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Model of Radial Diffusion of the Drug Phenylephrine Following Vein Injection

BENG 221

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I. BACKGROUND

Patients undergoing hospital stays are often exposed to pathogenic bacteria. An infection stemming from these bacteria can lead to the condition of sepsis, which can impede patient recovery. The CDC reports that the number of cases of sepsis doubled between 2000 and 2008 with the increased hospitalization cost due to this condition totaling $ 14.6 billion. Children, the elderly, and patients having autoimmune disorders are especially prone to sepsis.

Severe sepsis can lead to septic shock, which is characterized by decrease in blood pressure and multi-organ failure. There is not effective treatment for this condition; however, to alleviate symptomology and increase blood pressure, patients are administered fluids and vasopressure drugs. phenyleprhine (PE) is the most common vasopressure used, which acts on α_1-andgrenergic receptors on the smooth muscle cells of veins and arteries to effect a constriction. The drug can be administered as either an IV infusion or a bolus injection.

The Animal Model

The mechanism of PE vasculature constriction in human is mirror in the mouse model, where PE is provided in the form of venal catheter. The extent of vessel constriction is dose depending, with a concentration of 8 ug/kg resulting in an increase of 45 mmHg. Constriction occurs on a short timescale compared to the duration of the constriction, which is also dose dependent. Literature parameters for the case of a mouse model were used for the purposes of analysis.

PE Injection and Radial Diffusion

The system to be modeled is the injection of PE into the vein of a mouse under shock conditions where the injection is represented as a point source in the center of the vein. Diffusion of PE was modeled using radial coordinates. The point source is represented as a delta function. The boundaries for the system are the vessel wall and an arbitrary distance –L and +L from the impulse along the z axis. Also modeled is the unbounded case where –L and +L are changed to ± infinity, respectively.

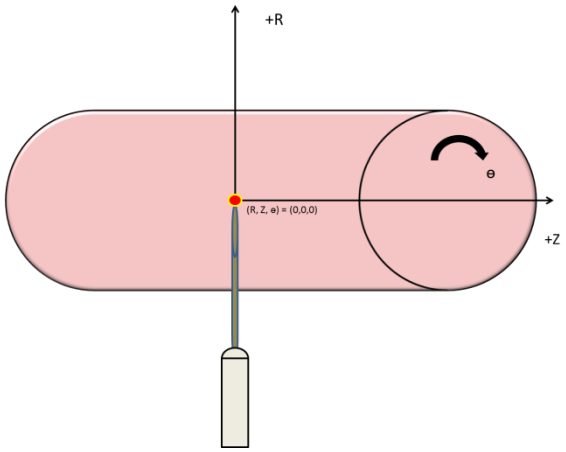

Figure 1: Schematic of System

The following is a list of assumptions compiled for this system:

- Initial concentration at the arterial center (r = 0).
- Blood as liquid without cellular components.
- All drug is injected at a point when t = t_0.
- Constriction along the artery is uniform and occurs once the reaches the vessel wall.
- When drug reaches vessel wall there is immediate constriction.
- No convection due to reduced blood pressure.
- Finite Length L is sufficiently large for C → 0

This system was modeled with the following boundary and initial conditions:

Boundary Conditions	Initial Conditions
$c(r = R_0) = 0$ $\frac{\partial c}{\partial r}(r = 0) = 0$ $c(z = -L) = 0$ or $c(z = -\infty) = 0$ $c(z = L) = 0$ $c(z = \infty) = 0$	$c(t = 0) = C_0\delta^3(r, \theta, z)$ Where: $\delta^3(r, \theta, z)$ → delta function. C_0 → initial concentration.

II. METHODS

Parameters

Femoral vein diameter = 0.54 mm

$D_{PE} = 1.01*10^{-11}$ m^2/s (calculated from bond lengths of PE using Einstein-Stokes equation)

Analytical Solution

Governing Equation:

$$\frac{\partial c}{\partial t} = D\left(\frac{\partial^2 c}{\partial r^2} + \frac{1}{r}\frac{\partial c}{\partial r} + \frac{1}{r^2}\frac{\partial^2 c}{\partial \theta^2} + \frac{\partial^2 c}{\partial z^2}\right) \quad (1)$$

Initial condition: $c(r, z, t = 0) = C_0\delta^3(r, \theta, z) = C_0\frac{\delta(r)\delta(z)}{\pi r}$ (2)

Boundary conditions:

$$\begin{cases} \frac{\partial c}{\partial r}(r = 0) = 0 \\ c(r = R_0) = 0 \end{cases} \quad (3)$$

First scenario: z direction with finite boundaries ($-L < z < L$)

$$\begin{cases} c(z = -L) = 0 \\ c(z = L) = 0 \end{cases} \quad (4)$$

Second scenario: z directions with infinite boundaries ($z \to \infty, z \to -\infty$)

$$\begin{cases} c(z \to -\infty) = 0 \\ c(z \to \infty) = 0 \end{cases} \quad (5)$$

1. Now we will solve the equation with z on finite boundaries.

Since concentration is not a function of θ, we can drop the θ term in the governing equation when solving.

The governing equation thus becomes:

$$\frac{\partial c}{\partial t} = D\left(\frac{\partial^2 c}{\partial r^2} + \frac{1}{r}\frac{\partial c}{\partial r} + \frac{\partial^2 c}{\partial z^2}\right) \quad (6)$$

$$c(r, z, t) = R(r)Z(z)T(t) \quad (7)$$

Substituting into the governing equation and divide both sides by $R(r)Z(z)T(t)$,

$$\frac{1}{D}\frac{1}{T}\frac{dT}{dt} = \frac{1}{R}\frac{d^2R}{dr^2} + \frac{1}{r}\frac{1}{R}\frac{dR}{dr} + \frac{1}{Z}\frac{d^2Z}{dz^2} \quad (8)$$

$$\frac{1}{D}\frac{1}{T}\frac{dT}{dt} = -\lambda, \text{ so } T(t) = T_0 e^{-\lambda D t} \quad (9)$$

$$-\lambda = \frac{1}{R}\frac{d^2R}{dr^2} + \frac{1}{r}\frac{1}{R}\frac{dR}{dr} + \frac{1}{Z}\frac{d^2Z}{dz^2} \quad (10)$$

$$\frac{1}{Z}\frac{d^2Z}{dz^2} = -n^2 \quad (11)$$

$$Z = A\cos(nz) + B\sin(nz) \tag{12}$$

substituting the boundary conditions (4):

$$\begin{cases} A\cos(nL) + B\sin(nL) = 0 \\ A\cos(nL) - B\sin(nL) = 0 \end{cases} \tag{13}$$

Therefore $A\cos(nL) = B\sin(nL) = 0$ (14)

The solution for Z turns out to be

$$B = 0,\ \cos(nL) = 0,\ n = \frac{(2k+1)\pi}{2L}\ (n = 0,1,2,\dots\dots) \tag{15}$$

or

$$A = 0,\ \sin(nL) = 0,\ n = \frac{k\pi}{L}\ (n = 1,2,\dots\dots) \tag{16}$$

Going back to equation (10) by substituting (11)

$$-\lambda = \frac{1}{R}\frac{d^2R}{dr^2} + \frac{1}{r}\frac{1}{R}\frac{dR}{dr} - n^2 \tag{17}$$

Multiply both sides by Rr^2,

$$r^2\frac{d^2R}{dr^2} + r\frac{dR}{dr} + (\lambda - n^2)r^2R = 0 \tag{18}$$

The solution for R is thus a Bessel function,

$$R(r) = J_0(\sqrt{\lambda - n^2}r) \tag{19}$$

The Bessel function of the second kind $Y_0$is dropped out due to its singularity at r =0, which doesn't satisfy the first boundary condition of (3).

The second boundary condition of (3) shows that $\sqrt{\lambda_{0i} - n^2}R_0$ are roots for J_0.

Therefore, the solution becomes

$$c(r,z,t) = \sum_{i=1}^{\infty}\sum_{k=0}^{\infty} A_{ik}J_0\left(\sqrt{\lambda_{0i} - \left[\frac{(2k+1)\pi}{2L}\right]^2}\,r\right)\cos\left[\frac{(2k+1)\pi z}{2L}\right]e^{-\lambda_{0i}Dt} + \sum_{i=1}^{\infty}\sum_{k=1}^{\infty} B_{ik}J_0\left(\sqrt{\lambda_{0i} - \left(\frac{k\pi}{L}\right)^2}\,r\right)\sin\left(\frac{k\pi z}{L}\right)e^{-\lambda_{0i}Dt} \tag{20}$$

Based on the initial condition in equation (2), the equation becomes

$$C_0\delta(\rho) = \sum_{i=1}^{\infty}\sum_{k=0}^{\infty} A_{ik}J_0\left(\sqrt{\lambda_{0i} - \left[\frac{(2k+1)\pi}{2L}\right]^2}\,r\right)\cos\left[\frac{(2k+1)\pi z}{2L}\right] + \sum_{i=1}^{\infty}\sum_{k=1}^{\infty} B_{ik}J_0\left(\sqrt{\lambda_{0i} - \left(\frac{k\pi}{L}\right)^2}\,r\right)\sin\left(\frac{k\pi z}{L}\right) \tag{21}$$

Multiply both sides of equation (20) by $J_0(\sqrt{\lambda_{0i} - \left(\frac{k\pi}{L}\right)^2}\, r) \sin\left(\frac{k\pi z}{L}\right)$ and integrate

$$B_{ik} = \frac{2C_0 \int_{-L}^{L} \int_0^{R_0} \delta^3(r,\theta,z)\, J_0(\sqrt{\lambda_{0i} - \left(\frac{k\pi}{L}\right)^2}\, r) \sin\left(\frac{k\pi z}{L}\right) r dr dz}{R_0^2 J_1^2(\sqrt{\lambda_{0i} - \left(\frac{k\pi}{L}\right)^2}\, R_0) L} \tag{22}$$

The integral form of delta-dirac function takes the value at $r = 0\ and\ z = 0$, so when $z = 0$, $\sin\left(\frac{k\pi z}{L}\right)$ becomes 0.

Therefore $B_{ik} = 0$.

Multiply both sides of equation (20) by $J_0(\sqrt{\lambda_{0i} - \left[\frac{(2k+1)\pi}{2L}\right]^2}\, r) \cos\left[\frac{(2k+1)\pi z}{2L}\right]$ and integrate

$$A_{ik} = \frac{2C_0 \int_{-L}^{L} \int_0^{R_0} \frac{\delta(r)\delta(z)}{r} J_0(\sqrt{\lambda_{0i} - \left[\frac{(2k+1)\pi}{2L}\right]^2}\, r) \cos\left[\frac{(2k+1)\pi z}{2L}\right] r dr dz}{\pi R_0^2 J_1^2(\sqrt{\lambda_{0i} - \left[\frac{(2k+1)\pi}{2L}\right]^2}\, R_0) L} \tag{23}$$

The integral form of dirac delta function takes the value at $r = 0\ and\ z = 0$. Since $J_0(0) = 1$ and $\cos(0) = 1$, the numerator of equation (23) becomes $2C_0$.

Therefore,

$$A_{ik} = \frac{2C_0}{\pi R_0^2 J_1^2(\sqrt{\lambda_{0i} - \left[\frac{(2k+1)\pi}{2L}\right]^2}\, R_0) L} \tag{24}$$

By substituting (24) into (20), we have the final solution as

$$c(r,z,t) = \sum_{i=1}^{\infty} \sum_{k=0}^{\infty} \frac{2C_0}{\pi R_0^2 J_1^2(\sqrt{\lambda_{0i} - \left[\frac{(2k+1)\pi}{2L}\right]^2}\, R_0) L} J_0(\sqrt{\lambda_{0i} - \left[\frac{(2k+1)\pi}{2L}\right]^2}\, r) \cos\left[\frac{(2k+1)\pi z}{2L}\right] e^{-\lambda_{0i} D t} \tag{25}$$

2. Now we will solve the equation with *z* on infinite boundaries.

We have the governing equation from (6) as

$$\frac{\partial c}{\partial t} = D\left(\frac{\partial^2 c}{\partial r^2} + \frac{1}{r}\frac{\partial c}{\partial r} + \frac{\partial^2 c}{\partial z^2}\right)$$

Since *z* has infinite boundary conditions, the function about z can be written as a Gaussian distribution,

$$\phi(z,t) = \frac{1}{\sqrt{4\pi D t}} e^{-\frac{z^2}{4Dt}} \tag{26}$$

The solution for *c* can be written as

$$c(r,z,t) = \phi(z,t) R(r) T(t) \tag{27}$$

Substituting into the governing equation

$$\frac{\partial \phi}{\partial t} RT + \frac{dT}{dt} \phi R = D \left(\frac{d^2 R}{dr^2} \phi T + \frac{1}{r} \frac{dR}{dr} \phi T + \frac{\partial^2 \phi}{\partial z^2} RT \right) \tag{28}$$

Based on the property of Gaussian distribution,

$$\frac{\partial \phi}{\partial t} = D \frac{\partial^2 \phi}{\partial z^2} \tag{29}$$

Substitute equation (29) into (28)

$$\frac{1}{D} \frac{1}{T} \frac{dT}{dt} = \frac{1}{R} \frac{d^2 R}{dr^2} + \frac{1}{r} \frac{1}{R} \frac{dR}{dr} \tag{30}$$

Let $\frac{1}{D} \frac{1}{T} \frac{dT}{dt} = -\lambda$, so $T(t) = T_0 e^{-\lambda D t}$.

Equation (30) then becomes

$$r^2 \frac{d^2 R}{dr^2} + r \frac{dR}{dr} + \lambda r^2 R = 0 \tag{31}$$

The solution to equation 31 is again a Bessel function

$$R(r) = J_0(\sqrt{\lambda} r) \tag{32}$$

The Bessel function of the second kind Y_0 is dropped out due to its singularity at r =0, which doesn't satisfy the first boundary condition of (3).

The second boundary condition of (3) shows that $\sqrt{\lambda_{0i}} R_0$ are roots for J_0.

Therefore, the solution becomes

$$c(r, z, t) = \sum_{i=1}^{\infty} A_i J_0(\sqrt{\lambda_{0i}} r)\, e^{-\lambda_{0i} D t} \frac{1}{\sqrt{4\pi D t}} e^{-\frac{z^2}{4Dt}} \tag{33}$$

Substituting the initial condition from equation (2)

$$C_0 \frac{\delta(r)\delta(z)}{\pi r} = \sum_{i=1}^{\infty} A_i J_0(\sqrt{\lambda_{0i}} r)\, \delta(z) \tag{34}$$

Multiply both sides by $J_0\left(\sqrt{\lambda_{0i}} r\right)$ and integrate

$$C_0 \int_0^{R_0} \frac{\delta(r)}{\pi r} J_0\left(\sqrt{\lambda_{0i}} r\right) r dr = A_i \int_0^{R_0} J_0^2(\sqrt{\lambda_{0i}} r) r dr \tag{35}$$

Therefore, the coefficient is solved as

$$A_i = \frac{2C_0}{\pi R_0^2 J_1^2(\sqrt{\lambda_{0i}} R_0)} \tag{36}$$

Substituting (36) into (33), the final solution is

$$c(r, z, t) = \sum_{i=1}^{\infty} \frac{2C_0}{\pi R_0^2 J_1^2(\sqrt{\lambda_{0i}} R_0)} J_0(\sqrt{\lambda_{0i}} r)\, e^{-\lambda_{0i} D t} \frac{1}{\sqrt{4\pi D t}} e^{-\frac{z^2}{4Dt}} \tag{37}$$

III. ANALYTICAL SOLUTION

The graphs generated here are based on equation (37), which is the analytical solution for infinite z boundaries. In the graphs below, z is fixed at a certain value while the concentration is expressed as a function of radius and time. Different z values result in different concentration profiles regarding radius and time. The greater the z value is, the flatter the plot is, meaning that it takes more time for the drug to diffuse down the z axis. Basically, the concentration decreases along the r direction and increases over time.

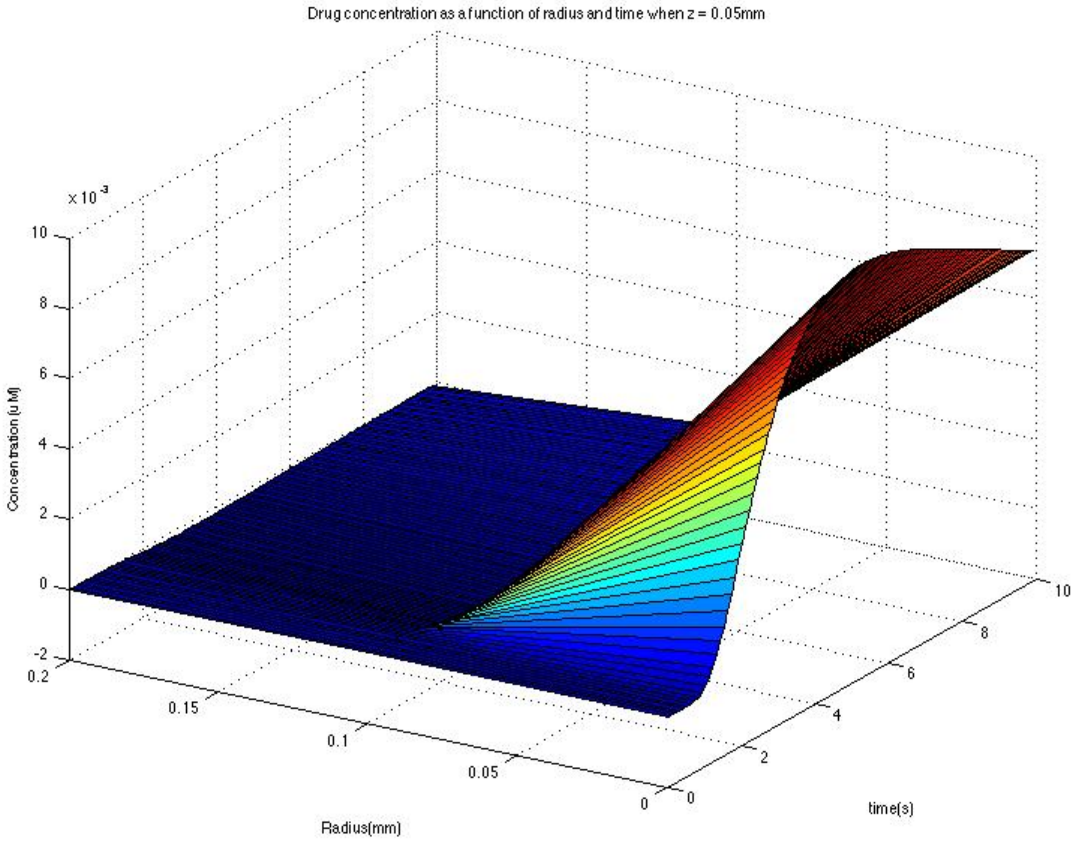

Figure 2: Concentration profile at z = 0.05mm.

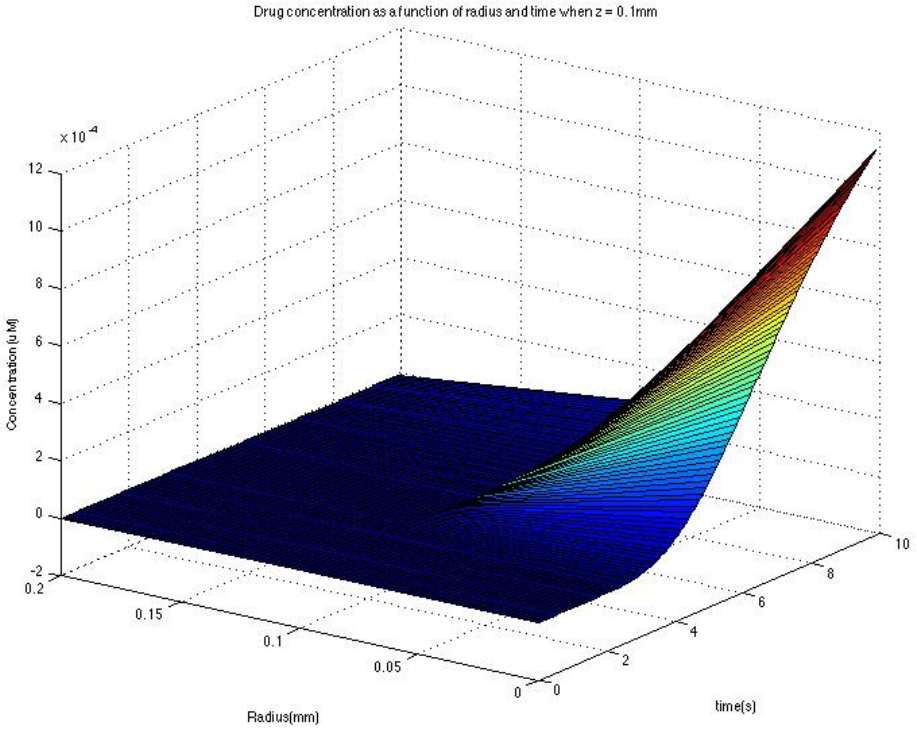

Figure 3: Concentration profile at z = 0.1mm.

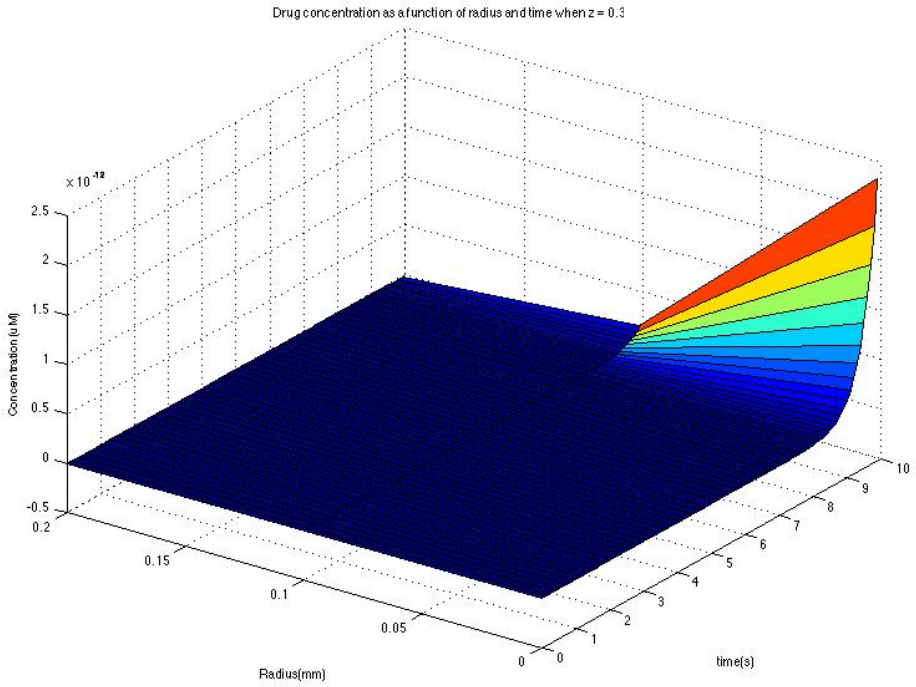

Figure 4: Concentration profile at z = 0.3mm.

IV. NUMERICAL SOLUTION

Numerical Solution

The numerical solution was generated using Matlab's build in pdetool GUI function. The model adheres to the specifications of the numerical model, except that we generated it over a 2 mm length, which behaves similarly to an infinite length over the time points we looked at, and our initial condition had to be changed to accommodate the numerical technique. The initial condition was taken as a 2-dimensional Gaussian function, where A and B will dictate the total concentration injected (e.g. the integral of the function) and B was taken to be very small, so that the function approximates to the point source used in the analytical solution.

$$u(x, y, t = 0) = A \exp\left(-\frac{x^2+y^2}{B}\right) \tag{38}$$

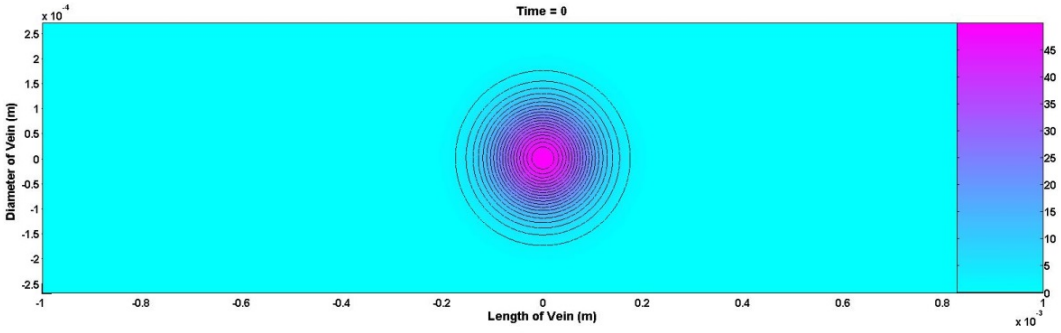

Figure 5: Numerical solution using Matlab pdetool at t = 0s.

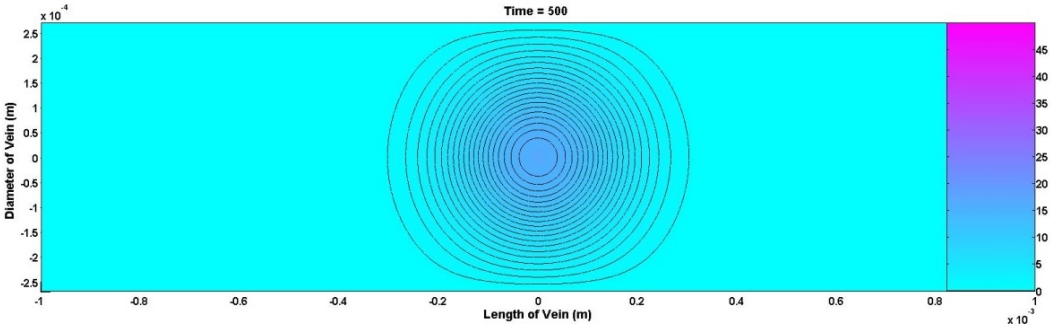

Figure 6: Numerical solution using Matlab pdetool at t = 500s.

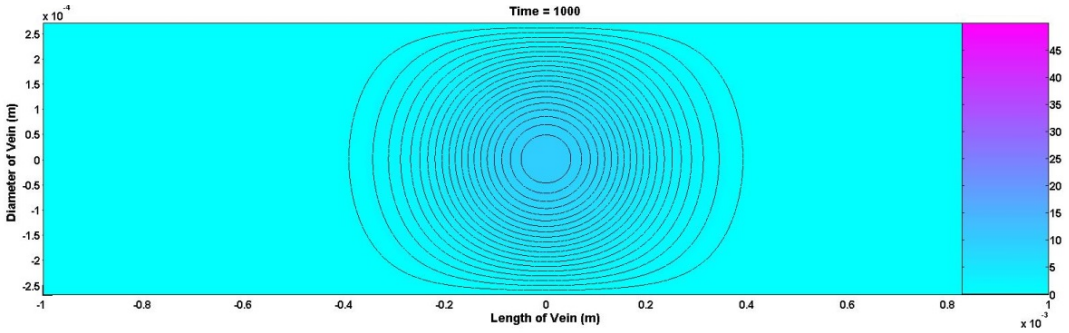

Figure 7: Numerical solution using Matlab pdetool at t = 1000s.

V. DISCUSSION

Analytical Solution

The analytical solution was modeled using different values for the vessel radius. The same characteristic profile develops for all conditions, which is a decrease to zero concentration as the drug diffuses in the R direction. The rapidity of this decrease in concentration with respect to R is a reflection of the chosen concentration. The delta-dirac selected used a pulse of 10 um. It is of import to realize that the physiological case would be comprised of an impulse of drug over a finite time span. This would effectively increase the amount of drug at the chosen concentration and allow the drug to reach zero concentration over a longer time scale. The concentration profile is substantially affected by changes in the R direction. For both sets of boundary conditions where the z boundary is either a finite or infinite condition, concentration decreases to zero at a fast time scale. This is the result of setting L to be a large value.

Numerical Solution

The numerical solution initially appears symmetric along both the z and R directions. This represents a Gaussian distribution in all directions with the impulse at the center being the maximum height of the Gaussian. This creates and elliptical shape along both directions. As time increases the profile along the R direction becomes restricted by the capillary wall. The physical interpretation of this profile is a fast accumulation of the drug at the R boundary over the long timescale. Thus the amount of drug crossing the boundary is greatly increased over longer periods of time. This is an important factor if the amount of drug leaving the vessel is to be considered for the purposes of activating vessel constriction. Due to properties of the Gaussian distribution the amount of drug in a given region may be estimated, prior to contact of the drug with vessel wall.

There are a number of modeling improvements that could be undertaken to improve on the accuracy and physiological veracity of the model. Although during conditions of shock blood flow in the animal is significantly reduced, there is convective blood flow. This would be incorporated in a more complete model of vascular diffusion. Under this condition diffusion along the –Z axis would become

negligible and the rate of diffusion along the +Z axis would increase. Convection would substantially affect the concentration profile and time scale of the model.

The constrictive effects of PE would also be explored. The current model assumes no constriction along the R direction; however the drug's actions on smooth muscle receptors would initiate a very brief contraction period. The contraction period could be modeled by a function dependent on time.

The model implemented a delta-dirac point injection at the center of the vessel. This initial condition could be altered to represent the injection of the drug over time through use of a function dependent on time that provides a value for the concentration in the vein. This would be particularly relevant given that contraction occurs on a very short time scale once the drug reaches the vessel wall. The location of the injection would also be changed to a location along the R axis closer to the vessel wall. This too would dramatically affect the concentration profile both in terms of simple diffusion as the drug reaches the boundary at different times and in terms of constriction, with the result being asymmetrical.

VI. REFERENCES

Liu, H. L. Microvascular anastomosis of submillimeter vessels – a training model in rats. *J. Hand & Microsurgery* **5**, 14-17 (2013).

Shaw, L. et al. Comparison of U46619-, endothelin-1- or phenylephrine-induced changes in cellular Ca^{2+} profiles and Ca^{2+} sensitisation of constriction of pressurised rat resistance arteries. *B. J. of Phama* **141**, 678-688 (2004).

VII. Appendix

Matlab Code

Analytical solution with z at infinite boundary

```
function analytical_solution_plot
J0_roots = [2.4048 5.5201 8.6537 11.7915 14.9309];

R0 = 0.27;
L = .4;
D = 1.01/10000;
C0 = 10^(-5);
r = 0:0.1:R0;
t = 0.0001:0.1:50;
root_lamda = J0_roots./R0;
lr= length(r);
lt= length(t);
f= zeros(lr,lt);

% size(besselj(0,r*root_lamda(1))')
% size(exp(-root_lamda(1)^2*D*t))
% size(exp(-L^2/4/D./t))
% size(sqrt(4*pi*D*t))
% size(exp(-root_lamda(1)^2*D*t).*exp(-L^2/4/D./t)./sqrt(4*pi*D*t))

for n = 1:1:5
    f= f + 2*C0/(pi*(R0^2)*(besselj(1,R0*root_lamda(n))^2))*
besselj(0,r*root_lamda(n))'*...
        (exp(-root_lamda(n)^2*D*t).*exp(-(L^2/4/D./t))./sqrt(4*pi*D*t));

end

colormap(jet);
rotate3d
figure(1)
surf(t,r,f);
xlabel('time(s)');
ylabel('Radius(mm)');
zlabel('Concentration(uM)');
title('Drug concentration as a function of radius and time when z = 0.4mm');

end
```

Numerical solution

```
function pdemodel
[pde_fig,ax]=pdeinit;
pdetool('appl_cb',1);
set(ax,'DataAspectRatio',[1 0.40499999999999997 1]);
set(ax,'PlotBoxAspectRatio',[3.7037037037037037 2.4691358024691361
3703.7037037037035]);
set(ax,'XLim',[-0.001 0.001]);
set(ax,'YLim',[-0.00027 0.00027]);
set(ax,'XTickMode','auto');
set(ax,'YTickMode','auto');

% Geometry description:
pderect([-0.001 0.001 0.00027 -0.00027],'R1');
set(findobj(get(pde_fig,'Children'),'Tag','PDEEval'),'String','R1')
```

```
% Boundary conditions:
pdetool('changemode',0)
pdesetbd(4,...
'dir',...
1,...
'1',...
'0')
pdesetbd(3,...
'dir',...
1,...
'1',...
'0')
pdesetbd(2,...
'dir',...
1,...
'1',...
'0')
pdesetbd(1,...
'dir',...
1,...
'1',...
'0')

% Mesh generation:
setappdata(pde_fig,'Hgrad',1.3);
setappdata(pde_fig,'refinemethod','regular');
setappdata(pde_fig,'jiggle',char('on','mean',''));
setappdata(pde_fig,'MesherVersion','preR2013a');
pdetool('initmesh')
pdetool('refine')
pdetool('refine')
pdetool('refine')
pdetool('refine')
pdetool('refine')

% PDE coefficients:
pdeseteq(2,...
'1.01E-11',...
'0',...
'0',...
'1',...
'0:250:500',...
'50*exp(-(x.*x+y.*y)/0.00000001)',...
'0.0',...
'[0 100]')
setappdata(pde_fig,'currparam',...
['1.01E-11';...
'0       ';...
'0       ';...
'1       '])

% Solve parameters:
setappdata(pde_fig,'solveparam',...
char('0','135168','10','pdeadworst',...
'0.5','longest','0','1E-4','','fixed','Inf'))

% Plotflags and user data strings:
setappdata(pde_fig,'plotflags',[1 1 1 1 1 1 1 1 0 0 0 3 1 1 0 0 0 1]);
setappdata(pde_fig,'colstring','');
setappdata(pde_fig,'arrowstring','');
setappdata(pde_fig,'deformstring','');
setappdata(pde_fig,'heightstring','');

% Solve PDE:
pdetool('solve')
```