

BENG 221 – Mathematical Methods in Bioengineering

Fall 2013 Term Project

# **Modeling the Concentration Profile of Paclitaxel through the Blood Vessel Wall for Drug-Eluting Stents**

University of California, San Diego

Rana Haddad, Michael Skinner

November 22, 2013

**Table of Contents:**

**Introduction/Background.....3**

- a. Coronary Heart Disease**
- b. Drug-Eluting Stents**

**Problem Statement/Results.....5**

- a. 1-Dimensional Model**
- b. Cylindrical Model**

**Conclusions.....16**

**Future Work.....16**

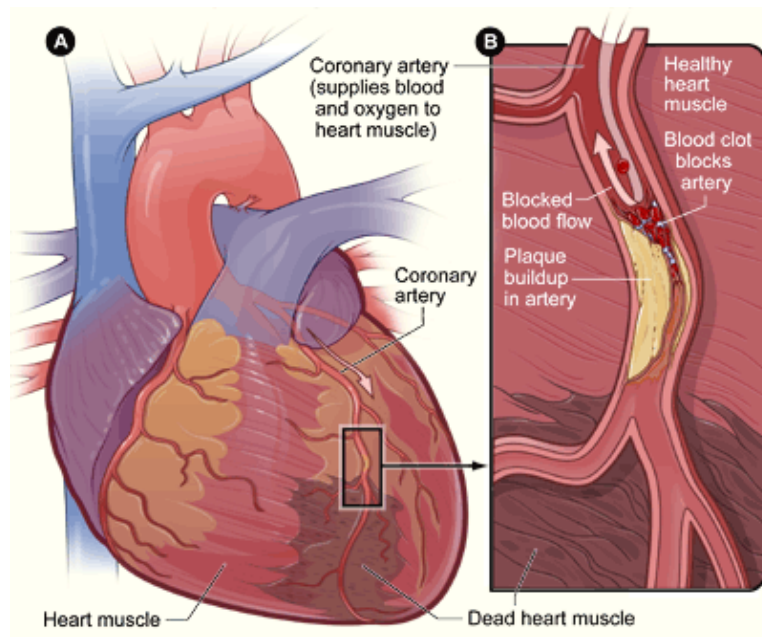
**MATLAB Code.....17**

**References.....19**

## Introduction

### *Coronary Heart Disease:*

Coronary heart disease is when plaque builds up in the coronary arteries<sup>1</sup>. This is a relatively common problem that occurs, especially as people age since this means that there has been a longer time for the plaque to build up<sup>1</sup>. There are numerous factors that can lead to the gradual onset of coronary heart disease, both genetic and based on lifestyle. Just a few of these factors include high blood pressure, high cholesterol, diabetes, smoking, and eating lots of trans-fatty acids<sup>3</sup>. As more and more plaque builds up in the arteries, they become smaller and blood flow through them is decreased. This loss of blood flow can lead to ischemia and myocardial infarction, which is when the heart tissue becomes damaged or dies completely<sup>1</sup>. At this point, there is a high likelihood of a heart attack occurring<sup>2</sup>. Depending on the severity of the plaque build-up, different treatment options exist including bypass surgery, angioplasty, or medication.



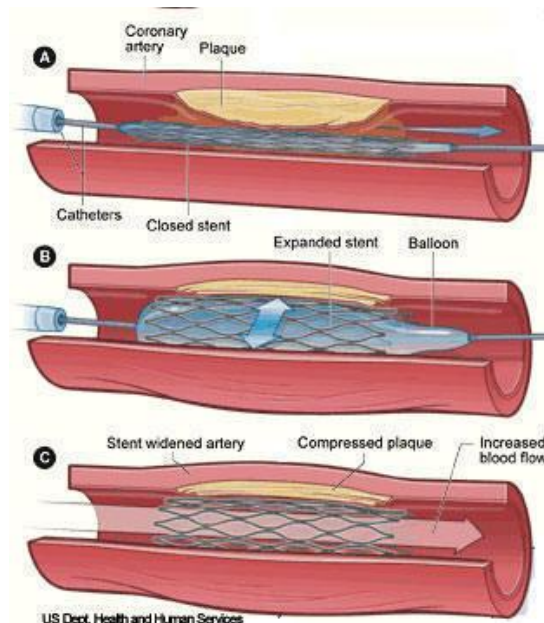
**Figure 1: Coronary Heart Disease is when plaque build-up in the coronary arteries leads to loss of blood flow in the heart. (Image from <http://cardiac.surgery.ucsf.edu/conditons--procedures/coronary-artery-disease.aspx>)**

### *Percutaneous Coronary Interventions (PCI):*

One of the large market dealing with coronary heart disease is percutaneous coronary interventions, where globally, over 2 million people undergo angioplasty to have a stent

implanted, most of these people located in developed nations<sup>4</sup>. This number will continue to increase because of the aging of the world population<sup>5</sup>.

PCI encompasses both angioplasty and stents<sup>6,7</sup>. In an angioplasty procedure, the surgeon inserts a balloon into a partially occluded blood vessel via a catheter, which is inflated to open up the vessel<sup>6,7</sup>. Then, also via a catheter, a stent is implanted in this widened vessel to keep it open<sup>6,7</sup>. Currently, the stent market is much more competitive than it was 5 years ago, when it was dominated by the Cypher, created by Johnson & Johnson<sup>8</sup>. The market is much more balanced now, with numerous companies having successful products<sup>8</sup>. There are also multiple types of drug-eluting stents, which elute both blood-thinning and anti-rejection drugs. The particular drug that we will be focusing on is paclitaxel, which is an immunosuppressant that is used in several stents, including the TAXUS Express2 Stent<sup>9</sup>. By suppressing the natural immune response of the body, paclitaxel decreases the chance of immune rejection by the body.



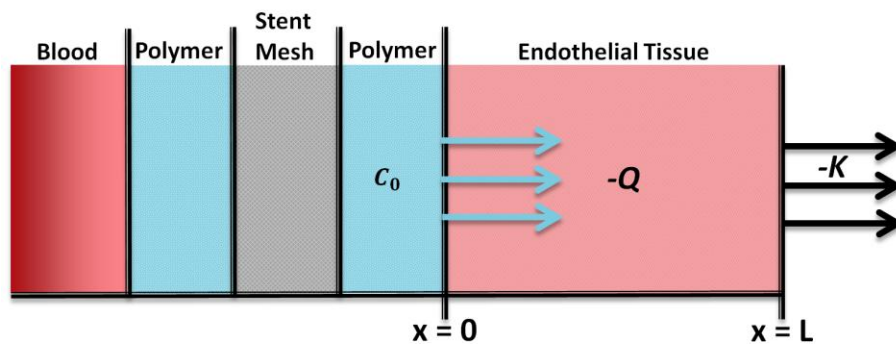
**Figure 2: Angioplasty procedure involves insertion of a balloon via catheter, inflation of the balloon, and stent placement. (Image from <http://www.drmcDougall.com/misc/2006nl/sept/angio.htm>)**

## Problem statement

In this study, we model the diffusion of the immunosuppressant paclitaxel from the polymer layer of an implanted stent through the endothelial tissue layer of the vein wall surrounding the drug-eluting polymer-coated stent. We provide both a one-dimensional and cylindrical model for the diffusion of the drug.

### Analytical Model – One-Dimensional Model

We first model diffusion in one-dimension, where the drug moves from the polymer coating through the endothelial tissue only in the x-direction, as shown in figure 3 below.



**Figure 3: One-Dimensional (Cartesian) Problem Design**

Here, we see the blue arrows indicating the drug's diffusion through the endothelial tissue of length  $L$ . The table below describes the variables used in the following calculations:

Variable	Description	Measurement Values
$L$	Endothelial Wall Thickness	1 mm
$C_0$	Initial Polymer Drug Concentration	$3.69 \frac{\mu g}{mm^3}$
$D$	Diffusivity of paclitaxel in tissue	$2.6 \text{ e-}6 \frac{mm^2}{s}$
$Q$	Consumption rate	$7.37 \text{ e-}5 \frac{\mu g}{mm^3 \cdot s}$
$K$	Endothelial wall drug leakage rate	See note below

**Table 1: Constant Values**

*Note:* In our model, we chose to have a constant flux from the outer boundary of the vessel. Because we are only looking at one layer of the vessel wall (the tunica media), we know that the outer boundary is not insulating, so there will be some outward flux of the drug. However, we could not find any information in literature about a number that we could use to model this outward flux. For our graphs, we decided to choose an arbitrary constant to model this flux. We chose a very small constant ( $0.1 \times$  consumption rate) because we intuitively thought that the amount of drug diffusing further outward would be much less than the amount in the layer we

are looking at. This number can easily be altered to represent a more physiologically relevant number if we are able to find a good estimate of this number.

In order to continue drug concentration calculations with this 1-D model, we will need to make several key assumptions:

1. One-dimensional drug diffusion: the drug moves only in the positive x-direction;
2. Constant initial drug concentration at the polymer/media boundary: The polymer layer remains with constant concentration of the drug, and does not deplete over time ( $C(0, t) = C_0$ );
3. No drug diffusion/insulated at polymer/blood boundary: there is no “backwards” drug diffusion, leading into the bloodstream;
4. Uniform diffusivity in endothelial tissue media: we can consider the diffusivity,  $D$ , to be constant along all sections of the endothelial tissue layer; and
5. Endothelial wall leakage rate is time invariant: the drug leakage rate,  $K$ , of the outer boundary of the endothelial tissue layer is constant.

With these assumptions in place, we are able to model the diffusion of paclitaxel beginning with the governing diffusion equation, describing the concentration of the drug at a given location  $x$  in the endothelial tissue at any time:

$$\text{1-D diffusion equation: } \frac{dC}{dt} = D \frac{d^2C}{dx^2} - Q$$

with the given initial and boundary conditions:

$$\text{Initial condition: } C(x, 0) = 0$$

$$\text{Boundary Condition 1: } C(0, t) = C_0$$

$$\text{Boundary Condition 1: } \frac{dC}{dx}(L, t) = -K$$

*Steady-State Solution:* In order to solve for the concentration of the drug,  $C(x, t)$ , we first solve for the steady-state concentration,  $C_{SS}(x)$ , and also the homogenous solution,  $C_H(x, t)$ , and finally combine the two solutions.

$$C(x, t) = C_{SS}(x) + C_H(x, t)$$

The steady-state solution,  $C_{SS}(x)$ , is obtained by first integrating the governing equation twice:

$$\iint \frac{dC}{dt} = D \frac{d^2C}{dx^2} - Q$$

and obtaining the following equation for the steady-state concentration  $C_{ss}(x)$ , where  $c_1$  and  $c_2$  are constants:

$$C_{ss}(x) = \frac{R}{D}x^2 + c_1x + c_2$$

Using the given boundary conditions, we solve for  $c_1$  and  $c_2$  and reach a final equation for the steady-state solution:

$$C_{ss} = -\frac{Q}{2D}x^2 - \left(\frac{QL}{D} + K\right)x + C_0$$

*Time-Variant (Homogenous) Solution:* We now solve for the time-variant homogeneous solution,  $C_H(x, t)$ , by using the method of separation of variables. Here we homogenize our boundary conditions and solve for the time-dependent,  $G(t)$ , and space-dependent,  $\Phi(x)$ , solutions separately, and then combine them as follows:

$$C_H(x, t) = \Phi(x)G(t)$$

Using homogenized boundary conditions, we first we solve for the time-dependent portion,  $G(t)$ :

$$G(t) = e^{-D\left(\frac{(2n+1)\pi}{2L}\right)^2 t}$$

and then solve for the space-dependent portion,  $\Phi(x)$ :

$$\Phi(x) = B_n \sin\left(\frac{(2n+1)\pi}{2L}x\right)$$

Combining the two solutions yields the final homogenous solution:

$$C_H(x, t) = \sum_{n=1}^{\infty} B_n \sin\left(\frac{(2n+1)\pi}{2L}x\right) e^{-D\left(\frac{(2n+1)\pi}{2L}\right)^2 t}$$

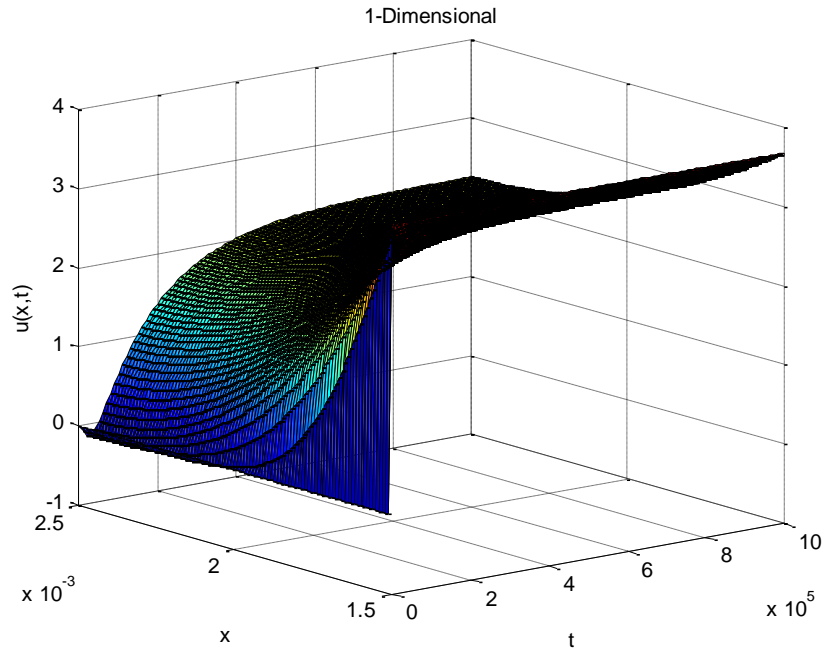
*Final 1-D Solution:* Now, we combine our steady-state and homogenous solutions for the final one-dimensional concentration profile,  $C(x, t)$ , where  $B_n$  is a constant:

$$C(x, t) = C_{ss} + \sum_{n=1}^{\infty} B_n \sin\left(\frac{(2n+1)\pi}{2L}x\right) e^{-D\left(\frac{(2n+1)\pi}{2L}\right)^2 t}$$

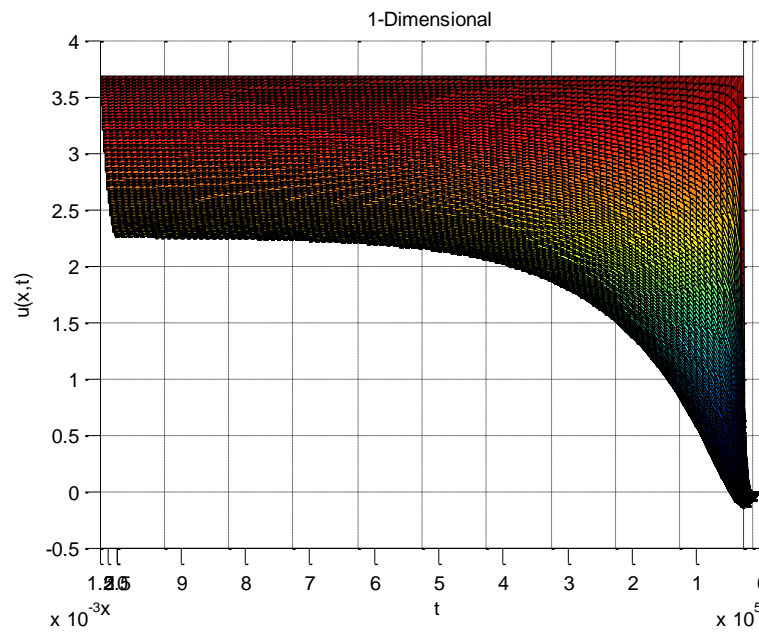
And using our given initial condition ( $C(r, 0) = 0$ ), we calculate the value of the  $B_n$  as follows:

$$B_n = \frac{2}{Lj} \left[ \frac{Q(Lj(-1)^n - 1)}{Dj^2} + \frac{\left(\frac{QL}{D} + K\right)(-1)^n}{j} - C_0 \right]$$

**Results – One-Dimensional Model**

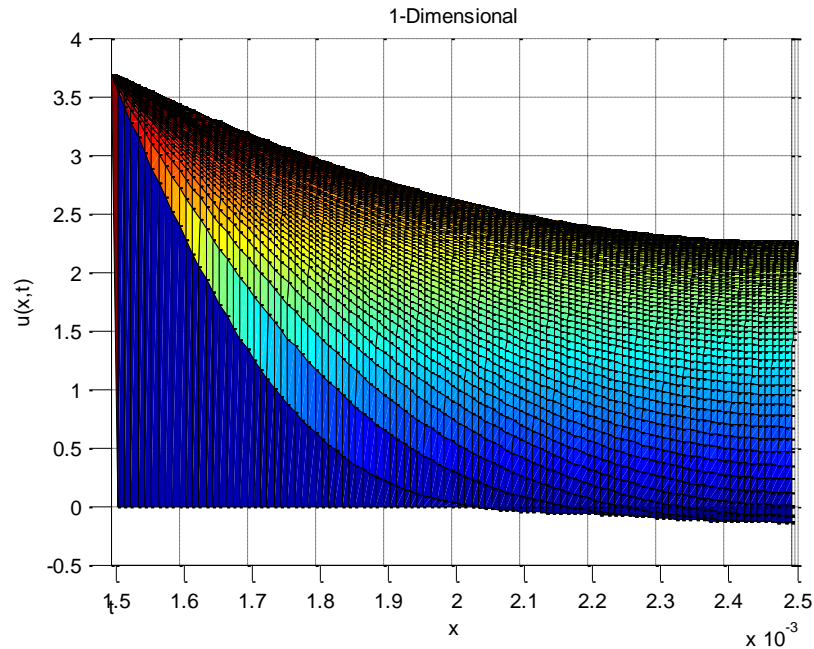


**Figure 4**



**Figure 5**



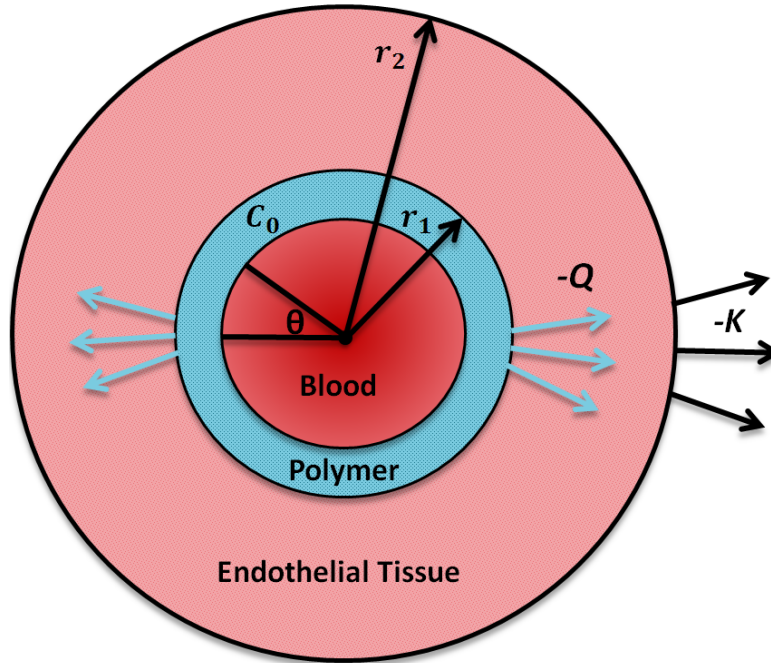


**Figure 6**

To model the 1-dimensional Cartesian diffusion model, we used the pdepe function in MATLAB. All of the surface plots that we show (Figures 4,5,6) are the same surface plot, shown from different planes. Figure 4 shows the overall shape of the entire graph. Figure 5 shows the plot from the plane at  $x=2.5$  mm, which shows the time scale for when diffusion will increase the concentration at the outside boundary. Figure 6 shows the plot from the plane at  $t = 10 \times 10^5$  s, which is close to what the steady-state profile will look like.

***Analytical Solution – Cylindrical Model***

We now – more-realistically– model the drug diffusion from the stent polymer layer through the endothelial wall in cylindrical coordinates, where drug diffused radially through the endothelial tissue only in the r-direction, as shown in figure 7 below:



**Figure 7: Cylindrical Coordinates Problem Design**

Here, we see the blue arrows indicating the drug diffusion through the endothelial tissue layer of thickness  $(r_2 - r_1)$ . The table below describes the variables used in following calculations:

Variable	Description	Measurement Values
$R_1$	Polymer Layer Outer Radius	1.5 mm
$R_2$	Endothelial Wall Outer Radius	2.5 mm
$C_0$	Initial Polymer Drug Concentration	$3.69 \frac{ug}{mm^3}$
$D$	Diffusivity of paclitaxel in tissue	$2.6 \text{ e-}6 \frac{mm^2}{s}$
$Q$	Consumption rate	$7.37 \text{ e-}5 \frac{ug}{mm^3*s}$
$K$	Endothelial Wall drug leakage rate	<i>See note in 1-D solution</i>

**Table 2: Constant Values**

The governing equation that we use to describe diffusion in cylindrical coordinates is as follows:

$$\text{Governing equation: } \frac{dc}{dt} = D \left( \frac{1}{r} \frac{d}{dr} \left( r \frac{dc}{dr} \right) + \frac{1}{r^2} \frac{d^2c}{d\theta^2} + \frac{d^2c}{dz^2} \right) - Q$$

In order to continue drug concentration calculations with this cylindrical model, we will need to make the following key assumptions:

1. Symmetrical drug diffusion along  $\theta$ : the drug diffuses radially, given the cylindrical nature of the stent and endothelial tissue
2. Infinite length along the  $z$  axis: drug diffusion along the  $z$ -axis will be ignored, as the length of the stent along  $z$  is much greater than the radial distance of the drug diffusion;
3. Constant initial drug concentration at the polymer/media boundary: The polymer layer remains with constant concentration of the drug, and does not deplete over time ( $C(r_1, t) = C_o$ );
4. No drug diffusion/insulated at polymer/blood boundary: there is no “backwards” drug diffusion, leading into the bloodstream;
5. Uniform diffusivity in endothelial tissue media: we can consider the diffusivity,  $D$ , to be constant along all sections of the endothelial tissue layer; and
6. Endothelial wall leakage rate is time invariant: the drug leakage rate,  $K$ , of the outer boundary of the endothelial tissue layer is constant.

With these assumptions in place, we are able to modify the governing equation of diffusion by eliminating all terms dependent on  $\theta$  and  $z$ , thus yielding a final governing partial differential equation dependent on  $r$  and  $t$ , describing the concentration of the drug at a given location along the radius,  $r$ , in the endothelial tissue at any time:

$$\text{Modified governing equation: } \frac{dC}{dt} = D \left( \frac{1}{r} \frac{d}{dr} \left( r \frac{dC}{dr} \right) \right)$$

with the given initial and boundary conditions:

$$\text{Initial condition: } C(r, 0) = 0$$

$$\text{Boundary Condition 1: } C(r_1, t) = C_o$$

$$\text{Boundary Condition 2: } \frac{dC}{dr}(r_2, t) = -K$$

We solve this equation using a similar approach as with our one-dimensional model, discussed in the previous section. We first solve for the steady-state solution,  $C_{ss}(r)$ , then the time-variant homogenous solution,  $C_H(r, t)$ , and finally combine both solutions for our final concentration equation,  $C(r, t)$ :

$$C(r, t) = C_{ss}(r) + C_H(r, t)$$

*Steady-State Solution:* The steady-state solution,  $C_{ss}(r)$ , is obtained by first integrating the governing equation twice:

$$\iint \frac{1}{r} \frac{d}{dr} \left( r \frac{dC_{ss}}{dr} \right) = \frac{Q}{D}$$

and obtaining the following equation for the steady-state concentration  $C_{ss}(x)$ , where  $c_1$  and  $c_2$  are constants:

$$C_{ss}(r) = \frac{Q}{4D} r^2 + c_1 \ln(r) + c_2$$

Using the given boundary conditions, we solve for  $c_1$  and  $c_2$ :

$$c_1 = -Kr_2 - \frac{Q}{2D} r_2^2$$

$$c_2 = C_0 - \frac{Q}{4D} r_1^2 + \left( Kr_2 + \frac{Q}{2D} r_2^2 \right) \ln(r)$$

*Time-Variant (Homogenous) Solution:* We now solve for the time-variant homogeneous solution,  $C_H(r, t)$ , by using the method of separation of variables. Here we homogenize our boundary conditions and solve for the time-dependent,  $G(t)$ , and space-dependent,  $\Phi(x)$ , solutions separately, and then combine them as follows:

$$C_H(x, t) = \Phi(x)G(t)$$

Using homogenized boundary conditions ( $C(r_1, t) = 0$ ;  $\frac{dC}{dr}(r_2, t) = 0$ ), we first we solve for the time-dependent portion,  $G(t)$ :

$$\frac{dG}{dt} = -\lambda^2 DG \quad \rightarrow \quad G(t) = Ae^{-D\lambda_n^2 t}$$

and then solve for the space-dependent portion,  $\Phi(r)$ , where we rearrange the equation as follows:

$$\frac{1}{\Phi r} \frac{d}{dr} \left( r \frac{d\Phi}{dr} \right) = -\lambda^2$$

$$\frac{d}{dr} \left( r \frac{d\Phi}{dr} \right) + \lambda^2 \Phi r = 0$$

$$r \frac{d^2 \Phi}{dr^2} + \frac{d\Phi}{dr} + \lambda^2 \Phi r = 0$$

where the solution to the above equation is in the following form, where  $c_1$  and  $c_2$  are constants :

$$\Phi(r) = c_1 J_0(\lambda r) + c_2 Y_0(\lambda r)$$

We now apply our homogenized boundary conditions to solve for the constants  $c_1$  and  $c_2$ , and obtain the following solution for  $\Phi(r)$ :

$$\Phi(r) = Y_0(\lambda_n r_1) J_0(\lambda_n r) - J_0(\lambda_n r_1) Y_0(\lambda_n r)$$

Combining the two solutions yields the final homogenous solution:

$$C_H(x, t) = \Phi(x)G(t) = [Y_0(\lambda_n r_1) J_0(\lambda_n r) - J_0(\lambda_n r_1) Y_0(\lambda_n r)] A e^{-D\lambda_n^2 t}$$

where  $J_0$  is a Bessel function of the first kind and zeroth order, and  $Y_0$  is a Bessel function of the second kind and zeroth order.

*Final 1-D Solution:* Our last step is to combine our steady-state and homogenous solutions for the final cylindrical drug concentration profile,  $C(r, t)$ , where  $A_n$  is a constant:

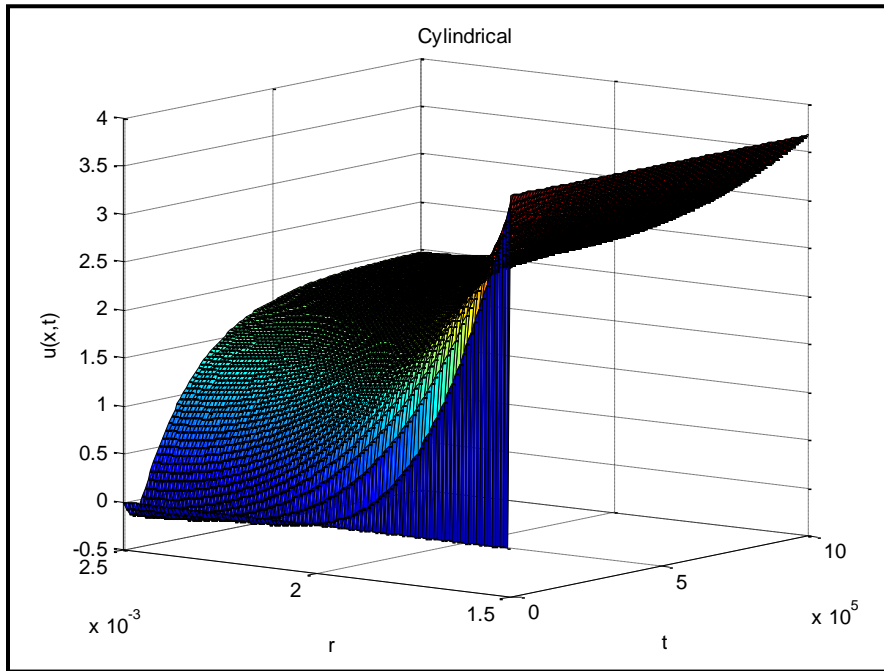
$$C(r, t) = C_H(r, t) + C_{ss}(r)$$

$$C(r, t) = \sum_{n=1}^{\infty} A_n \Phi(r) e^{-D\lambda_n^2 t} - \frac{Q}{4D} (r - r_1^2) + \left( KR_2 - \frac{Q}{2D} r_2^2 \right) \ln\left(\frac{r}{r_1}\right) - c_o$$

And finally, we solve for  $A_n$  using our given initial condition ( $C(r, 0) = 0$ ):

$$A_n = \frac{\int_{r_1}^{r_2} r \Phi(r) \left[ \frac{Q}{4D} (r - r_1^2) + \left( KR_2 - \frac{Q}{2D} r_2^2 \right) \ln\left(\frac{r}{r_1}\right) - c_o \right] dr}{\int_{r_1}^{r_2} r \Phi^2(r) dr}$$

*Results – Cylindrical Model*



**Figure 8**

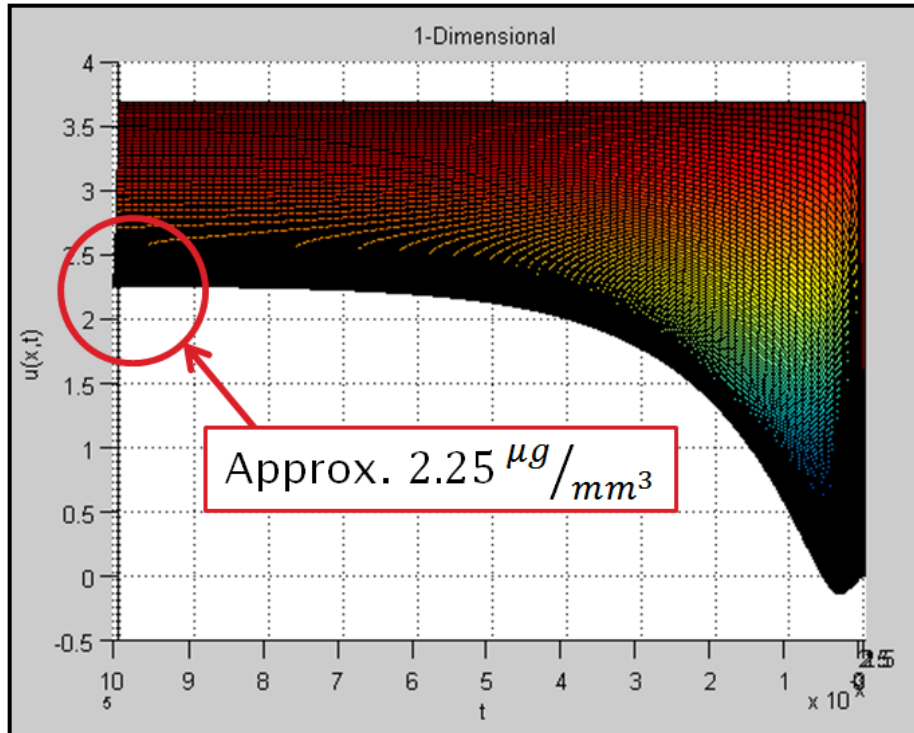


Figure 9

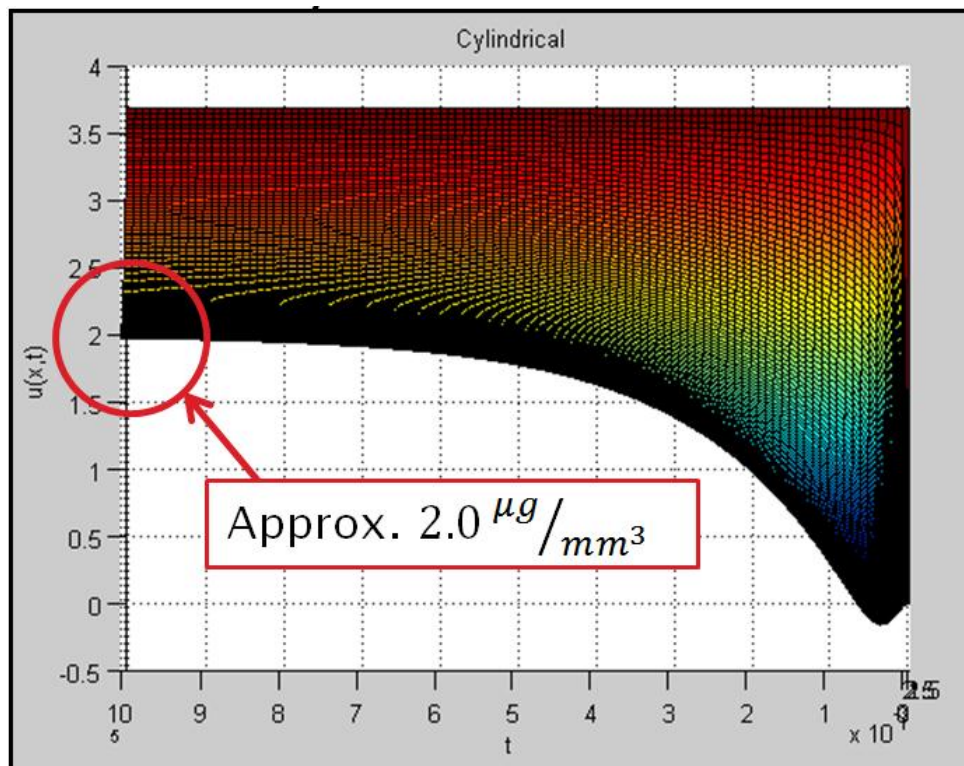


Figure 10

To model the cylindrical diffusion model, we again used the pdepe function in MATLAB. The surface plots are essentially the same as the 1-dimensional Cartesian diffusion model (Figure 8), so it is not necessary to show the different planes of the graph. Instead, we will compare the graphs at the  $x=2.5$  mm plane to show the difference between the two models (Figure 9,10). Figure 9 represents the planar model while Figure 10 represents the cylindrical model, and these figures clearly shows that in the cylindrical model, it takes a longer period of time for the drug to diffuse to the outside, and as the graphs near steady-state, the cylindrical model has a lower concentration than the planar model. Additionally, this means that in the cylindrical model, at steady-state there is a faster concentration drop-off than in the planar model.

## **Conclusion**

The main point of this project is to show the difference between a one dimensional diffusion model when taken in Cartesian versus cylindrical coordinates. We have shown that radial diffusion results in the concentration dropping off at a higher rate than planar diffusion. This statement intuitively makes sense, as concentration is dependent on volume, and in a cylindrical model, the volume of the shells increases as the radius increases. This means that as diffusion occurs radially outward, concentration will decrease at a faster rate than when diffusion occurs in a plane.

For our particular model, we can conclude that simple diffusion is sufficient for the drug paclitaxel to spread through the vessel wall. In the context of stents, it is important for this to occur so that paclitaxel can have the intended effect on the body. As an immunosuppressant, it gives the stent a greater success rate since the immune response of the body is limited, allowing the stent to be integrated into vessel, physically holding it open.

## **Future Work**

There are many ways to improve on our model to more accurately represent the diffusion of paclitaxel through the vessel wall. One of the simplifying assumptions to our model is that the stent is infinitely long so that diffusion in the z-direction could be ignored. Although this is a good assumption when looking at the radial diffusion around the center of the stent, it is clearly insufficient when looking at the diffusion towards the edges of the stent. To make a more accurate model, we must bound our problem in the z-direction, meaning that diffusion will not only occur in the radial direction, but also in the z-direction.

A second assumption that we made was that the concentration of paclitaxel is kept constant at the surface of the stent. This simplifies the problem because the first boundary condition is now a constant. However, in a realistic model, the concentration of paclitaxel at the surface of the stent



will be a function of time, as it slowly decreases over time as the drug diffuses through the vessel wall. Therefore, we can change this boundary condition to be a time-dependent function and investigate the time range for which paclitaxel can have a significant effect in the body. Similarly, we can also model our second boundary condition (the flux at the outside) as a function of time.

## MATLAB Code

```
global C0;
global D;
global R;

T=10^6;
r1=.0015;
r2=.0025;
L=1;
D=2.6*10^-12;
C0=3.68;
R=C0*2*10^-6;

x=r1:.00001:r2;
t=0:10000:T;
c=zeros(length(x),length(t));

sol_pdepe = pdepe(0,@pdefun_cyl,@ic_cyl,@bc_cyl,x,t);

figure(2)
surf(t,x,sol_pdepe')
title('1-Dimensional')
xlabel('t')
ylabel('x')
zlabel('u(x,t)')

sol_pdepe_cyl = pdepe(1,@pdefun_cyl,@ic_cyl,@bc_cyl,x,t);

figure(3)
surf(t,x,sol_pdepe_cyl')
title('Cylindrical')
xlabel('t')
ylabel('r')
zlabel('u(x,t)')

function [c, f, s] = pdefun(x, t, u, DuDx)
```

```
% PDE coefficients functions
```

```
global R
```

```
global D
```

```
c = 1;
```

```
f = D*DuDx; % diffusion
```

```
s = -R; % driving term
```

```
function u0 = ic(x)
```

```
% Initial conditions function
```

```
global C0
```

```
u0=C0;
```

```
function [pl, ql, pr, qr] = bc(xl, ul, xr, ur, t)
```

```
% Boundary conditions function
```

```
global C0;
```

```
global R;
```

```
pl = ul-C0; % left boundary condition
```

```
ql = 0; % no flux left boundary condition
```

```
pr = 0; % right boundary condition
```

```
qr = -R/10; % no flux right boundary condition
```

## References

1. National Heart, Lung, and Blood Institute. “What is Coronary Heart Disease?” 2012. <<http://www.nhlbi.nih.gov/health/health-topics/topics/cad/>>
2. Bogaert, J., Dymarkowski, S., & Taylor, A. M. (2004). 14 Coronary Artery Disease.
3. Mente, A., De Koning, L., Shannon, H. S., & Anand, S. S. (2009). A systematic review of the evidence supporting a causal link between dietary factors and coronary heart disease. *Archives of internal medicine*, 169(7), 659–69. doi:10.1001/archinternmed.2009.38
4. Medtronic. “What is Balloon Angioplasty and Stenting?” 2010. <<http://www.medtronic.com/patients/coronary-artery-disease/therapy/balloon-angioplasty-and-stenting/what-is-stent-and-balloon-therapy/>>
5. PR Newswire. “Atherosclerosis or Coronary Artery Disease Therapeutics (CAD) - Pipeline Assessment and Market Forecast to 2018.” 2011. <<http://www.prnewswire.com/news-releases/atherosclerosis-or-coronary-artery-disease-therapeutics-cad--pipeline-assessment-and-market-forecasts-to-2018-132680888.html>>
6. MedlinePlus. “Angioplasty and stent placement.” 2012. <<http://www.nlm.nih.gov/medlineplus/ency/article/007473.htm>>
7. eMedicineHealth. “Percutaneous Coronary Intervention (PCI).” 2013. <[http://www.emedicinehealth.com/percutaneous\\_coronary\\_intervention\\_pci/article\\_em.htm](http://www.emedicinehealth.com/percutaneous_coronary_intervention_pci/article_em.htm)>
8. Fierce Medical Devices. “The top drug-eluting stents.” 2012. <<http://www.fiercemedicaldevices.com/special-reports/top-drug-eluting-stents>>
9. U.S. Food and Drug Administration. “TAXUS Express2 Paclitaxel-Eluting Coronary Stent System.” 2013. <[http://www.fda.gov/medicaldevices/productsandmedicalprocedures/](http://www.fda.gov/medicaldevices/productsandmedicalprocedures/deviceapprovalsandclearances/recently-approveddevices/ucm081189.htm)
10. Pontrelli, G. & De Monte, “Mass diffusion through two-layer porous media: an application to the drug-eluting stent.” 2007. *Int. J. Heat Mass Transf.*, 50, 3658–3669.
11. McGinty, S., McKee, S., Wadsworth, R. M., and McCormick, C. “Modelling drug-eluting stents.” 2010. *Mathematical Medicine and Biology*.
12. Higgins, Brian G., “Application of Bessel functions: Transient heat conduction in a thin wall pipe.” 2012.