid flow, mass transport, heat transfer, solid mechanics, and electrostatics.

This study uses COMSOL to examine the sensitivity of shear-induced nanoparticle drug delivery for treatment of CAD. A focus was placed on parts of the process that have yet to be investigated, such as the process of drug diffusion after release from nanoparticles, and optimization of the controllable treatment parameters such as the breaking shear stress of the nanoparticles.

2.1 Problem Statement

The purpose of this study is to determine whether shear stress-induced nanoparticle drug delivery is an effective method for treatment of coronary artery disease. Non-specific delivery of nitroglycerin can lead to a number of side-effects such as dizziness, severe headaches, chest pain, and anaphylaxis in severe cases. As such, it is necessary to model the shear and velocity profiles of nanoparticles and drug in the artery to ensure that a shear stress dependent delivery system is targeted and precise. Additionally, it is important to measure the effects of parameters such as critical nanoparticle shear stress, nanoparticle inlet concentration, and drug diffusivity on such a system.

2.2 Design Objectives

The goals for this project are as follows:

1. Model the shear profile in a typical adult male right coronary artery with 35% stenosis by simulating blood flow under physiological conditions.
2. Determine the effects of pathological blood flow on nanoparticle diffusion.
3. Visualize subsequent effects on diffusion of nitroglycerin through the blood and vessel tissue.
4. Determine the sensitivity of nitroglycerin delivery to treatment design parameters
5. Optimize this drug delivery method by varying most sensitive design parameters

3. Methods

3.1 Schematic

A 2D geometric model was created in SolidWorks®. This geometry was imported into in COMSOL Multiphysics® to create a 2D axisymmetric model that simulates blood flow through the right coronary artery. The model approximates the geometry of the artery as concentric cylinders, as shown in Figure 2, with the following layers: tunica adventitia, tunica media, tunica intima, and plaque. Plaque dimensions were constructed based on the average morphology obtained from intravascular ultrasound. In order to determine whether flow past an arterial plaque would cause proper drug release from the shear-sensitive nanoparticles, the flow characteristics in a simplified coronary artery were modeled. The plaque, tunica adventitia, tunica media, and tunica intima were assumed to have identical physical properties.

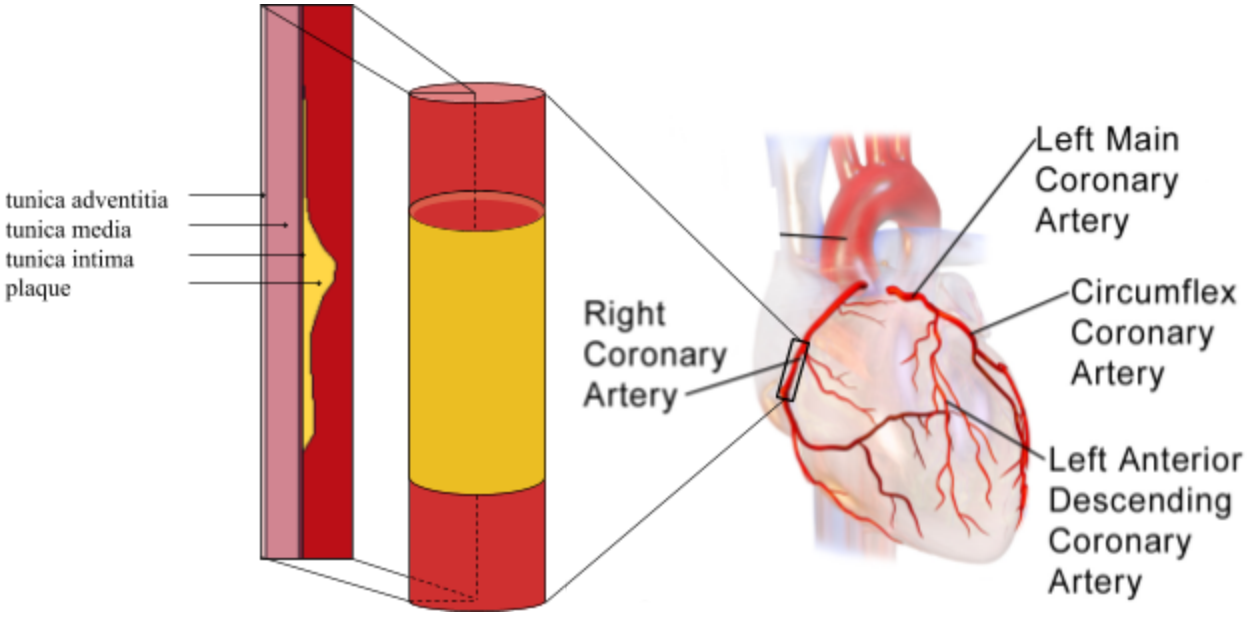


Figure 2: Schematic of the right coronary artery and its location in the heart. The right coronary artery geometry was simplified to an axisymmetric cylinder for ease of computation. The type I plaque can be seen on the inner vessel wall. Heart cartoon courtesy of Blausen.com.

The four most common plaque morphologies, based on a study of 42 patients with Coronary Artery Disease, is shown in Figure 3. A type I plaque was chosen for sufficient computational complexity.

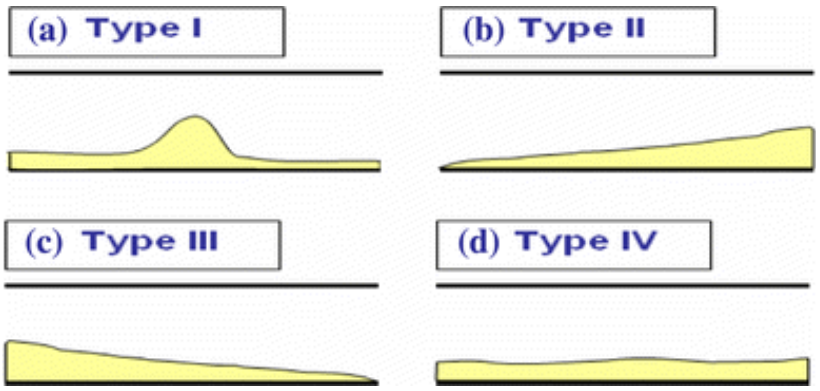


Figure 3: The four most common plaque morphologies, based on a study of 42 patients with Coronary Artery Disease [9]. Types I-IV are characterized by a smooth protrusion, gradual incline, gradual decline, and flat surface respectively.

3.2 Variables

The variables referenced in the governing equations and boundary conditions are listed in Table 1 along with their units and descriptions. The values used for the input parameters can be found in Table 2 of Section 3.6.

Table 1: Variables used in governing equations

Symbol	Unit	Name/Description
ρ	kg/m^3	Density of blood
D_n	m^2/s	Diffusion coefficient of nanoparticle
$D_{d,a}$	m^2/s	Diffusion coefficient of drug in artery
$D_{d,b}$	m^2/s	Diffusion coefficient of drug in blood
u	m/s	Velocity of blood
t	s	Time
c_d	g/m^3	Drug concentration
c_n	g/m^3	Nanoparticle concentration
μ	$Pa \cdot s$	Viscosity of blood
P	Pa	Pressure of blood
τ	Pa	Shear stress in blood

3.3 Governing Equations

The flow was first simulated assuming a pulsatile inlet condition to more accurately model the system. Using the initial and boundary conditions specified in Figure 4, COMSOL could solve the Navier-Stokes and continuity equations in a time-dependent manner to determine the velocity profile, from which the shear gradient can be deduced:

Conservation of momentum:

$$\rho\left(\frac{\partial \bar{u}}{\partial t} + \bar{u}\cdot\nabla\bar{u}\right) = -\nabla P + \nabla\cdot\left(\mu(\nabla\bar{u} + (\nabla\bar{u})^T - \frac{2}{3}\mu(\nabla\cdot\bar{u})\boldsymbol{I}\right) \quad (1)$$

Conservation of mass:

$$\frac{\partial \rho}{\partial t} + \nabla\cdot(\rho\bar{u}) = 0 \quad (2)$$

where ρ and u are the density and velocity of the fluid respectively.

The spread of nanoparticles and drug were modeled using the diffusion equation.

Transport of nanoparticle:

$$\frac{\partial c_n}{\partial t} = \nabla\cdot(D_n\nabla c_n) - \nabla\cdot(\bar{u}c_n) + G_n \quad (3)$$

where D_n is the diffusivity of nanoparticle in blood, u is the velocity due to natural convection, and G_n is a conditional first order reaction term defined as:

$$if(\tau \geq \tau_{crit})$$
$$G_n = -1000\cdot c_n$$
$$else$$
$$G_n = 0$$

Transport of drug in blood:

$$\frac{\partial c_d}{\partial t} = \nabla\cdot(D_d\nabla c_d) - \nabla\cdot(\bar{u}c_d) + G_d \quad (4)$$

where D_d is the diffusivity of nitroglycerin in blood, u is the velocity due to natural convection, and G_d is a conditional first order reaction term defined as:

$$if(\tau \geq \tau_{crit})$$
$$G_d = 1000\cdot c_n$$
$$else$$
$$G_d = 0$$

Transport of drug in plaque:

$$\frac{\partial c_d}{\partial t} = \nabla\cdot(D_{d,p}\nabla c_d) \quad (5)$$

3.4 Boundary Conditions

Inlet boundary conditions are applied at the top of the entire domain to maintain conservation of mass and to ensure that the fluid in the vessel is incompressible. Pressure at the inlet and velocity at the outlet are defined by functions shown in Appendix A. Flux of the velocity, nanoparticle, and drug are 0 at the axis of symmetry. Concentration of nanoparticle and drug at the outlet are 0. Concentration of nanoparticle at the inlet was implemented as a smooth step function going from 0 to 0.1 g/m^3 in .1 secconds. Concentration of drug at the inlet is 0 as well. Velocity of the fluid is 0 at the vessel walls. Flux of nanoparticle and drug is 0 between all subdomains. These boundary conditions are summarized in Figure 4.

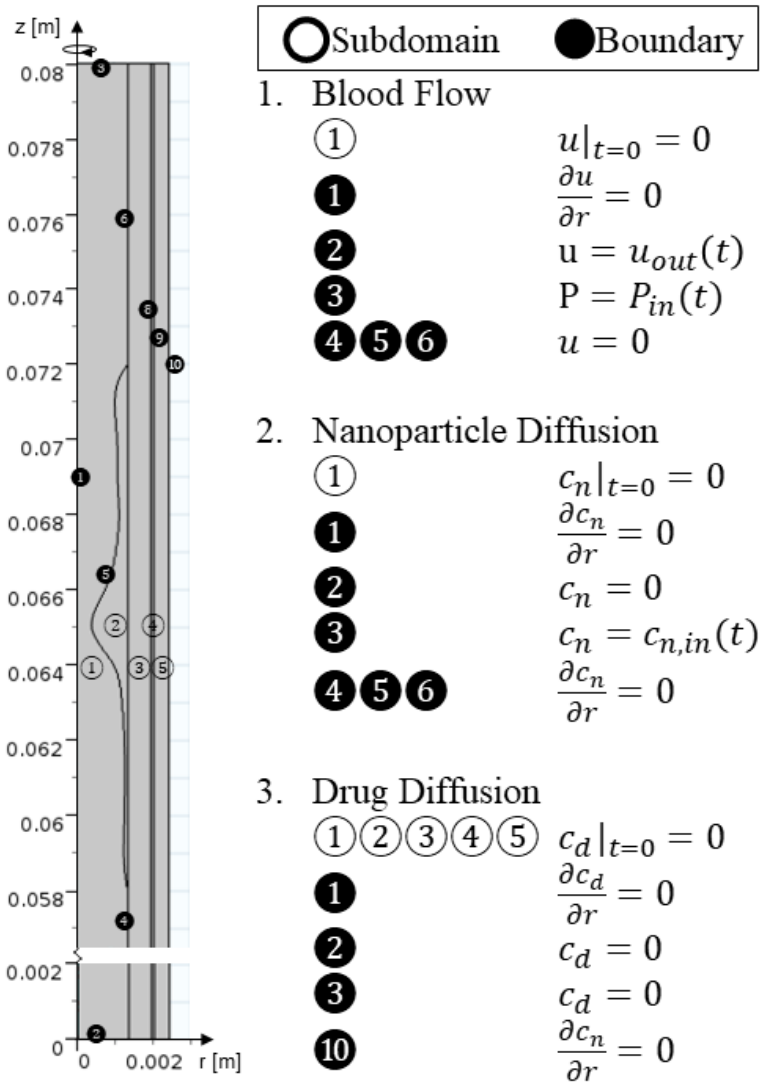


Figure 4: Schematic of the coronary artery as employed in the COMSOL model. Boundary conditions and initial conditions have been labeled for each of the three main physics.

3.5 Initial Conditions

There is no concentration of nanoparticle or drug in the artery at zero seconds. Furthermore, the initial fluid velocity in the domain is zero.

$u|_{t=o} = 0$ (6)

$c_n|_{t=0} = 0$ (7)

$c_n|_{z=0.08m} = c_{n,in}$ (8)

$c_d|_{t=0} = 0$ (9)

3.6 Input Parameters

Constants and parameters derived from literature can be seen in Table 2. The pressure and velocity boundary conditions were obtained as experimental data from Armstrong et al., to generate pulsatile flow [2]. The graphs of these values can be seen in Appendix A. Input pressure for pulsatile flow is a function of time given by data from Siogkas et al [10]. For stationary flow, the inlet pressure is a constant 11549 Pa, equal to the average of the corresponding pulsatile flow condition. Outlet velocity was similarly chosen as a pulsatile function of time, taken from data in Siogkas et al, with the outlet velocity for stationary flow being the average of 0.11375 m/s. The diffusivity of nanoparticle in blood was chosen as that of PLGA, a common polymer from which nanoparticles are made [11]. Nitric oxide values were used for diffusivity of drug in blood and in plaque [12][13]. Critical shear stress is taken from Korin et al. [1] Viscosity and density of blood are commonly known values. Concentrations of nanoparticle and drug at the inlet were estimated from Korin et al [2].

Table 2: A list of input parameters used in this model

Parameter	Symbol	Value	Unit	Source
Pressure at inlet	P	$P_{in}(t)$	Pa	[10]
Outlet velocity	u	$u_{out}(t)$	m/s	[10]
Diffusivity of nanoparticle in blood	D_n	$1 \cdot 10^{-3}$	$\mu m^2/s$	[11]
Diffusivity of drug in blood	$D_{d,b}$	3300	$\mu m^2/s$	[12]
Diffusivity of drug in plaque	$D_{d,p}$	848	$\mu m^2/s$	[13]
Critical shear stress	τ_{crit}	10	Pa	[1]
Viscosity of blood	μ	0.0032	$Pa \cdot s$	[14]
Density of blood	ρ	1060	kg/m^3	[15]
Concentration of nanoparticle at inlet	$c_{n,in}$	0.1	g/m^3	N/A
Concentration of drug at inlet	c_d	0	g/m^3	N/A

4. Results & Discussion

4.1 Mesh

To determine the element size for the mesh, a mesh convergence was performed as shown in Appendix C. It was performed by calculating the volume integral of the velocity field in the entire blood flow subdomain. It was found that the integral only changed by 1% by altering the mesh from 'fine' to 'extra fine'. All of the discrepancies in the mesh occured in the area around the plaque. So, in order to make calculations more accurate, the area around the plaque was refined, as shown in Figure 5. This decreased discretization error in the areas where there are larger changes. The volume integral of drug concentration over the entire domain only changed by .15% from 3x to 4x refinement, therefore a "fine" mesh with 3x refinement over the region of plaque was chosen for the model. This mesh can be seen in Figure 4.

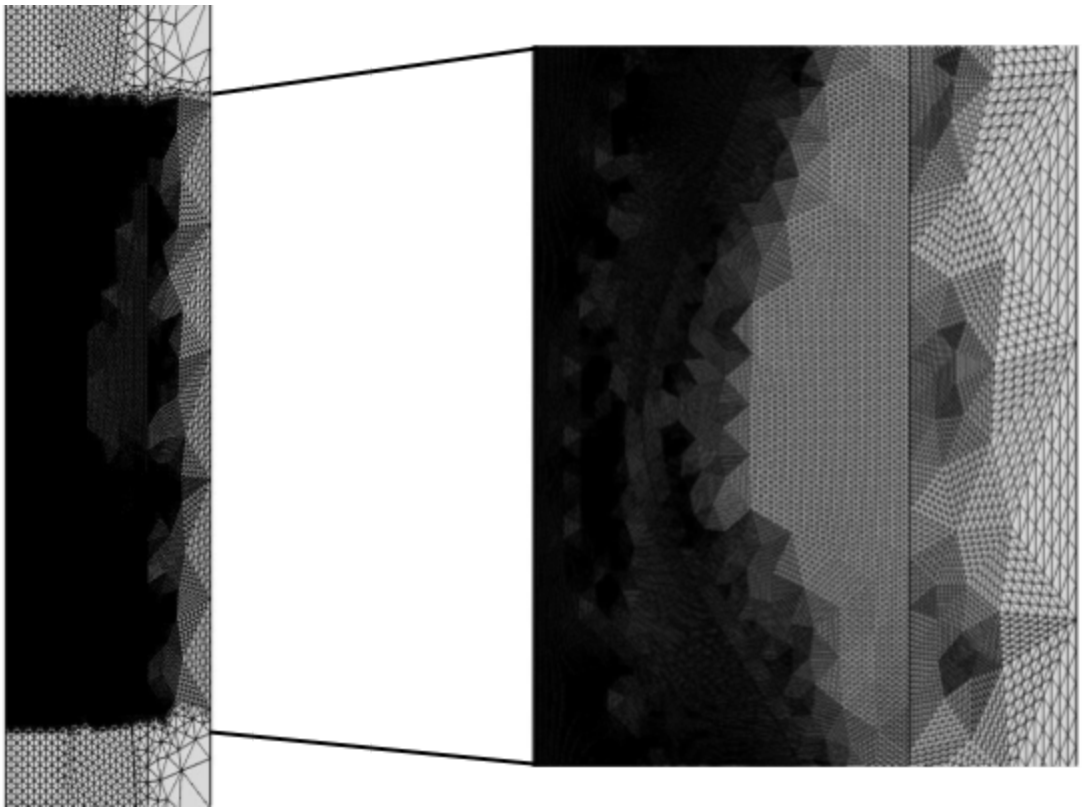


Figure 5: Mesh for fluid flow and transport of diluted species shown at the stenotic section of the artery. The element size chosen in COMSOL for this mesh is "fine," with a 3x refinement over the expanded region.

4.2 Flow Characteristics

The velocity profile in the blood vessel at various time points is shown in Figure 6. The pulsating nature can be observed by the drastic changes in velocity magnitude over time. This profile agreed with the intuition that the velocity should have increased at the beginning of the plaque to satisfy continuity due to a smaller vessel diameter. Total mass continuity can be used to relate the fluid velocity to the cross-sectional area of the flow for incompressible fluids. Specifically, fluid velocity is inversely related to the cross-sectional area, meaning that the fluid velocity should increase where the cross-sectional area is decreasing, such as at the apex of the plaque. It can also be seen in Figure 6 that the profile becomes more homogeneous further down the length of the vessel, where it eventually returns to a fully formed flow.

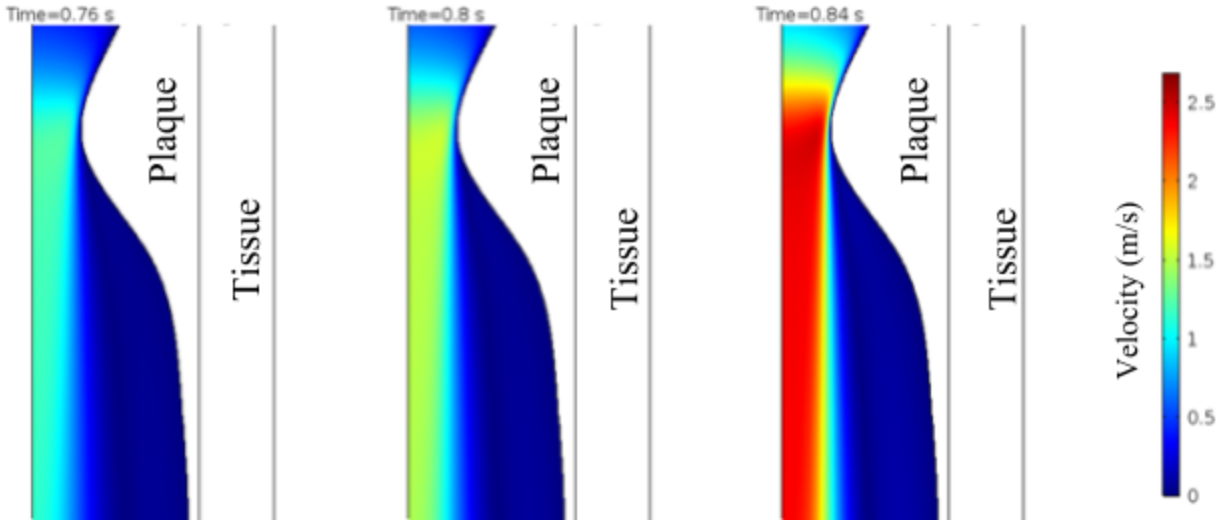


Figure 6: Velocity profile in the model at 0.76, 0.8, and 0.84 s. The velocity (m/s) is highest at the center of the artery and lowest at the wall. It increases considerably in the area near the constriction. The velocity magnitude varies in short amounts of time due to the pulsatile flow.

The shear stress profile in the blood vessel at nine seconds is shown in Figure 7. One can see the shear stress reaching a maximum value of around 100 Pa along the edge of the plaque, upstream of the midpoint, where the constriction is increasing. A band of higher-than-average (but not maximum) shear stress can be seen continuing from that point down through the bottom of the frame. As defined, Newtonian flow has shear stresses which are linearly proportional to the velocity gradient at that point, where the constant of proportionality is the fluid's viscosity. Since this model assumes incompressible, Newtonian flow, and since the viscosity is not changing, the magnitude of the shear stress at any point should be indicative of the magnitude of the velocity gradient at that point. Along that cross-section, for fully-formed laminar flow the velocity profile should be parabolic which implies that the rate of change in the velocity should

be decreasing as it approaches its inflection point (the axis of symmetry), where the rate of change in the velocity is zero. This profile explains why the shear stress decreases as one moves toward the axis of symmetry where the velocity gradient is zero. To explain why the shear stress is only higher than average upstream of the midpoint of the plaque, consider that an element of fluid moving through the constriction will gain significant axial momentum while moving through the constriction. When the lumen widens downstream, it will require significant axial displacement before the smaller radial forces are able to re-attain fully formed flow by spreading this fast moving flow in the radial direction. This explains why the maximum shear stresses only occur on the upper half of the constriction and why the band of higher-than-average shear stresses continues a significant distance downstream from that point. Essentially, the fluid is moving so fast that is is unable to account for the rapid change in lumen diameter. It is important to note that many points in this area exceed the critical shear stress of the nanoparticle, which is 10 Pa. One must also keep in mind that this shear stress varies with time due to the pulsatile flow.

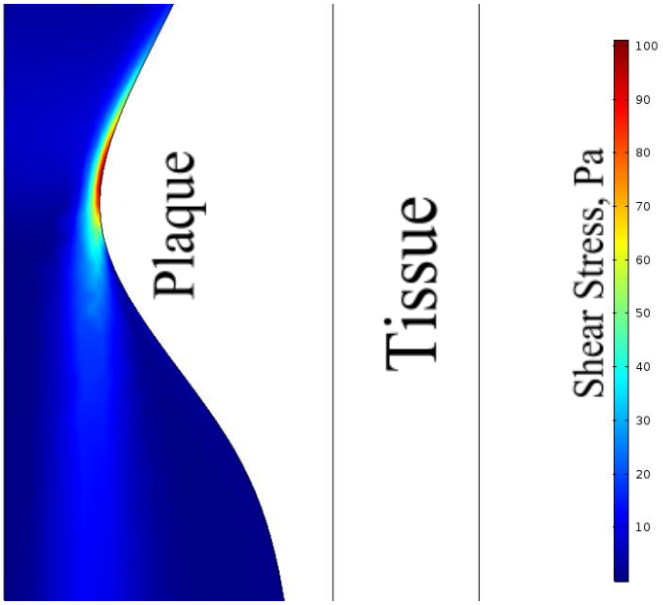


Figure 7: Shear stress profile in the model stenotic coronary artery. The highest shear stress occurs near the peak of the plaque formation. It can also be seen that a higher-than-average shear stress is present downstream of the plaque and closer to the center of the vessel.

4.3 Short Term Nanoparticle Diffusion

Diffusion of nanoparticle was coupled with fluid flow, simulated earlier. The concentration of the nanoparticles can be seen in Figure 8. The amount and profile of nanoparticles that breakdown vary with time as a result of the pulsatile flow. When the shear stress was generally higher, more nanoparticles were broken down as seen in Figure 8 at time

1.36 seconds; when the shear stress is smaller in the blood, fewer nanoparticles overall were broken down and this occurred closer to the plaque as seen at time 1.7 seconds.

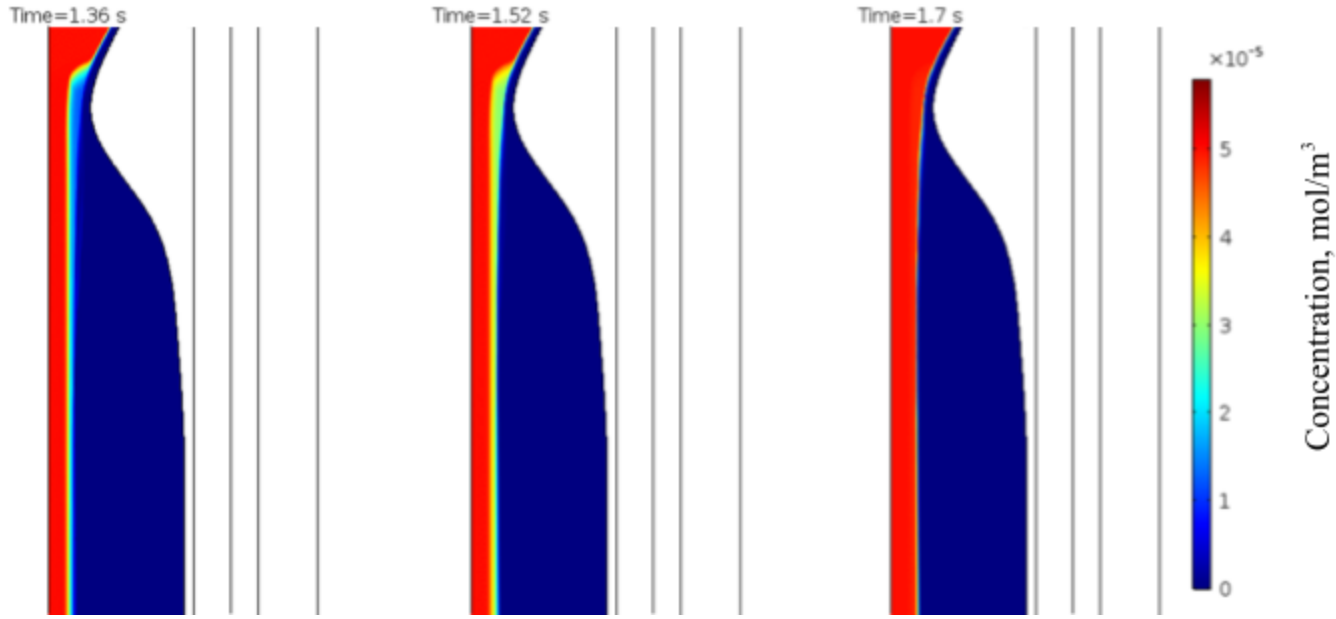


Figure 8: Nanoparticle concentration profile in blood of stenotic coronary artery for various time points. Nanoparticles were released closest to the point of greatest stenosis as expected. The concentration profile stays confined to a linear region close to the axis of symmetry as the plaque declines.

4.4 Short Term Drug Diffusion

Diffusion of the drug was coupled with the earlier simulations of fluid flow and nanoparticle diffusion. The amount of drug released from the nanoparticle varies with time as a result of the pulsatile flow. It can be observed that initially the drug penetrates the plaque. As the flow changes so does the the amount of drug released. Corresponding with Figure 8, more drug was released as more nanoparticle was broken down. As seen in Figure 9, more drug was released at time 1.36 seconds, while less was released at 1.7 seconds.

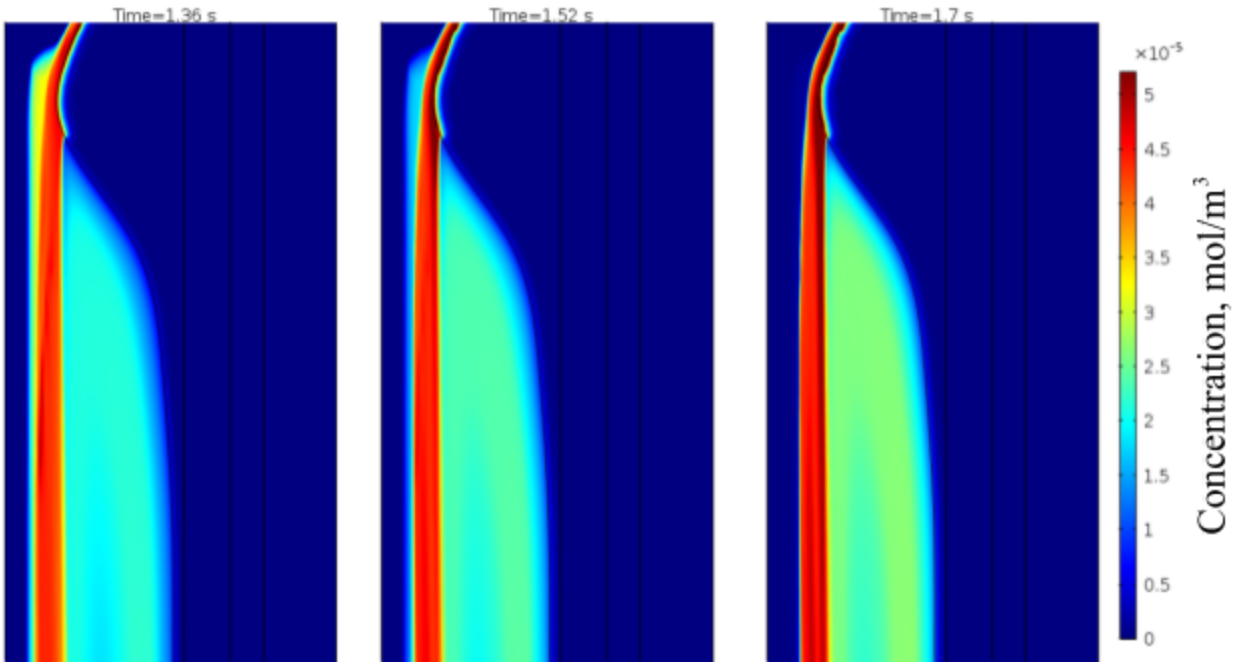


Figure 9: Drug concentration profile in the blood of the model stenotic coronary artery for various time points. Drug generation is only present in areas of sufficient shear stress, which occurs by the plaque. At early times it can be seen that the drug only begins to penetrate the plaque and diffuse into the tunica intima.

4.5 Long Term Diffusion

Due to computational constraints, it was not feasible to simulate pulsatile flow along with diffusion for long durations. Therefore, it was necessary to use steady flow for long term calculations. Using the longest pulsatile flow simulation, there was an observed difference of <0.5% in the amount of drug released between pulsatile flow and stationary flow models. Therefore, the stationary flow assumption was deemed acceptable for modeling long term drug delivery. Stationary flow was implemented using the average values of the pulsatile boundary conditions (pressure inlet and velocity outlet).

A 30 minute simulation of nanoparticle transport is seen at several time points in Figure 10. A steady stream of nanoparticles was observed near the center of the vessel after passing through the constriction. More importantly, one can see sections along the tissue side of the nanoparticle stream where one would intuitively expect nanoparticles but where none are present. These areas of low nanoparticle concentration approximately correspond to the areas where the shear stress is the highest. In a barely discernible section between the high and low concentration areas, one can observe mid-range concentrations. This could be caused by partial breakdown of nanoparticles in those regions or by radial diffusion of the nanoparticles in the

adjacent region. In any case, this effect is rapidly overcome by the influx of nanoparticles from upstream and by 80 seconds appears to reach a steady state.

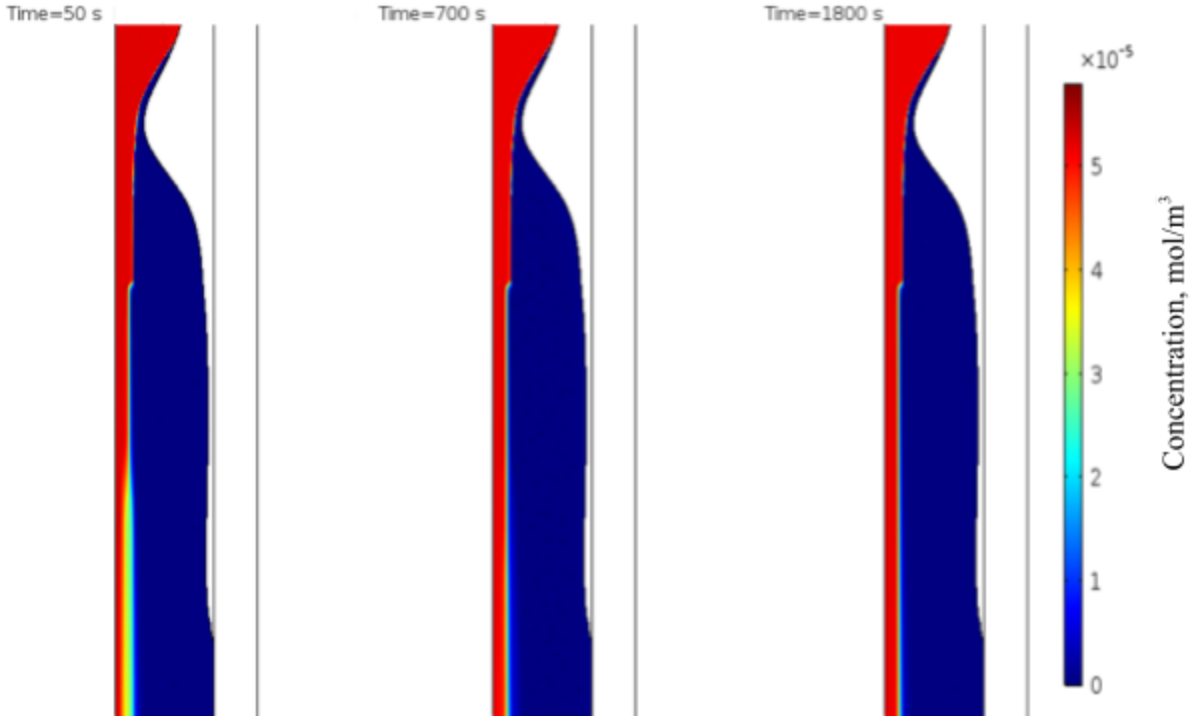


Figure 10: Long-term nanoparticle concentration profile in model stenotic coronary artery over multiple time points. The nanoparticles breakdown close to the plaque in the constriction and remain in the center of the vessel as the blood flows.

Drug diffusion shows results which are practically complementary to the long-term nanoparticle diffusion simulations. This is expected, since drug is generated only where nanoparticle is destroyed which occurs in areas where shear stress is higher than average. Most drug is released just before the plaque reaches its maximum thickness, as shown in Figure 11 and the concentrations downstream are mainly due to transport from that area as opposed to generation in that location. Though most drug is released before the narrowest section of the vessel, convection significantly outweighs diffusion due to the high blood velocity. As a result, most drug is transported downstream and diffuses into the arterial walls unaffected by plaque. By 1800 seconds the drug reaches a significant concentration within the plaque.

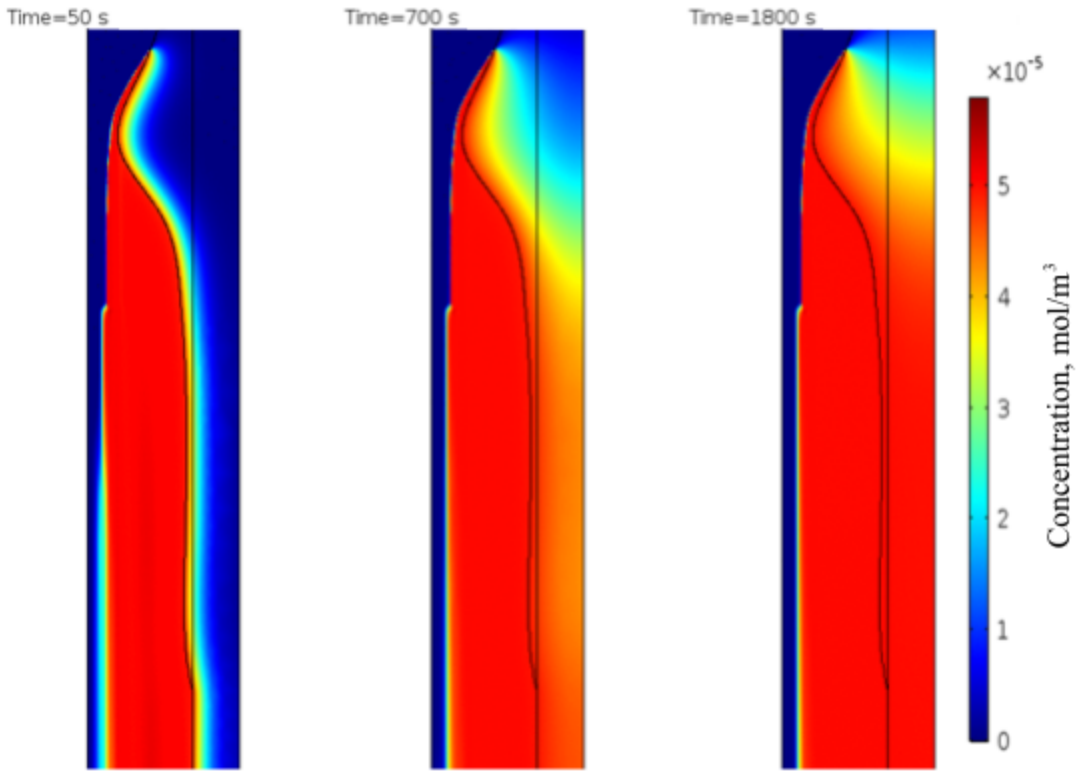


Figure 11: Drug concentration profiles in model stenotic coronary artery for multiple time points. Most of the drug is released near the plaque. However, much of it is transported downstream of the constriction before it diffused into the artery walls.

4.6 Validation

To check the model's validity, a literature search was performed on characterizations of obstructed coronary arteries. The accuracy of the velocity data from the COMSOL model was validated using the Ofili et. al. paper characterizing the blood flow in coronary arteries. The mean velocity in the paper for the coronary arteries measured for healthy patients varied from 0.2 to 0.3 m/s as compared to the average velocity measured in this study of 0.18 m/s measured at the thickest portion of the plaque [16]. An additional emphasis was placed on validating the shear stress profile, since the shear stress is what determines whether or not nanoparticles release drug.

The accuracy of the shear stress data from the COMSOL model can be validated by a 1993 study of hemodynamic factors in a stenotic right coronary artery as seen in Figure 12. Shear stress at the center of stenosis ranged between 50-200 Pa over 18 trials, with an average of 135 Pa. This is close to the computed value of 115 Pa [17].

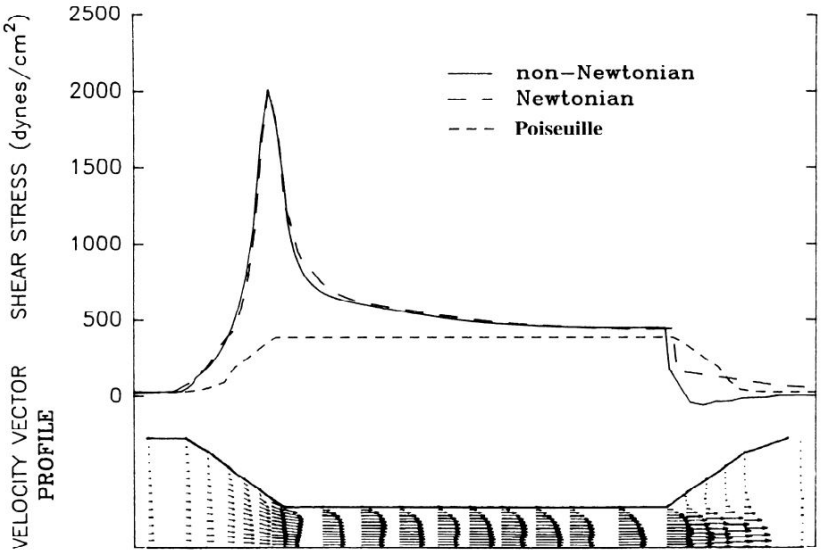


Figure 12: Average Shear Stress profile for 18 different trials. Shear stress drastically increases nearest to where the plaque begins. It gradually declines due to a smooth plaque morphology [17].

4.7 Sensitivity Analysis

Four input parameters were tested for the sensitivity analysis: particle critical stress, the initial nanoparticle concentration, and the diffusion coefficient of the drug in the blood and plaque. Each parameter was varied by ± 20%. The effect of these changes was observed by taking the integral of drug concentration over the entire domain and comparing the relative difference. The integral was most sensitive to changes in the concentration and critical particle stress and very insensitive to the diffusivity in the blood and plaque. From a treatment standpoint, only initial nanoparticle concentration and the critical particles shear stress can be manipulated.

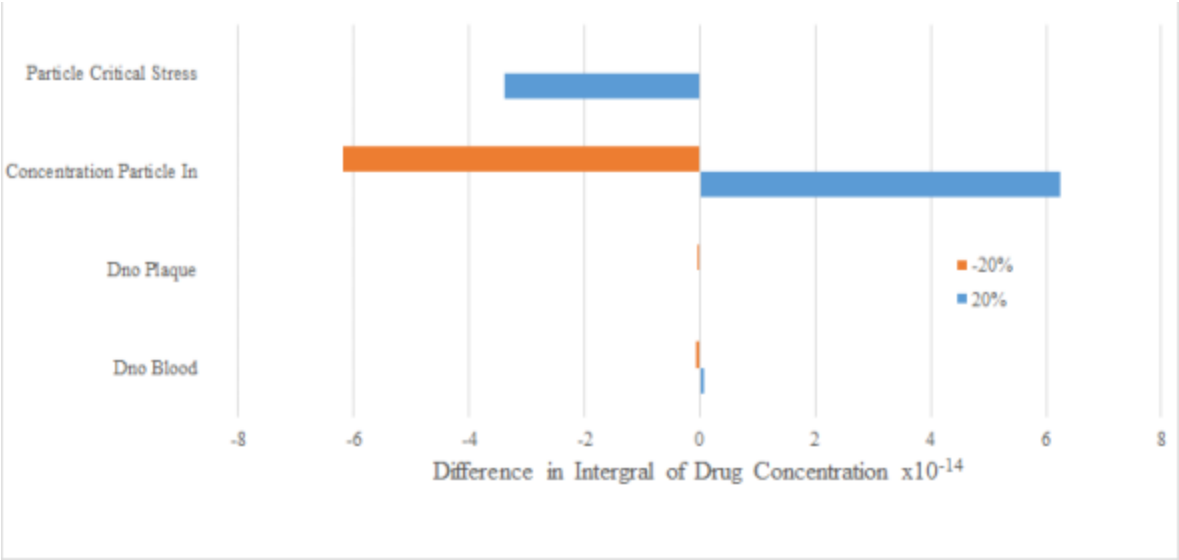


Figure 13: Sensitivity analysis of drug concentration over entire domain (fluid, plaque, and tissue) with varying diffusivities, inlet drug concentrations, and nanoparticle critical stress. From this analysis, the most influential parameters were found to be the critical shear stress of the particle, and the concentration of the nanoparticle at the inlet of the vessel.

4.8 Optimization

The objective function was applied to two parameters: the critical shear stress and the nanoparticle perfusion concentration because these are the two parameters that can realistically be controlled when designing a nanoparticle carrier. The following concentration flow rate constraints were used to formulate an optimization function [2].

$$\dot{m}_{no,min} = 5\ \mu g/min$$
$$\dot{m}_{no,max} = 500\ \mu g/min$$

These yielded the following optimization function:

$$L(\bar{c}_i(t)) = \sum_{i}^{n}(c_{drug,plaque,i}(t))/(c_{drug,out,i}(t)) \quad (6)$$

The optimization showed a higher critical stress for the nanoparticle until it exceeded 75 Pa. This result is expected since having a higher critical stress means the nanoparticle will not breakdown until it is closer to the wall. However, this also results in less drug getting released overall. The optimal value of 75 Pa was close to the highest recorded shear stress in our stationary flow model. Therefore when the critical shear stress of the nanoparticle was above 75 Pa no drug was released.

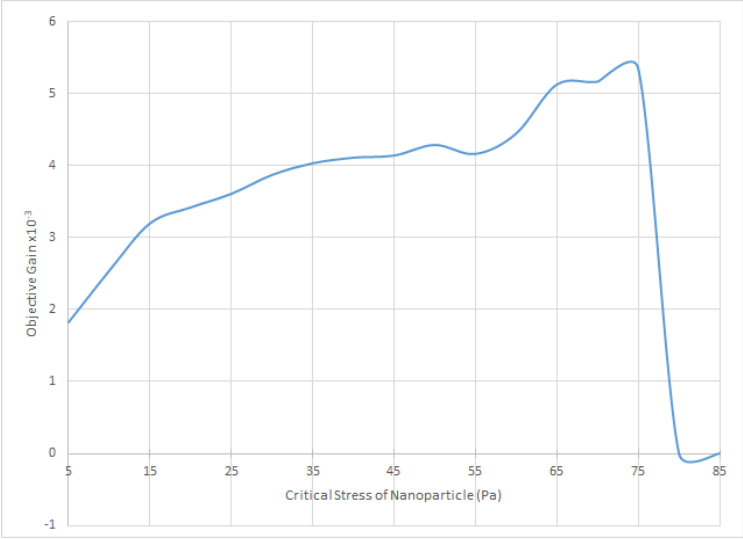


Figure 14: Optimization objective gain function was applied to determine the optimum critical shear stress of the nanoparticle for maximum drug diffusion into the arterial wall and minimum amount of drug flowing out of the vessel. The optimum critical shear stress was found to be 75 Pa.

Next the nanoparticle inlet concentration was optimized. The range for the objective function for nanoparticle perfusion is between $5.78 \cdot 10^{-4}$ mol/m^3 and 0.046 mol/m^3. The function seems to achieve similar maxima at several different perfusion concentrations. However, based on current clinical guidelines for the administration of nitroglycerin, maximum allowable amount of nitroglycerin infused is about, .05 mol/m^3. So we chose the maximum of 0.045 mol/m^3 to be under the maximum allowable dosage in case all nanoparticles were to spontaneously break down and release drug.

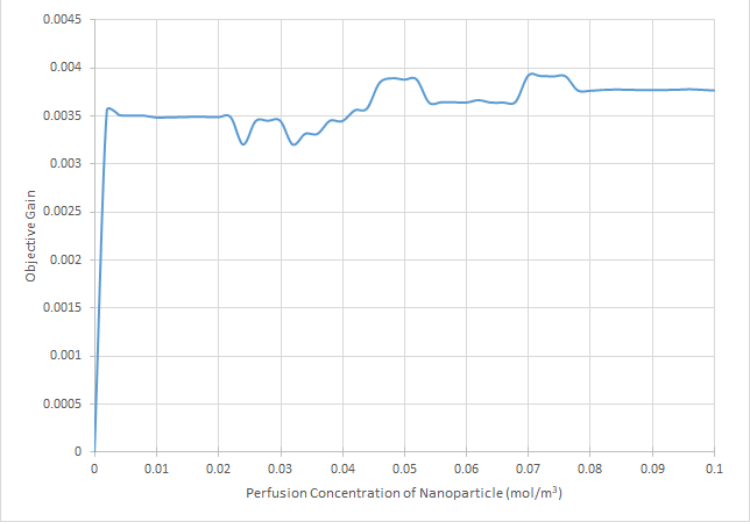


Figure 15: The objective gain function was applied to find the nanoparticle inlet concentration that maximizes drug diffusion into the arterial wall while minimizing drug remaining in the blood. The optimum inlet concentration was chosen to stay within recommended clinical maximum of 0.5 mol/m^3.

5. Conclusion & Design Recommendations

The model demonstrates that shear stress-induced nanoparticle drug delivery for treatment of coronary artery disease may not be as effective as imagined since little to no drug diffused into the artery wall upstream of the plaque apex. The effectiveness of this method is certainly dependent on the encapsulated drug as well as the disease severity and other individual variations. This study showed that the specificity of this method can be improved by simple optimization of the critical shear stress and inlet concentration of the nanoparticle. However, even with optimization the process still delivers almost all of the drug downstream of the plaque apex. Therefore shear stress sensitive nanoparticles do not appear to optimally deliver nitroglycerin to coronary artery stenoses. However, clinical experiments must be performed to accurately evaluate the effectiveness of this method.

For further investigation, it is important to look at the effect of treatment on other plaque morphologies and in other blood vessels as well as on a realistic 3D geometry, with non-newtonian flow, or even with artery dilation in response to drug release. It is expected that this method will perform better in type III plaque morphologies where the greatest constriction occurs at the beginning of the plaque, allowing a full plaque length for drug diffusion as opposed to only a half plaque length. It would also be important look at the release of the drug in capillaries where shear stresses may also be high. While this may not be an effective means of targeted drug delivery for coronary artery disease, shear stress induced nanoparticles could potentially be useful in other diseases. For example, it has been shown that fluid shear stress activates YAP1, which affects cancer cell motility [18]. This method could be used as a means of targeted gene therapy to prevent metastasis.

Acknowledgements

We would like to thank Professor Ashim Datta for his support and guidance, Mayuri Ukidwe for her dedication and COMSOL advice, and Dr. Rick Evans and Dr. Traci Nathans-Kelly for reviewing and critiquing our report. Without all of their assistance, this project would not have been possible.

Appendix A: Mathematical Model

Pulsatile Flow Pressure and Velocity Profiles

A periodic pressure function, as shown in the figure below, was used to describe the pressure boundary condition at the inlet for pulsatile flow.

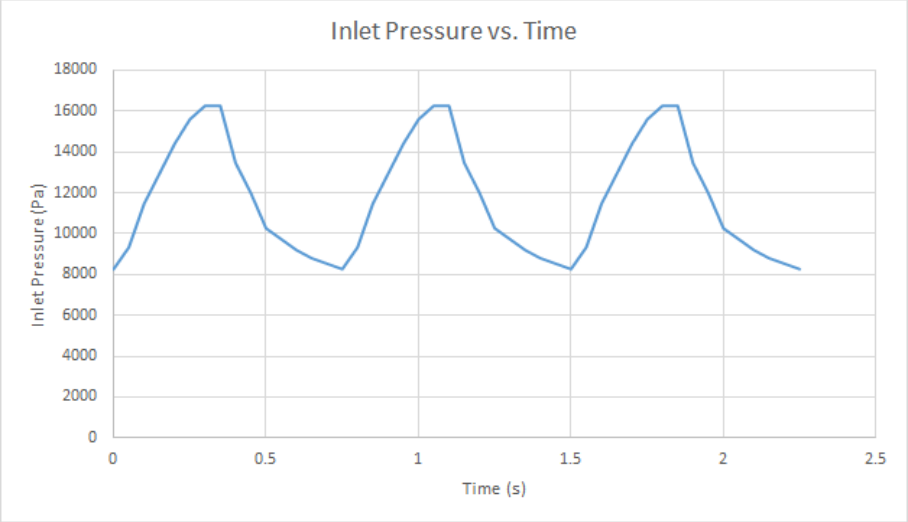


Figure 16. The inlet pressure boundary condition for pulsatile blood flow shown over 3 periods. Pressure oscillates approximately between 8000-16000 Pa [10].

A periodic velocity function, as shown in the figure below, was used to describe the velocity boundary condition at the outlet for pulsatile flow.

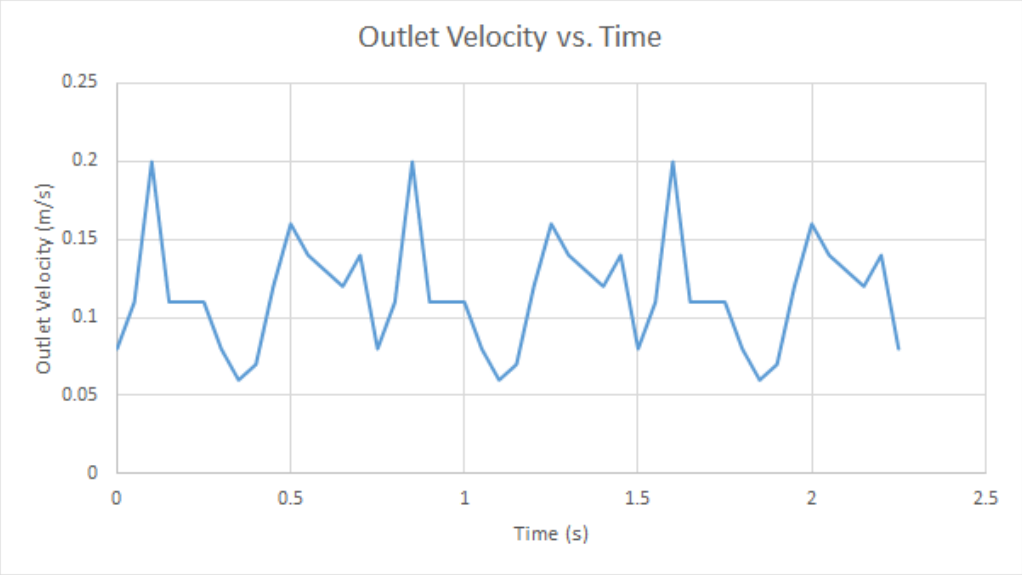


Figure 17. The outlet velocity boundary condition shown over 3 periods. It oscillates approximately between 0.05 and 0.2 m/s [10].

Appendix B: Solution Strategy

The calculation time took approximately 3 hours and 2GB memory. The PARADISO Solver was used by default and there was no reason to change it. Time stepping was free by default and did not cause any issues. The relative tolerance was default at 0.01. Triangular mesh elements were used.

Mesh Convergence

To ensure that discretization error was minimized a mesh convergence was performed on both velocity and drug concentration as can be seen in Figures 18 and 19, respectively. The integral of the values over the domain was calculated, which give more accurate values rather than only calculating the value at a given point.

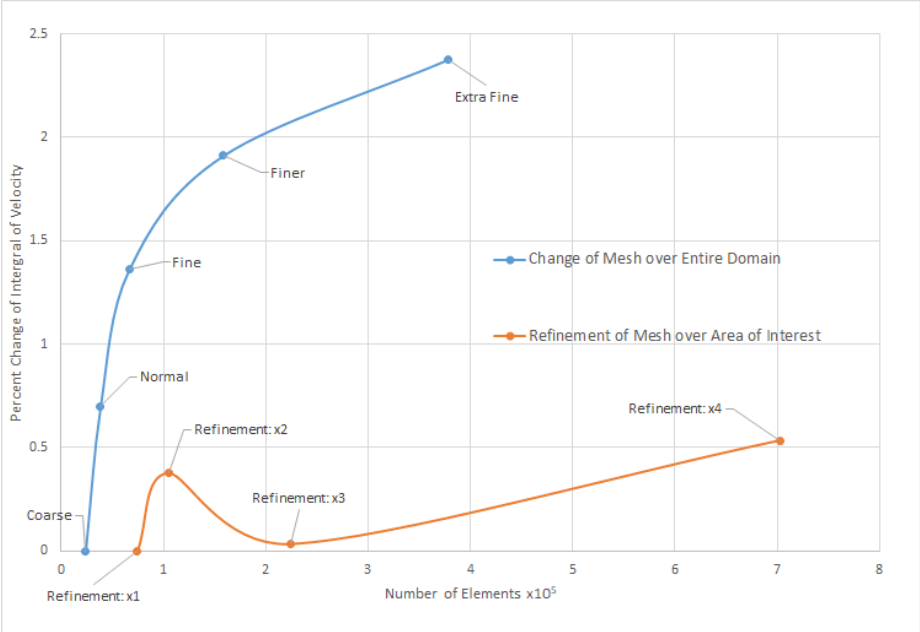


Figure 18: Mesh Convergence using the integral of the velocity over the entire vessel domain at two seconds. One was done by changing the mesh for the entire structure from coarse to extra fine. The other was performed by setting the entire mesh to fine and refining the area containing plaque. Marginal changes can be seen after a refinement of x2 by the plaque.

Figure 19: Mesh Convergence using the integral of the drug concentration over the entire vessel domain at two seconds. The entire mesh is fine and the area containing plaque was increasingly refined. Marginal changes can be seen after a refinement of x3 by the plaque.

Appendix C: References

1. Korin, Netanel, et al. “Shear-Activated Nanotherapeutics for Drug Targeting to Obstructed Blood Vessels.” Science, vol. 337, no. 6095, 10 Aug. 2012, pp. 738–742., doi:10.1126/science.1217815.
2. Armstrong, P. W., et al. “Pharmacokinetic-Hemodynamic Studies of Intravenous Nitroglycerin in Congestive Cardiac Failure.” Circulation, vol. 62, no. 1, Jan. 1980, pp. 160–166., doi:10.1161/01.cir.62.1.160.
3. Centers for Disease Control and Prevention, Centers for Disease Control and Prevention, wonder.cdc.gov/ucd-icd10.html.
4. “Coronary Artery Disease.” Mayo Clinic, Mayo Foundation for Medical Education and Research, 28 Dec. 2017, www.mayoclinic.org/diseases-conditions/coronary-artery-disease/diagnosis-treatment/drc-20350619.
5. “Nitroglycerin (Oral Route, Sublingual Route) Side Effects.” Mayo Clinic, Mayo Foundation for Medical Education and Research, 1 Mar. 2017, www.mayoclinic.org/drugs-supplements/nitroglycerin-oral-route-sublingual-route/side-effects/drg-20072863.
6. “Statin Side Effects: Weigh the Benefits and Risks.” Mayo Clinic, Mayo Foundation for Medical Education and Research, 26 Apr. 2016, www.mayoclinic.org/diseases-conditions/high-blood-cholesterol/in-depth/statin-side-effects/art-20046013.
7. Nature News, Nature Publishing Group, www.nature.com/subjects/nanoparticles.
8. Till Saxer, Andreas Zumbuehl, Bert Müller; The use of shear stress for targeted drug delivery, Cardiovascular Research, Volume 99, Issue 2, 15 July 2013,Pages 328–333, https://doi.org/10.1093/cvr/cvt102
9. Beaumont, Ryan, et al. “Using Fuzzy Logic for Morphological Classification of IVUS-Based Plaques in Diseased Coronary Artery in the Context of Flow-Dynamics.” Soft Computing, vol. 14, no. 3, May 2009, pp. 265–272., doi:10.1007/s00500-009-0401-9.
10. Siogkas, Panagiotis K., et al. “Patient-Specific Simulation of Coronary Artery Pressure Measurements: AnIn Vivo Three-Dimensional Validation Study in Humans.” BioMed Research International, vol. 2015, 2015, pp. 1–11., doi:10.1155/2015/628416.
11. X. Zhu and R. D. Braatz, “A mechanistic model for drug release in PLGA biodegradable stent coatings coupled with polymer degradation and erosion,” Journal of Biomedical Materials Research Part A, vol. 103, no. 7, pp. 2269–2279, Dec. 2014.

12. Butler, Anthony R., et al. “Diffusion of Nitric Oxide and Scavenging by Blood in the Vasculature.” Biochimica Et Biophysica Acta (BBA) - General Subjects, vol. 1425, no. 1, 1998, pp. 168–176., doi:10.1016/s0304-4165(98)00065-8.
13. Liu, Xiaoping, et al. “Nitric Oxide Diffusion Rate Is Reduced in the Aortic Wall.” Biophysical Journal, vol. 94, no. 5, 2008, pp. 1880–1889., doi:10.1529/biophysj.107.120626.
14. Sloten, Jos Vander. 4th European Congress of the International Federation for Medical and Biological Engineering: ECIFMBE 2008, 23-27 November 2008, Antwerp, Belgium. Springer, 2008.
15. Cutnell, John D., and Kenneth W. Johnson. Physics. John Wiley, 2004.
16. Ofili, Elizabeth O., et al. “Differential Characterization of Blood Flow, Velocity, and Vascular Resistance between Proximal and Distal Normal Epicardial Human Coronary Arteries: Analysis by Intracoronary Doppler Spectral Flow Velocity.” American Heart Journal, vol. 130, no. 1, 1995, pp. 37–46., doi:10.1016/0002-8703(95)90233-3.
17. Strony, J., et al. “Analysis of Shear Stress and Hemodynamic Factors in a Model of Coronary Artery Stenosis and Thrombosis.” American Journal of Physiology-Heart and Circulatory Physiology, vol. 265, no. 5, 1993, doi:10.1152/ajpheart.1993.265.5.h1787.
18. Lee, H., et al. “Fluid shear stress activates YAP1 to promote cancer cell motility.” Nature Communications, vol. 8, January 2017, p. 14122., doi:10.1038/ncomms14122.