Drug Delivery from PLGA-Coated Stents: Optimization of Strut Geometry and Extent of Embedment in the Arterial Wall

BEE 4530 Computer-Aided Engineering: Applications to Biomedical Processes
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Executive Summary

Patients with atherosclerosis experience plaque buildup in the coronary artery, reducing blood flow and increasing the likelihood of a blood clot. Balloon angioplasty and the implantation of a metal stent are physical mechanisms that have been used to treat atherosclerosis and the associated stenosis of the coronary artery with some success; however, restenosis occurs in a substantial amount of patients. Most recently, biodegradable drug eluting stents have been shown to significantly lower restenosis rates, where an implanted stent is coated with biodegradable polymer and an immunosuppressant therapeutic drug; however, many parameters have yet to be optimized in this method of treatment.

This project considers a stent coated with the biodegradable polymer poly lactic-*co*-glycolic acid (PLGA) and immunosuppressant sirolimus (also known as rapamycin), for circular and square geometries, and half and full extents of embedment. A mass transport simulation in COMSOL 5.1 Multiphysics was used to quantitatively simulate this process with the objective of optimizing these design options with respect to drug delivery. Further, this project aimed to suggest potential improvement to current stent designs.

Our model showed that the fully embedded stent resulted a significantly higher concentration profile over a 50-day period for both geometries. Likewise, the square model resulted in a slightly preferred elution profile than the circular model for both extents of embedment. The major limitation of the half-embedded model was loss of drug to the bloodstream; hence, we propose two models for improvement: (1) creating an impermeable membrane at the coating-bloodstream interface, and (2) exclusively coating the half of the stent that is in contact with the arterial wall. Design 1 resulted in a significantly increased spatially averaged concentration profile in the arterial wall at all time points in comparison with the benchmark model, and design 2 showed similar profile to the benchmark, despite containing half the mass of drug.

1.0 Problem Statement

In designing arterial stents, several parameters can be considered for optimization. This model seeks to determine the effects on the concentration elution profile (spatially and temporally) of sirolimus in the arterial wall with varying extent of embedment, and stent geometry. Specifically, half- and full-embedment of the stent were studied in circular and rectangular geometries. Further, the biodegradability of the stent coating, poly lactic-co-glycolic acid (PLGA), was taken into consideration in terms of its effect on sirolimus diffusivity.

2.0 Introduction to Drug Delivery via Biodegradable Coronary Stents

Atherosclerosis is a disease characterized by the deposition of cholesterol-laden plaque on the inner arterial walls. Over time, plaque narrows the coronary arteries, reduces blood flow to cardiac muscle, and increases the probability blood clot formation in the arteries.

Percutaneous coronary intervention, also known as coronary angioplasty, is a non-surgical procedure used to widen the stenotic coronary arteries and restore blood flow. However, restenosis, defined as the repeated narrowing of a blood vessel, was observed in 40% (Zhu & Braatz, 2015) of the arteries treated by percutaneous coronary intervention. Stents were developed and designed for insertion into the artery immediately after percutaneous coronary intervention. First-generation models were bare-metal stents (BMS), and both eliminated the risk of the artery collapsing post-procedure and reduced the risk of restenosis to 25% (Zhu & Braatz, 2015). More recently, through the development and refinement of drug-eluting stents (DEG), the risk of developing restenosis post-procedure has dropped below 10% (Zhu & Braatz, 2015). As foreign bodies, the presence of stents in the vessel wall will normally induce a foreign body response, resulting in the occurrence of neointimal hyperplasia, characterized by platelet adhesion, coagulation cascade activation, and a thickening of the arterial walls at the expense of arterial lumen space (Purcell, Tennant & McGeachine, 1997). As a result, drugs such as ticlopidine and clopidogrel, which are characterized as P2Y-receptor antagonists, act as platelet inhibitors that reduce the formation of blood clots within the opened vessel, therefore reducing vessel thrombosis following stent implementation (Lüscher et al., 2007).

As one of the leading treatment methods of atherosclerosis, several models and studies have been performed to analyze the impact that stent design has on drug delivery and restenosis. In particular, a study on the impact that stent design has on a drug-coated BMS found that the thickness of the stent resulted in an increase of flow separation, stagnation, and reattachment that would likely enhance platelet deposition and fibrin present, demonstrating that thin struts elicited less restenosis than thick struts (Kolandaivelu et al., 2011). The computation model used by this study set, however, was focused primarily on flow, and placed little focus on the how the thickening of the struts impacted the diffusion and delivery of drug from the coating.

Another computation model, this time modeling the concentration of drug within the arterial wall, was studied by Bozsak and Barakat (2014) to analyze the transport of different eluted drugs within the arterial walls. This model consisted of a 2D axisymmetric geometry with the axis of symmetry parallel to the flow within the vessel. The stent was implemented in a way so that each stent segment was wrapped around the inner circumference of the vessel, and the model was considered to represent only a 7mm segment of the vessel. While this model offers an alternative method of modeling the stent within the artery wall, we found that it would be more desirable to understand the impact of drug diffusion in longer segments of the vessel, and as such this model was rejected.

Zhu and Braatz (2014) presented a mathematical model that described the interconnected drug release in a PLGA-coated stent, and ensuing drug delivery, distribution, and pharmacokinetics in the arterial wall. The resulting integrative model was implemented in COMSOL 4.2. Zhu and Braatz first compared the intravascular drug delivery resulting from the PLGA-coated stent simulation with that from a biodurable stent. Although there was no observed difference in the resulting drug distribution between the PLGA-coated stent and biodurable stent, their research document that the PLGA-coated stent ensured a higher overall drug concentration

in the arterial wall over time. These findings reflect the low drug diffusivity and slow drug release associated with biodurable coatings.

The model for the PLGA stent coating was then utilized to investigate how drug delivery is affected by strut embedment, drug internalization, and interstitial fluid flow in the arterial wall. Simulation results demonstrated these three factors could greatly alter the arterial drug distribution, and, consequently, the average drug concentration. Simulations done to determine the impact that strut embedment has on the arterial wall revealed that the average drug concentration within the arterial wall tissue increases as the stent is further embedded within the arterial wall and surrounded by endothelial tissue. Increased interstitial fluid flow, caused by an increased transmural pressure difference between the perivascular space and lumen, resulted in lower average drug concentration in the arterial wall due to increased convection of the drug away from the arterial wall. Finally, Zhu and Braatz observed high internalization rates resulted in a high degree of spatial non-uniformity in arterial drug distribution for both the bound and free drug.

For our study, the paper done by Zhu and Braatz presented a first computation model of a biodurable model of a PLGA stent. We intend to improve the research done in this experiment by determining the impact that geometry and degree of embedment plays in the delivery and internalization of proliferation inhibiting drugs. As such, much of the set up and procedures are heavily based upon the Zhu and Braatz paper, including aspects such as the governing equations, parameter values, geometries, and initial conditions.

2.1 Problem Schematic

For computational simplicity, we modeled a one eighth section of the artery. Although the polymer coating decays via bulk erosion and degradation, it has been shown that the integral structure of the stent coating is maintained during the time scale under study (Xi et al., 2010), thus this domain is modelled as to not change in size during elution. Theoretical quantification of the drug diffusivity anisotropic ratio is not found in previous literatures, but Zhu and Braatz (2014) observed that anisotropic diffusivity ratio is around 9.1-15.7 based on expression estimation and they use an anisotropic ration of D_θ/D_r equals to 10 throughout the simulation. In this project, we follow the same step and assume D_θ/D_r equals to 10. While previous studies have reported the breakage of the coating on the drug eluting stent (Wang, Li, et al. 2014), in this project we assume that the PLGA coating is well reserved and that the stents do not undergo migration within the tissue.

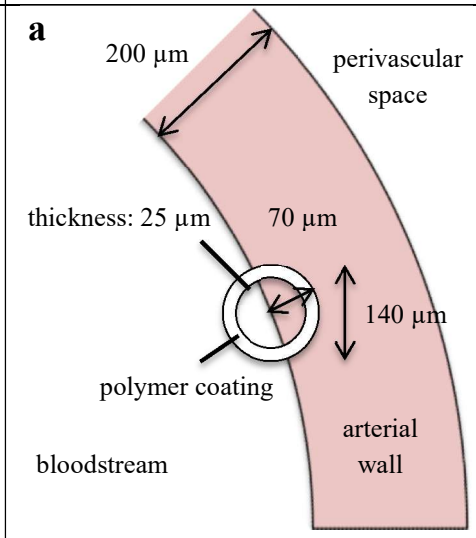
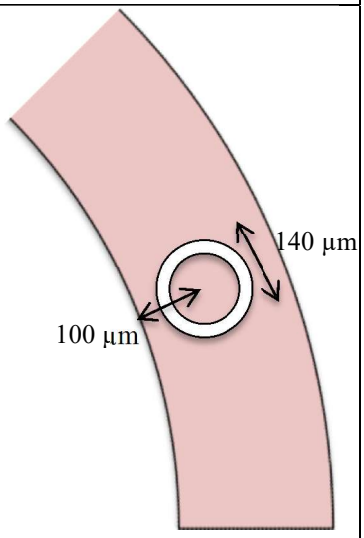
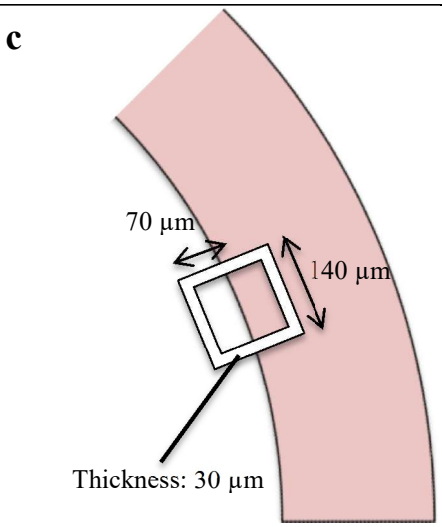
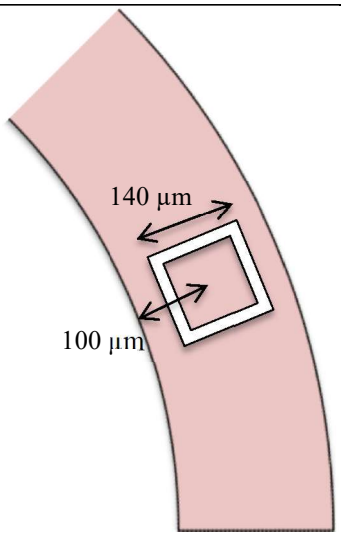
	Extent of Embedment	
Geometry	Half	Full
Circle		
Square		

Figure 1a, 1b, 1c, 1d. Each figure displays an eighth segment of the wall of the artery. Each figure differs in the geometry and degree of embedment of the drug delivering stent. Figure 1a's stent has a circular geometry and is half embedded into the arterial wall. Figure 1b's stent has a circular geometry and is fully embedded into the arterial wall, centered in the middle of the wall. Figure 1c's stent has a square geometry and is half embedded into the arterial wall. Figure 1d's stent has a square geometry and is fully embedded into the arterial wall, centered in the middle of the wall.

2.2 Design Objectives

In designing arterial stents, several parameters can be considered for optimization. This model seeks to determine the effects of varying extent of strut embedment and stent geometry on the concentration elution profile (spatially and temporally) of sirolimus in the arterial wall.

The first and primary design objective of this project is to understand how different factors affect the efficiency of drug delivery process with a poly lactic-co-glycolic acid stent coated with PLGA. To specify this problem, we use model simulation to compare the drug delivery under different stent embedment (half stent embedment and full stent embedment) and the different shapes of the stent (square and circle). Refer to Figure 1 for an illustration of these distinctions.

The second design objective of this simulation is to modify existing stent design in order to increase the efficiency of drug-delivery from the stent strut into the arterial wall. In pursuing these design objectives, we seek to improve upon existing computational models for drug eluting stents.

3.0 Governing Equations

While the models utilized in the paper are generally applicable, specific parameters of the model, such as reaction kinetic values, can vary depending on the drug being used. For the simulation studies done within this project, we used the model parameters based upon sirolimus. Table A1 in the appendix shows the model input parameters, the mesh size information, and the reaction kinetic values for this study.

Sirolimus, c_D, diffuses out of the PLGA coating and into the surrounding arterial wall. Drug elution spatially and temporally out of the stent is dependent on the varying effective diffusivity of the PLGA coating, according to the governing equation:

$$\frac{\partial \mathrm{c}}{\partial \mathrm{t}} = \mathrm{D_{D,S}} \nabla^2 \mathrm{c_D} \qquad (1)$$

Effective diffusivity ($D_{D,S}$) of sirolimus in the stent coating varies as a result of erosion, defined as PLGA mass loss over time, and degradation, defined as the chemical breakdown of the polymer network. Zhu & Braatz (2015) have determined analytically that the effective drug diffusivity is described by:

$$D_{D,S} = \frac{(1-\phi) D_{S0} \left(\frac{M_w}{M_{w0}}\right)^{-a} + \kappa \phi D_{aq}}{1-\phi+\kappa\phi} \qquad (2)$$

Erosion is accounted for by the changing coat porosity ϕ, and degradation by the evolving PLGA molecular weight M_w. The constants D_{aq} and D_{S0} represent the diffusivity of sirolimus in water and initial diffusivity in solid PLGA respectively, where κ is the partition coefficient

between the two phases. Finally, M_{w0} is the initial molecular weight of the PLGA polymer, and a is a constant defining the dependency of drug diffusivity on PLGA molecular weight.

The molecular weight of PLGA follows a first order exponential decay:

$$M_w = M_{w0} e^{-k_w t} \quad (3)$$

Assuming the initial porosity of the coating is negligible, Zhu & Braatz (2014) analytically determined that porosity change follows the model:

$$\phi = 1 + e^{-2k_n t} - 2e^{-k_n t} \quad (4)$$

Above, k_w and k_n are experimentally determined rate constants corresponding to weight- and number-average molecular weight changes respectively.

Sirolimus diffusion within the arterial wall is described by:

$$\frac{\partial c_D}{\partial t} = D_{D,a} \nabla^2 c_D - k_a (S_o - c_B) c_D + k_d c_B \quad (5)$$

The diffusivity of sirolimus in the arterial wall ($D_{D,a}$) is an experimentally determined constant (Zhu & Braatz, 2014).

The binding of Sirolimus with the wall, c_B, has been modelled as a reversible binding reaction of the drug molecules with the binding sites, *S*:

Drug binding: $c_D + S \underset{k_a}{\overset{k_d}{\leftrightarrows}} c_B \quad (7)$

Once drug molecules are associated with binding sites, the cells take up and metabolize drug molecules as a first-order reaction:

Drug internalized: $c_B \xrightarrow{k_i} S + c_I \quad (8)$

Where c_I is the internalized drug concentration. The drug transport and interactions in the arterial wall are a combination of free drugs, bound drugs and internalized drugs described as follows:

$$\frac{\partial c_B}{\partial t} = k_a (S_o - c_B) c_D - k_d c_B - k_i c_B \quad (9)$$

$$\frac{\partial c_I}{\partial t} = k_i c_B \quad (10)$$

Above, S is the available binding sites and S_o is the initial concentration of binding sites in the arterial wall.

4.0 Boundary Conditions

For the half embedded models, a perfect sink condition is applied to the coating-lumen interface as a result of transport into the bloodstream. Sirolimus is assumed to be cleared away at the interface between the perivascular space and the arterial wall and thus a zero concentration condition is applied. Due to rotational symmetry, a no flux boundary condition is considered at the sides of the arterial wall. Finally, the epithelial cells lining the lumen prevent convective transport into the bloodstream, hence a no flux condition is applied to lumen-wall interface as well. See Figure 2 for a visual representation of the boundary conditions. It is important to note that neither internalized nor bound drug undergo transport within the arterial wall, and thus do not require boundary conditions.

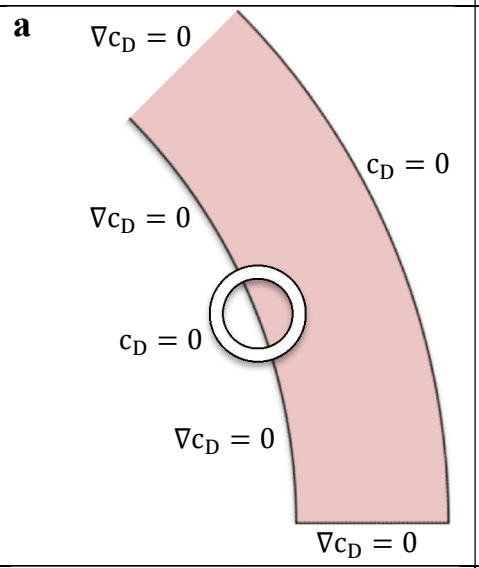
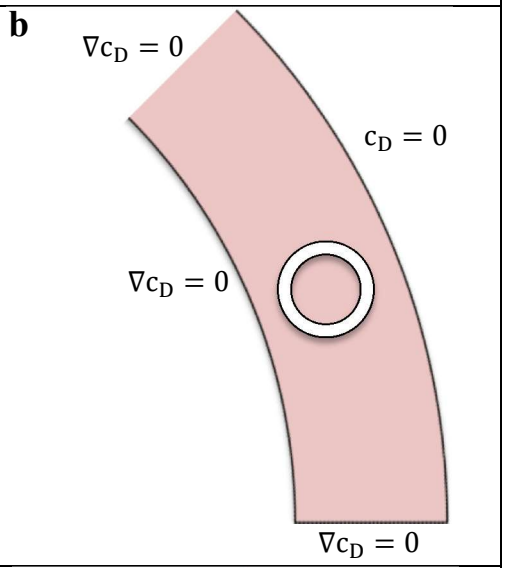
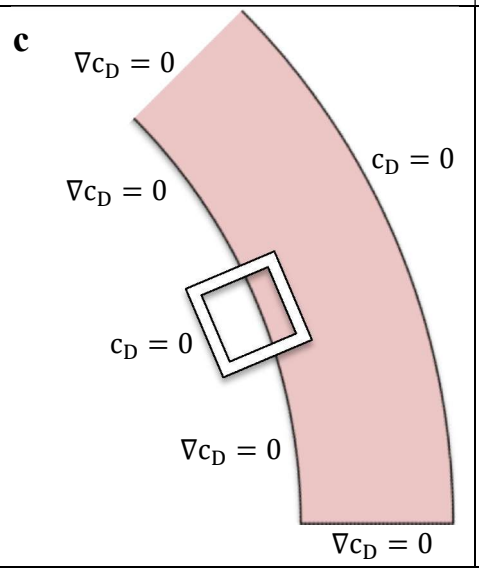
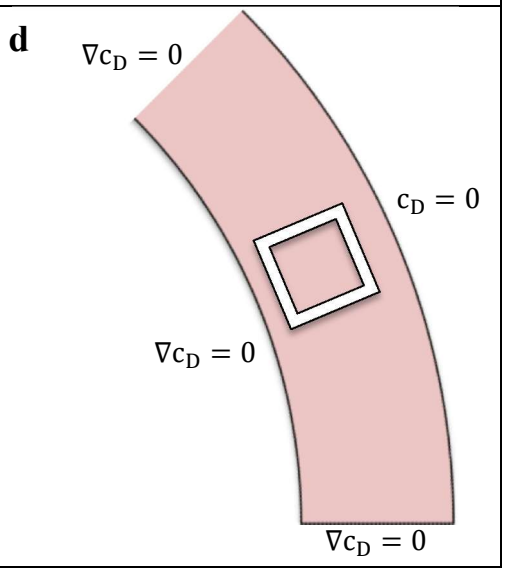
Domains	Extent of Embedment	
Geometry	Half	Full
Circle		
Square		

Figure 2a, 2b, 2c, 2d: Mathematical representations of the boundary conditions for (a) circular geometry, half embedment; (b) circular geometry, full embedment; (c) square geometry, half embedment; (d) square geometry, full embedment.

5.0 Initial Conditions

The initial conditions are the same for all four models. The initial free sirolimus concentration within the stent domain is defined as c_D which equals 10^{-5} M. For both the bound drug and internalized drug concentrations, the lack of tissue presence within the stent means that both c_B and c_I are equal to zero, as drug bound and drug internalized are variables exclusive to the arterial wall domain.

Initially, sirolimus present exclusively within the stent, thus the concentrations of free drug, bound drug, and internalized drug are all equal to zero within the arterial wall domain at the initial time step.

6.0 Results

6.1 Model Validation

From the COMSOL simulation, a concentration profile displaying the spatially averaged concentration of both free and bound drug over the course of 50 days was obtained for the half embeded, square geomoetry stent (Figure 3b). The simulation results were validated by comparing the spacially averaged free and bound sirolimus concentration with respect to time for the half embedded, square geometry stent with the results obtained from Zhu & Braatz 2014 (Figure 3a).

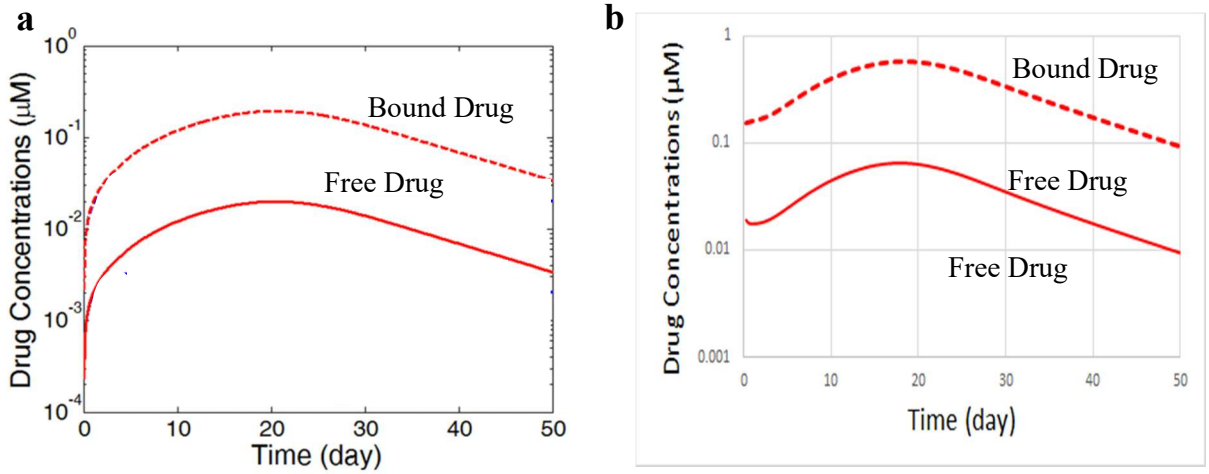


Figure 3a, 3b: Spatially averaged concentration in the arterial wall (square geometry, half embedment) over 50 days according to peer reviewed study (Zhu & Braatz, 2014) (3a), and our model (3b).

When comparing these results, both the free and bound drug concentration profiles demonstrate similar trends and magnitudes. Both plots demonstrate logorithmic growth until a maximum is reached near the 20 day mark. From that point onward the concentration begins to show an almost constant rate of degredation.

While the fact that the trends and patterns onserved in our simulation results is a positive indication that the simulation was set up correctly, the profiles from Zhu and Braatz further validated our results due to how both results are within the same magnitude. The bound drug concentration in both plots remained between 0.01 μM and 1 μM of sirolimus, while the free drug concentration in both plots was lower by a factor of 10 at around 0.001 and 0.01 μM.

Imperfections between the two data sets can be explained by differences in geometries implemented in our models.

6.2 Sensitivity Analysis

A sensitivity analysis was performed on the experimental unknown parameter k_i to determine the impact of drug internalization on the concentration profiles of free, bound, and internalized drug.

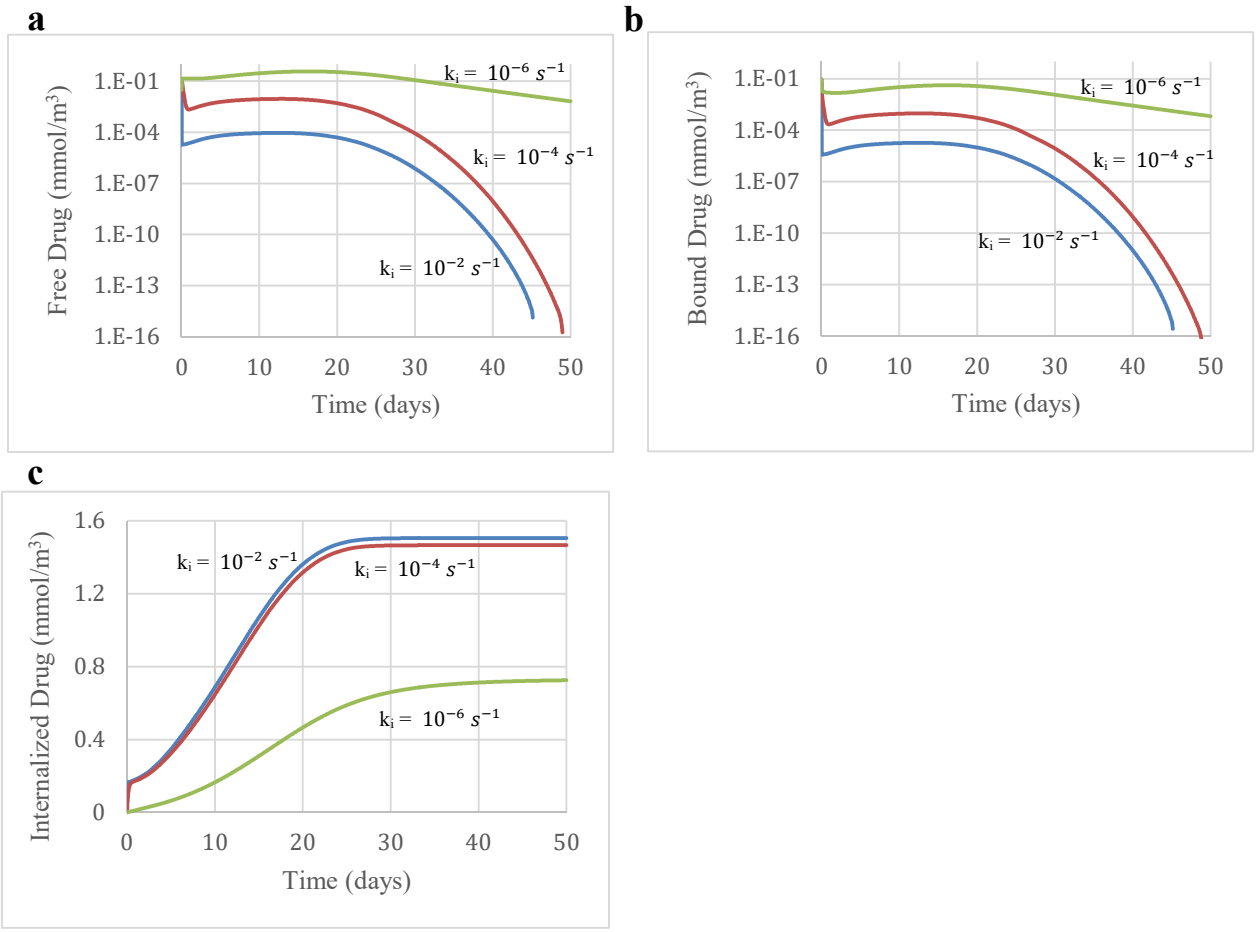


Figure 4a, 4b, 4c: Spatially averaged concentration in the arterial wall (square geometry, half embedment) over 50 days of free drug (4a), bound drug (4b), and internalized drug (4c), at three different internalization rate constant values (labelled on graph).

As an unknown parameter that directly impacts the amount of drug bound to the cell within the arterial wall, the rate of drug internalization k_i was analyzed by generating concentration plots with the k_i at 10^{-2} s^{-1}, 10^{-4} s^{-1}, and 10^{-6} s^{-1}. From the plots generated, the rate of drug internalization was shown to demonstrate similar concentration curves under the free, bound, and internalized drug concentration under higher k_i values given by 10^{-4} and 10^{-2} s^{-1} (Figure 4a, 4b). Noticeably, the concentration plots of the internalized drug were found to be near identical (Figure 4c), however, in both the free and bound drug concentration profiles, k_i were similar in

curve trend but not matched in value. (Figure 4a, 4b). The concentration plots showed that very small k_i values, given in this case by 10^{-6} s^{-1}, lead to a much more minimal change in free and bound drug concentration. Given this information, it can be concluded that k_i begins to have a significant impact if it is determined to be around 10^{-4} s^{-1}; conversely, if below this benchmark, it is likely to have a small effect on the elution profiles of free and bound drug.

6.3 Optimal Design

Our simulation showed that full embedment resulted in a higher spatially averaged concentration profile in the arterial wall at all time points over a 50 day period for both geometries. This is highly likely due to the higher degree of surface contact between the drug-containing PLGA coating and the arterial wall tissue. Similarly, square stents resulted in a higher concentration profile than circular stents likely for the same reasoning, though the effect was not as dramatic. Free drug concentration profiles are shown in Figure 5.

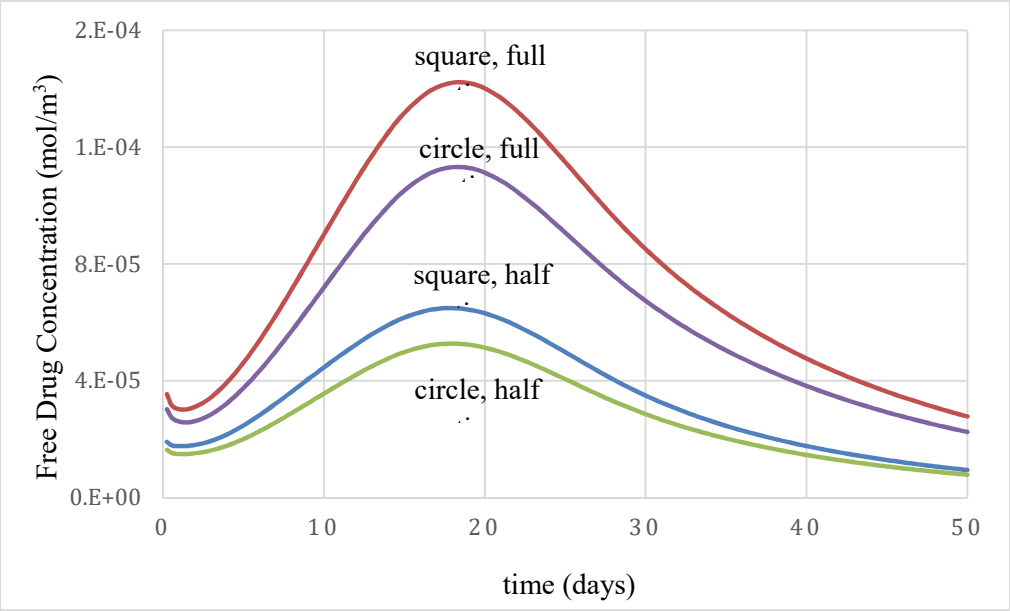


Figure 5: Spatially averaged concentration of free drug in the arterial wall (circular geometry, half embedment) for two different amounts of PLGA coating

These results indicate that the square, fully embedded stent results in the most optimal release profile by nearly an order of magnitude in comparison to the circular half embedded stent.

6.4 Design Improvements

Although full embedment results in an improved elution profile, often half embedment is preferred as it is gentler on the arterial wall (Kolandaivelu et al, al, 2011). The major limitation of the half embedded design for both geometries is that a significant amount of sirolimus gets washed into the bloodstream via convection at the coating-lumen interface. As a result, much of the drug is wasted as it is not transported to its target site, and systemic levels of sirolimus are increased. We propose two novel designs to address this shortcoming in current biodegradable stents.

Our first model considers adding an additional impermeable layer on the boundary between the PLGA coating and the blood, in effect, converting the perfect sink boundary condition to a no flux condition. Our simulation shows this would significantly improve drug delivery over an extended time frame (Figure 6a), and would facilitate near zero order release of sirolimus from the PLGA coating as indicated by an R^2 value of 0.96 of a release profile best fit to a line (Figure 6b).

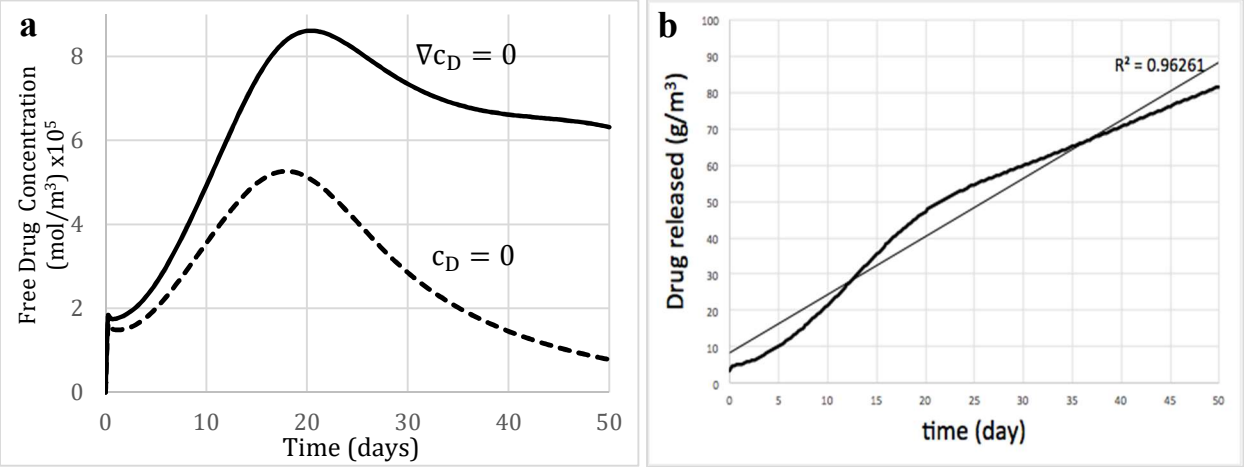


Figure 6a, 6b: Free drug concentration in the arterial wall over 50 days for no flux and perfect sink boundary conditions at coating-lumen interface (6a) and drug released from PLGA coating over 50 days given the no flux boundary condition with best-fit line (6b).

A visual comparison of the two designs at 15 days reveals a higher concentration of drug in the coating, specifically at the half that is in contact with the blood (Figure 7a, 7b). Sirolimus in this region has a longer diffusion path to the arterial wall, no means of exit to the blood stream, and as a result the coating elutes the drug for a longer period of time. By 15 days, the PLGA coating in the zero concentration model is nearly depleted.

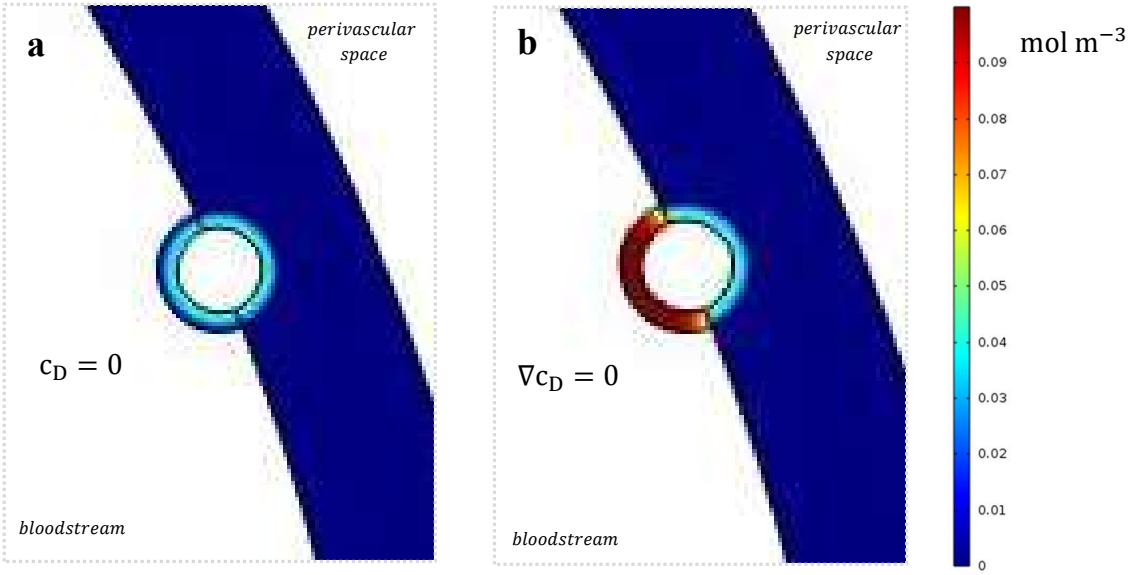


Figure 7a, 7b: drug concentration in the PLGA coating at 15 days for zero concentration boundary condition at coating-lumen interface (7a) and zero flux condition (7b).

A second proposed design is to exclusively coat the half of the stent strut that is in contact with the arterial wall as an approach to reduce drug transport into the blood. While the total mass of drug to be released was reduced by a factor of two, the concentration profiles between the two designs showed negligible difference (Figure 8).

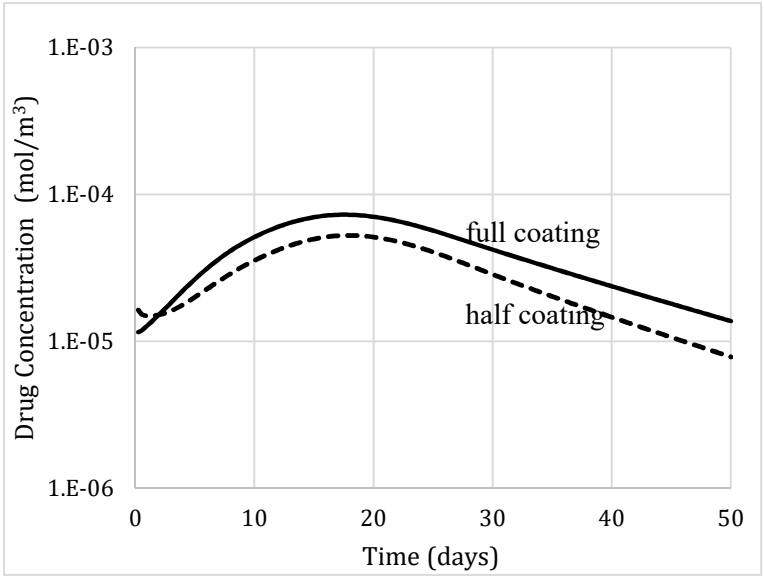


Figure 8: Spatially averaged concentration of free drug in the arterial wall (circular geometry, half embedment) for two different amounts of PLGA.

These findings suggest that current stent models are inefficient in terms of their drug eluting capabilities, and a number of modifications may be implemented to improve their design.

7.0 Conclusion

In this project, we compared the effect of different stent geometries and extent of embedment on drug concentration profile through circular and square geometries, and half and full extents of embedment. The results showed that full-embedded stent had a significantly higher drug concentration profile over a period of 50 days than half-embedded stent in both geometries (Figure 3), while square model showed a slightly higher drug concentration profile than circular geometries (Figure 4).

During the simulation, we found that a large amount of drug was washed away through blood flow under half extent of embedment conditions. Due to the inefficiency in half-embedded model, we made two novel improvements on current design: (1) creating an impermeable membrane at the coating-lumen interface; (2) exclusively coating on the half of the extent that is in contact with the arterial wall. The first improvement resulted in a significantly increase on the drug concentration profile in the arterial wall (Figure 6), and the second improvement showed similar profile to the benchmark, despite containing half of the drug (Figure 7). Both designs improve the use of the drug in stents efficiently.

Overall, this project contributes to the current stent development and drug delivery model. It provides the optimized geometry and embedment for drug-eluting stent design and it gives an insight on more efficient drug-coating design.

8.0 Future Recommendations

To further mimic the drug delivery in arterial wall, our current two-dimensional schematic was extended into three dimensions in COMSOL. The data generated was not significantly different than that of the two-dimensional simulation. Thus, we recommend that further research be done towards constructing more comprehensive three-dimensional models that accurately capture the complexity of actual stent designs.

A.0 APPENDIX

A.1 Summary of model parameters

Table A1: Table shown below shows the parameter values used when implementing the stent model into COMSOL. Physical dimensions of both the stent and the vessel, as well as most sirolimus reaction kinetic values were taken from published values utilized by Zhu and Braatz (2014).

Input Parameter	Value	Unit	Source
Outer diameter of the artery	3	mm	(Zhu & Braatz, 2014)
Thickness of the arterial wall	200	μm	(Zhu & Braatz, 2014)
Thickness of the stent strut	140	μm	(Zhu & Braatz, 2014)
Thickness of the stent coating	30	μm	(Zhu & Braatz, 2014)
Drug diffusivity in the initial PLGA polymer (D_{S0})	10^{-5}	$\mu m^2/s$	(Zhu & Braatz, 2014)
Drug diffusivity in the aqueous phase (D_{aq})	50	$\mu m^2/s$	(Zhu & Braatz, 2014)
Transmural drug diffusivity in the arterial wall ($D_{D,a}$)	10^{-1}	$\mu m^2/s$	(Zhu & Braatz, 2014)
Anisotropic ration of drug diffusivity in the arterial wall (D_θ/D_r)	10		(Zhu & Braatz, 2014)

Association rate constant (k_a)	10^4	l/mol·s	(Zhu & Braatz, 2014)
Dissociation rate constant (k_d)	10^{-2}	1/s	(Zhu & Braatz, 2014)
Weight-based PLGA degradation rate constant (k_w)	7.5×10^{-7}	1/s	(Zhu & Braatz, 2014)
Number-based PLGA degradation rate constant (k_n)	2.5×10^{-7}	1/s	(Zhu & Braatz, 2014)
Molecular weight dependency of diffusivity (a)	1.714		(Zhu & Braatz, 2014)
Drug partitioning coefficient (κ)	10^{-4}		(Zhu & Braatz, 2014)
Initial drug concentration in the coating (c_{D0})	10^{-5}	mol/l	(Zhu & Braatz, 2014)
Initial binding site concentration in the arterial wall (S_o)	10^{-5}	mol/l	(Zhu & Braatz, 2014)

A.2 Solution Strategy, Solver Configuation, and Mesh Convergence

The governing equations, boundary conditions, and initial conditions were implemented in COMSOL 5.1. A direct solver was utilized to obtain our solutions. We utilized a time-step of 0.25 days over the 50 day period over which our solutions were computed. Additionally, we specified a relative tolerance of 0.01 and absolute tolerance of 0.001 for the solver configuration. Due to the curvature of the arterial wall, we elected to use a mesh composed of free triangular elements. The triangular elements were identically sized within all domains of the mesh constructed for our simulation.

A mesh convergence was performed to assure that the results obtained by our simulation were independent of the mesh. To perform this mesh convergence, the element size was reduced until the computed spatially-averaged concentration of sirolimus at day 25 was independent of the mesh. Figure A1 shows convergence of the average Sirolimus concentration at approximately 11,000 mesh elements. The final analysis was conducted with 11,291 mesh elements. The mesh elements generated with this final analysis had a maximum element size of 6 μm and a minimum element size of 0.1 μm. Figure A2 shows a close-up graphic of elements utilized for the circular, half embedded stent. One important aspect to note is that the mesh was not made coarser at the areas far away from the interface between the arterial wall and stent. This is primarily due to the occurrences of singularities within larger elements that would disrupt the concentration profiles.

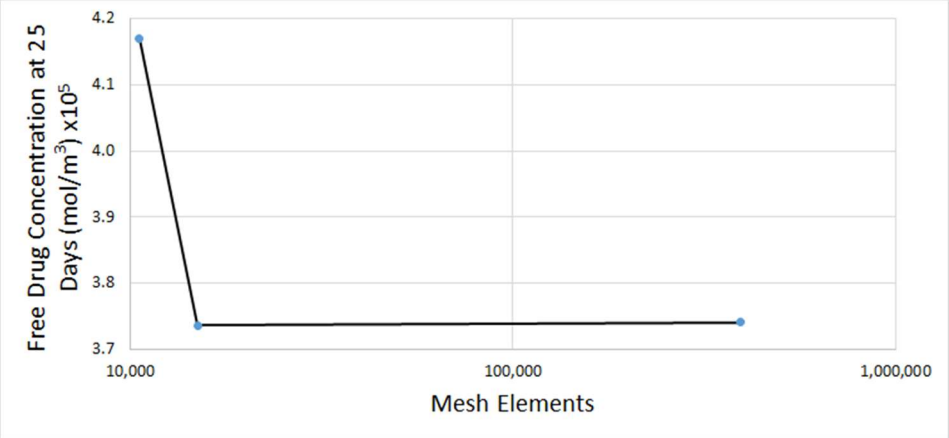


Figure A1: Mesh convergence displaying element number versus average sirolimus concentration in arterial wall. The solution converges around 11,000 elements. Only three mesh elements were analyzed due to the difficulty in obtaining both results for the concentration as well as the sensitivity of the concentration in response to the mesh elements.

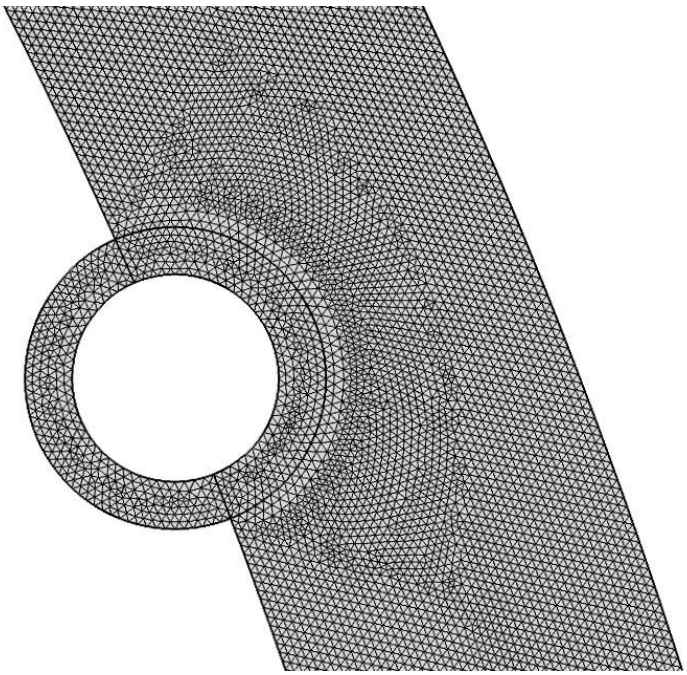


Figure A2: Close up of the mesh for a half embedded, circular stent within the arterial wall. An important aspect to note is that the elements at the stent-arterial wall interface are no finer than those elements utilized elsewhere in the arterial wall.

A.3 References

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