UNIVERSITY OF CALIFORNIA, SAN DIEGO

Mathematical Model for Leukocyte Migration in Prosthetic Materials

BENG 221 – Mathematical Methods for Bioengineers – Fall 2012 Term Project

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By means of the "convection-diffusion partial differential equation", a model for the migration of leukocyte towards the implantation site of a vascular prosthetic material has been developed. Although this is a simplified version of more complex models used to describe cell populations' dynamics, it provides meaningful data on leukocytes' behavior in the presence of chemotactic factors released by the implanted prosthetic material. Both the analytical solution and the numerical approximation are provided along with three-dimensional graphs to accompany the results.

INTRODUCTION

Cardiovascular disease is the second leading cause of death the world and the second leading cause of death in the United States [1]. Among all cardiovascular diseases, atherosclerosis is the most important because almost all life-threatening cardiovascular disorders (e.g. coronary artery disease) are derived from it.

Atherosclerosis, in brief, is the abnormal accumulation of plaque (which is mainly composed of fat and calcium) inside the arteries [2]. This plaque abates the artery's normal blood flow and, at an advanced stage of the disease, ruptures (becomes a thrombus) and eventually starts to flow in the bloodstream until it completely occludes one small-diameter artery. This finally leads to ischemia and infarction of the organ (e.g. heart or even the brain) that used to be nourished by the now occluded artery [3].

Tissue engineered vascular grafts (TEVG) are promising alternatives for treating cardiovascular diseases related to atherosclerosis (e.g. carotid artery disease). A TEVG is a prosthetic material that behaves as an artificial blood vessel to replace atherosclerotic arteries in the patient's circulatory system. Although much effort and many years of research have been dedicated to the task of improving these prosthetic materials, it has not been possible to build a reliable and durable TEVG yet. It has been well established that the presence of a foreign body in the tissue, such as a prosthetic material, increases the risk of infection [4] and this is actually the main reason that lies beneath complications with vascular prosthetic materials implantation [5].

Because leukocytes serve as the key acute inflammatory mediators, the control of their motility on the surfaces of vascular prosthetic materials is a crucial factor in promoting implant infection resistance [6]. Whereas leukocyte behavior and motility on normal vascular tissue has been extensively studied [7], very few details are known in terms of the regulation of their migration on vascular prosthetic biomaterials. Right after a prosthetic material is implanted, an immune response is triggered and, eventually, several circulating proteins begin to modulate the behavior of adherent leukocytes in order to direct their migration to the implant site [8]. Leukocytes will then flow in the blood towards the prosthetic material to adhere to its surface in order to attack any infectious agent that could be present along the prosthetic vascular graft and try to eliminate them.

PROBLEM STATEMENT

We consider the following problem: A linear prosthetic material (i.e. engineered vascular graft) of length L and constant cross sectional area has just been implanted in one of the arteries of a patient and immediately triggers an immune response with the subsequent migration of leukocytes towards the implantation site. We would like to find a mathematical expression for the concentration of leukocytes $C(x,t)$ along the vascular prosthetic material as a function of distance x and time t.

Assumptions

- We assume the concentration of leukocytes is constant on the left boundary of the prosthetic at all times (it can be seen as a source of leukocytes) and equal to C_0.

- Also, we assume the site of infection is at the right boundary and leukocytes would move out of the endothelium of a prosthetic blood vessel only at this point. Therefore the concentration of leukocytes on the right boundary will always be equal to zero.
- The initial concentration of leukocytes along the prosthetic material is 0.
- The migration of leukocytes along the prosthetic device is not only determined by their constant diffusivity μ_D but also by their constant drift velocity v_{eff} caused by blood flow.
- Chemotactic factors that attract leukocytes are released at the infection site (right boundary).
- Leukocytes displace in the direction of the blood flow.

With these assumptions made, we can now consider the "mass balance" for the concentration of leukocytes along the prosthetic material at any time. The migration of leukocyte is determined by both diffusion and convection. Then, the flux of leukocytes concentration J_L is given by:

$$J_L = \phi_{diffusion} + \phi_{convection}$$

$$\phi_{diffusion} = -\mu_D \frac{\partial C}{\partial x} \qquad \phi_{convection} = v_{eff} C$$

Since the number of leukocytes is conserved, we have:

$$\frac{\partial C}{\partial t} + \frac{\partial}{\partial x} J_L = 0$$

$$\frac{\partial C}{\partial t} = -\frac{\partial}{\partial x}\left(-\mu_D \frac{\partial C}{\partial x} + v_{eff} C\right)$$

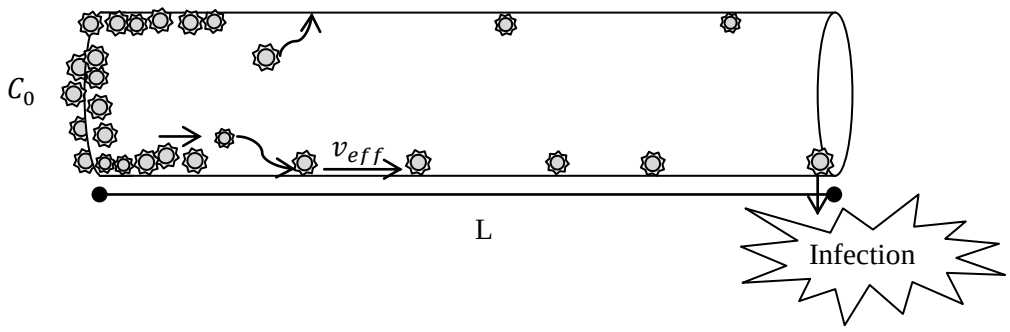
This model is known as the "convection-diffusion" equation and, therefore, our final partial differential equation is [9]:

$$\frac{\partial C}{\partial t} = \mu_D \frac{\partial^2 C}{\partial x^2} - v_{eff} \frac{\partial C}{\partial x}$$

With Initial and Boundary Conditions given as:

$$IC:\ C(x,0) = 0 \qquad BC1:\ C(0,t) = C_0 \qquad BC2:\ C(L,t) = 0$$

Note: The values of both v_{eff} and μ_D for various types of arteries have been experimentally determined in several works found in literature such as that of Keller and Segel [10].



ANALYTICAL SOLUTION

Part 1: Simplified model

Assumption: Convection (drift) term is zero, i.e. $v_{eff} = 0$.

The diffusion-convection equation can be reduced to diffusion equation.

Reduced to Diffusion Equation (The migration of Leukocyte in the absence of blood flow.)	$\frac{\partial C(x,t)}{\partial t} = \mu_D \frac{\partial^2 C(x,t)}{\partial x^2}$
Boundary Conditions Initial Condition	$C(0,t) = C_0, C(L,t) = 0, t > 0$ $C(x,0) = 0, 0 < x < L$

To homogenize the boundary conditions, let $C(x,t) = C_t(x,t) + C_s(x)$, we can solve steady-state solution $C_s(x)$ and make time-varying solution $C_t(x,t)$ easy to solve.

Steady-state solution $C_s(x)$	Time-varying solution $C_t(x,t)$
$\mu_D \frac{\partial^2 C_s(x)}{\partial x^2} = 0$	$\frac{\partial C_t(x,t)}{\partial t} = \mu_D \frac{\partial^2 C_t(x,t)}{\partial x^2}$
$C_s(0) = C_0,\ C_s(L) = 0$	$C_t(0,t) = 0, C_t(L,t) = 0$ $C_t(x,0) = -C_s(x)$

(1) Steady-state solution: $C_s(x)$

The second derivative of the steady-state solution is equal to zero. The solution has the general form:

$$C_s(x) = Ax + B$$

Implementing with the boundary conditions shown above we get the following equations:

$$C_s(0) = B = C_0$$

$$C_s(L) = AL + B = 0$$

Using these equations the variable A can be found:

$$A = -{}^{C_0}/_{L}$$

***Plugging A back into the general form of the steady-state solution results,

$$C_s(x) = C_0\left(1 - \frac{x}{L}\right), 0 < x < L$$

(2) Time-varying solution: $C_t(x,t)$
Solve for diffusion equation with homogeneous boundary conditions:

Use separation of variables:

$$C_t(x,t) = \phi(x) \cdot G(t)$$

We can solve for time-dependence and space-dependence solutions separately.

$$\frac{1}{\mu_D}\frac{\frac{\partial G(t)}{\partial t}}{G(t)} = \frac{\frac{\partial^2 \phi(x)}{\partial x^2}}{\phi(x)} = -\lambda$$

(a) Time-dependence solution

$$G(t) = Ae^{-\mu_D \lambda t}$$

(b) Space-dependence solution:

(i) For $\lambda = 0$, $\phi(x) = Ax + B$. With boundary conditions, $A = B = 0$
$$\phi(x) = 0$$

(ii) For $\lambda < 0$, $\phi(x) = Ae^{\sqrt{-\lambda}x} + Be^{-\sqrt{-\lambda}x}$, With boundary conditions,
$$\phi(x) = 0$$

(iii) For $\lambda > 0$, $\phi(x) = A\cos(\sqrt{\lambda}x) + B\sin(\sqrt{\lambda}x)$, With boundary conditions,
$\phi(x) = B\sin(\sqrt{\lambda}x)$, where $\sqrt{\lambda} = \frac{n\pi}{L}$, $n = 1,2, \ldots$

Combine (a) and (b),

$$C_t(x,t) = \sum_{n=1}^{\infty} A_n \sin\left(\frac{n\pi}{L}x\right) e^{-\mu_D\left(\frac{n\pi}{L}\right)^2 t}$$

Solve coefficient A_n to satisfy the initial condition.

$$C_t(x,0) = \sum_{n=1}^{\infty} A_n \sin\left(\frac{n\pi}{L}x\right) = -C_s(x) = C_0\left(\frac{x}{L} - 1\right)$$

$$A_n = \frac{2}{L}\int_0^L C_0\left(\frac{x}{L} - 1\right)\sin\left(\frac{n\pi}{L}x\right)dx = -\frac{2C_0}{n\pi}$$

Combine steady-state and time-varying solution, we obtain the final solution:

$$C(x,t) = C_0\left(1 - \frac{x}{L}\right) - \sum_{n=1}^{\infty}\frac{2C_0}{n\pi}\sin\left(\frac{n\pi}{L}x\right)e^{-\mu_D\left(\frac{n\pi}{L}\right)^2 t}$$

Part 2: General Model

Now we consider the effect of blood flow and thus the convection (drift) term in our general model.

Diffusion-convection Equation	$\frac{\partial C(x,t)}{\partial t} + V_{eff}\frac{\partial C(x,t)}{\partial x} = \mu_D \frac{\partial^2 C(x,t)}{\partial x^2}$
Boundary Conditions Initial Condition	$C(0,t) = C_0, C(L,t) = 0, t > 0$ $C(x,0) = 0, 0 < x < L$

Similarly, we can homogenize the boundary condition. Let $C(x,t) = C_t(x,t) + C_s(x)$,

Steady-state solution $C_s(x)$	Time-varying solution $C_t(x,t)$
$V_{eff}\frac{\partial C_s(x)}{\partial x} = \mu_D \frac{\partial^2 C_s(x)}{\partial x^2}$	$\frac{\partial C(x,t)}{\partial t} + V_{eff}\frac{\partial C(x,t)}{\partial x} = \mu_D \frac{\partial^2 C(x,t)}{\partial x^2}$
$C_s(0) = C_0,\ C_s(L) = 0$	$C_t(0,t) = 0, C_t(L,t) = 0$ $C_t(x,0) = -C_s(x)$

(1) Steady-state solution: $C_s(x)$
Integrating both sides two times, we have the general form of the solution:

$$C_s(x) = Ae^{\frac{V_{eff}}{\mu_D}x} + B$$

By boundary conditions,

$$A + B = C_0,\ Ae^{\frac{V_{eff}}{\mu_D}L} + B = 0$$

$$A = \frac{C_0}{1-e^{\frac{V_{eff}}{\mu_D}L}},\ B = C_0\frac{-e^{\frac{V_{eff}}{\mu_D}L}}{1-e^{\frac{V_{eff}}{\mu_D}L}}$$

We have the steady-state solution.

$$C_s(x) = C_0\frac{1-e^{-\frac{V_{eff}}{\mu_D}(L-x)}}{1-e^{-\frac{V_{eff}}{\mu_D}L}}$$

Note that the steady-state solution is not linear as in reduced model. It's the effect of blood flow which carries leukocytes further. For more discussion, please see the numerical simulation.

(2) Time-varying solution: $C_t(x,t)$
Solve for diffusion equation with homogeneous boundary conditions.

Use separation of variables:

$$C_t(x,t) = \phi(x) \cdot G(t)$$

We can solve for time-dependence and space-dependence solutions separately.

$$\frac{1}{\mu_D}\frac{\partial G(t)}{\partial t}\frac{}{G(t)} = \frac{\frac{\partial^2 \phi(x)}{\partial x^2} - \frac{V_{eff}}{\mu_D}\frac{\partial \phi(x)}{\partial x}}{\phi(x)} = -\lambda$$

(a) Time-dependence solution:

$$G(t) = Ae^{-\mu_D \lambda t}$$

(b) Space-dependence solution:
The general model has a convection term. It is a secondary derivative ordinary differential equation.

$$\frac{\partial^2 \phi(x)}{\partial x^2} - \frac{V_{eff}}{\mu_D}\frac{\partial \phi(x)}{\partial x} + \lambda\phi(x) = 0$$

Its auxiliary equation is,

$$r^2 - \frac{V_{eff}}{\mu_D} r + \lambda = 0$$

The roots of the auxiliary equation are,

$$r_{\pm} = \frac{V_{eff}/\mu_D \pm \sqrt{(V_{eff}/\mu_D)^2 - 4\lambda}}{2}$$

(i) For $\lambda = \frac{1}{4}\left(\frac{V_{eff}}{\mu_D}\right)^2$, the equation has double root $r = \frac{V_{eff}}{2\mu_D}$
The solution has the form $\phi(x) = Ae^{rx} + Bxe^{rx}$.
With boundary conditions: $A = 0$, $BLe^{rL} = 0$, $B = 0$

$$\phi(x) = 0$$

(ii) For $\lambda < \frac{1}{4}\left(\frac{V_{eff}}{\mu_D}\right)^2$, the equation has positive real roots and the solution is

$$\phi(x) = Ae^{r_+ x} + Be^{r_- x}$$

With boundary conditions: $A + B = 0$, $Ae^{r_+ L} + Be^{r_- L} = 0$, $A = B = 0$

$$\phi(x) = 0$$

(iii) For $\lambda > \frac{1}{4}\left(\frac{V_{eff}}{\mu_D}\right)^2$,
The equation has complex roots and solution has general form,

$$\phi(x) = e^{\frac{V_{eff}}{2\mu_D}x}\left(A\sin\left(\frac{\sqrt{\lambda'}}{2}x\right) + B\cos\left(\frac{\sqrt{\lambda'}}{2}x\right)\right)$$

where $\lambda' = 4\lambda - (V_{eff}/\mu_D)^2$.

With boundary conditions: $B = 0$, and

$$\phi(L) = e^{\frac{V_{eff}}{2\mu_D}L} A\sin\left(\frac{\sqrt{\lambda'}}{2}L\right) = 0$$

For non-trivial solution,

$$\frac{\sqrt{\lambda'}}{2}L = n\pi,\ \sqrt{\lambda'} = \frac{2n\pi}{L},$$
$$\lambda = \frac{\lambda'}{4} + \frac{1}{4}\left(\frac{\mathrm{V_{eff}}}{\mu_D}\right)^2 = \frac{\mathrm{n^2\pi^2}}{L^2} + \frac{1}{4}\left(\frac{\mathrm{V_{eff}}}{\mu_D}\right)^2,\ n = 0,1,\ldots$$

Combine (a) and (b), we have time-varying solution,

$$\mathrm{C_t(x,t)} = \mathrm{e}^{\frac{\mathrm{V_{eff}}}{2\mu_D}(x - \frac{\mathrm{V_{eff}}}{2}t)} \sum_{\mathrm{n=1}}^{\infty} \mathrm{A_n} \sin\left(\frac{\mathrm{n\pi}}{\mathrm{L}}\mathrm{x}\right) \mathrm{e}^{-\mu_\mathrm{D}\frac{\mathrm{n^2\pi^2}}{\mathrm{L^2}}\mathrm{t}}$$

Solve coefficients An to satisfy the initial condition.

$$\mathrm{C_t(x,0)} = \mathrm{e}^{\frac{\mathrm{V_{eff}}}{2\mu_D}x} \sum_{\mathrm{n=1}}^{\infty} \mathrm{A_n} \sin\left(\frac{\mathrm{n\pi}}{\mathrm{L}}\mathrm{x}\right) = -\mathrm{C_0}\frac{1 - e^{-\frac{\mathrm{V_{eff}}}{\mu_D}(L-x)}}{1 - e^{-\frac{\mathrm{V_{eff}}}{\mu_D}L}}$$

Rewrite the equation above,

$$\sum_{\mathrm{n=1}}^{\infty} \mathrm{A_n} \sin\left(\frac{\mathrm{n\pi}}{\mathrm{L}}\mathrm{x}\right) = -\mathrm{C_0}\frac{1 - e^{-\frac{\mathrm{V_{eff}}}{\mu_D}(L-x)}}{1 - e^{-\frac{\mathrm{V_{eff}}}{\mu_D}L}} \mathrm{e}^{-\frac{\mathrm{V_{eff}}}{2\mu_D}x}$$
$$= \frac{-\mathrm{C_0}\mathrm{e}^{-\frac{\mathrm{V_{eff}}}{2\mu_D}L}}{1 - e^{-\frac{\mathrm{V_{eff}}}{\mu_D}L}}\left(e^{-\frac{\mathrm{V_{eff}}}{2\mu_D}(L-x)} - e^{\frac{\mathrm{V_{eff}}}{2\mu_D}(L-x)}\right)$$
$$= -\mathrm{C_0}\frac{\sinh\left(\frac{\mathrm{V_{eff}}}{2\mu_D}(\mathrm{L}-\mathrm{x})\right)}{\sinh\left(\frac{\mathrm{V_{eff}}}{2\mu_D}\mathrm{L}\right)}$$

By multiplying $\sin\left(\frac{\mathrm{n\pi}}{\mathrm{L}}\mathrm{x}\right)$ and integrating both sides, we have

$$\mathrm{A_n} = \frac{2}{\mathrm{L}}\int_0^{\mathrm{L}} -\mathrm{C_0}\frac{\sinh\left(\frac{\mathrm{V_{eff}}}{2\mu_D}(\mathrm{L}-\mathrm{x})\right)}{\sinh\left(\frac{\mathrm{V_{eff}}}{2\mu_D}\mathrm{L}\right)} \sin\left(\frac{\mathrm{n\pi}}{\mathrm{L}}\mathrm{x}\right) dx$$
$$= \frac{-2\mathrm{C_0}}{\mathrm{L}\sinh\left(\frac{\mathrm{V_{eff}}}{2\mu_D}\mathrm{L}\right)} \int_0^{\mathrm{L}} \sinh\left(\frac{\mathrm{V_{eff}}}{2\mu_D}(\mathrm{L}-\mathrm{x})\right) \sin\left(\frac{\mathrm{n\pi}}{\mathrm{L}}\mathrm{x}\right) dx$$
$$= -\frac{2n\pi C_0}{n^2\pi^2 + \mathrm{V_{eff}^2}\mathrm{L}^2/4\mu_D^2}$$

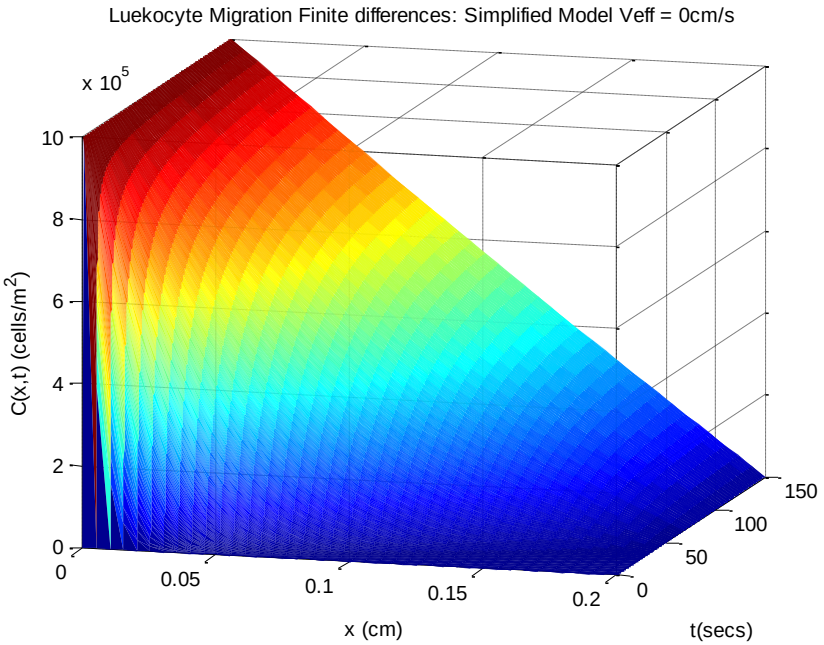
Combining steady-state and time-varying solution, we obtain the final Solution:

$$C(x,t) = e^{\frac{V_{eff}}{2\mu_D}(x-\frac{V_{eff}}{2}t)} \sum_{n=1}^{\infty} -\frac{2n\pi C_0}{n^2\pi^2 + V_{eff}^2 L^2/4\mu_D^2} \sin\left(\frac{n\pi}{L}x\right) e^{-\mu_D \frac{n^2\pi^2}{L^2}t} + C_0 \frac{1 - e^{-\frac{V_{eff}}{\mu_D}(L-x)}}{1 - e^{-\frac{V_{eff}}{\mu_D}L}}$$

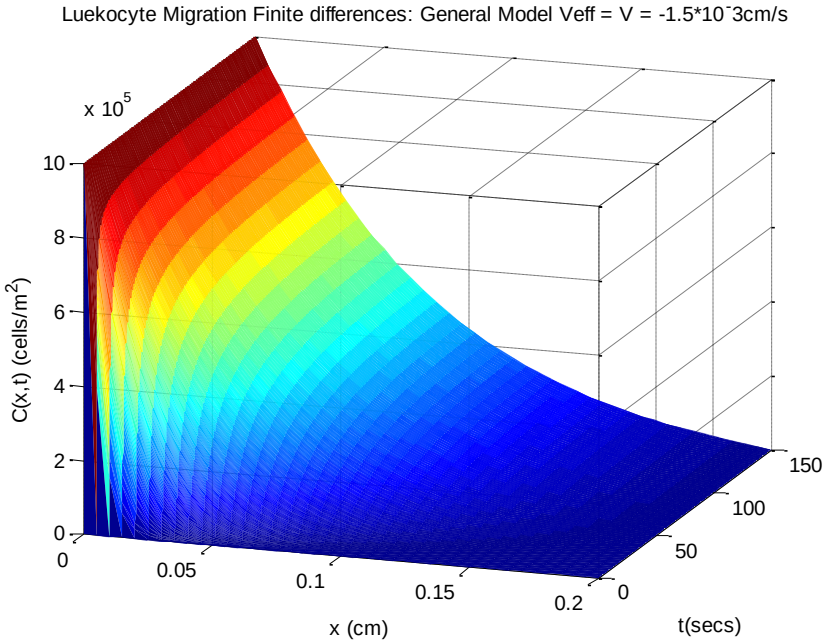
At a quick inspection of the solution, except for the nonlinear steady-state term, there is a $e^{\frac{V_{eff}}{2\mu_D}(x-\frac{V_{eff}}{2}t)}$ moving wave term with velocity $\frac{V_{eff}}{2}$ and direction of +x. This is the result of convection term and thus the blood flow.

NUMERICAL SOLUTION

To obtain a better understanding of what the analytical solution means, numerical solutions can be used to graphically show the concentration profile in regards to length(x) and time(t). The next four plots were used to see the effect Veff has on the system. For these cases the diffusion coefficient was kept constant. The first numerical solution pictured below represents the simplified version of the differentail equation; which means Veff=0. From this surface plot, it is evident that the concentration profile becomes linear at time goes to innfinty, which also agrees with the analytical solution for the steady state profile of the simplified equation.



The next surface plot looks at the concentration profile when Veff is present and has a negative value. In reality Veff will never be negative because that would entail the blood flow to go backwards. The plot shows that as time goes to infinity the concentration profile tends toward a concave up ramp shape; the higher side being at x=0. This makes senses because the blood flow would be fighting against the efforts of diffusion and push back the leukocytes. This is especially evident when comparing this plot to the first plot at x = 1.



The third surface plot Is the closest representation to what the leukocyte concetration would be in real life. In this case Veff is a positive number and is of the same magnitude as the previous plot. Having Veff as a positive number represents the flow of blood in the forward direction. The forward flow helps the diffusion of leukocytes by pushing them further down the prosthetic implant. This produces a concave down concentration profile for leukocytes as time goes to infinity

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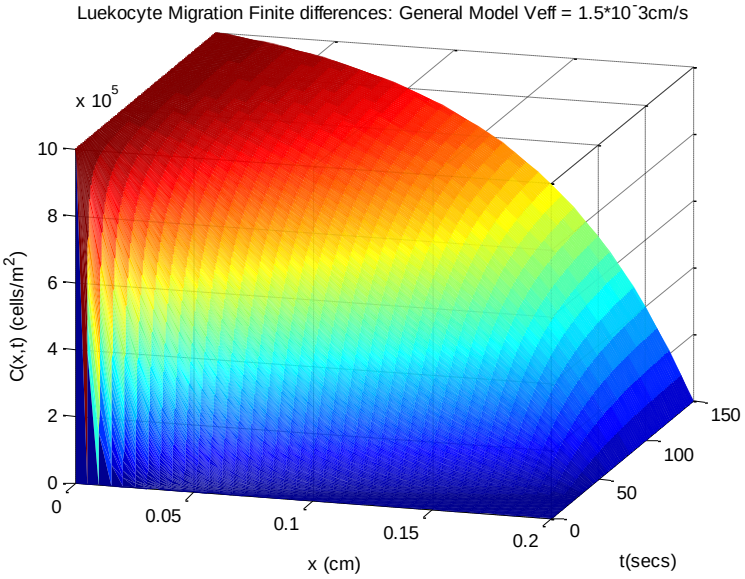
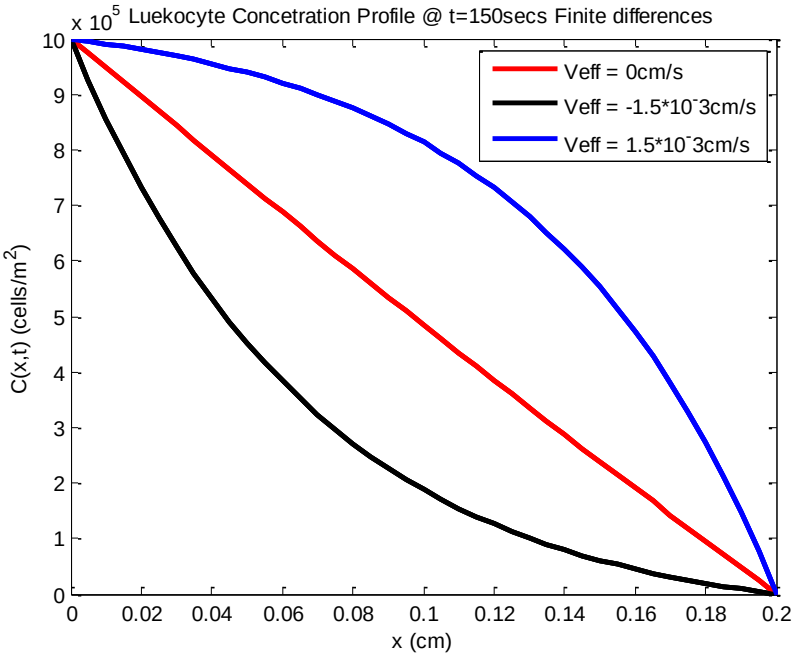
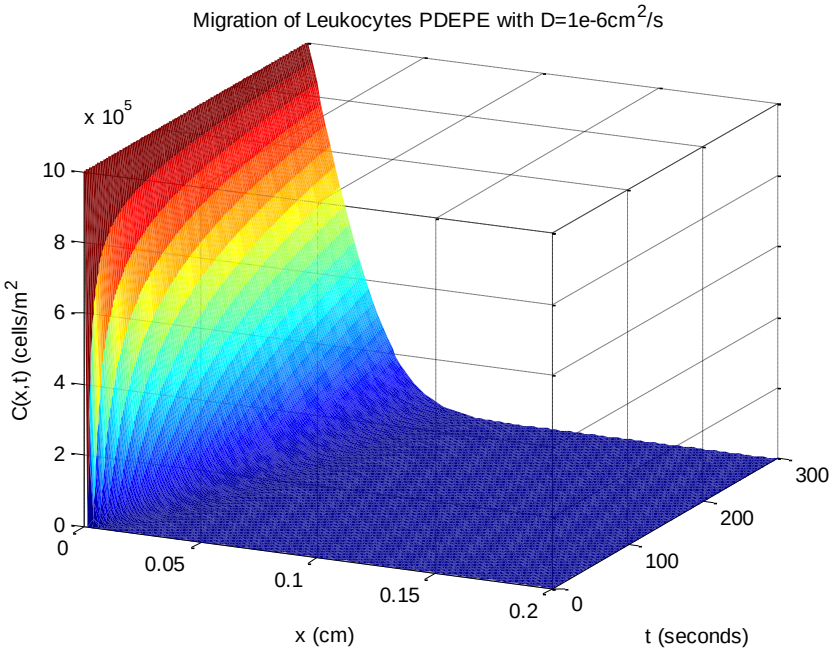
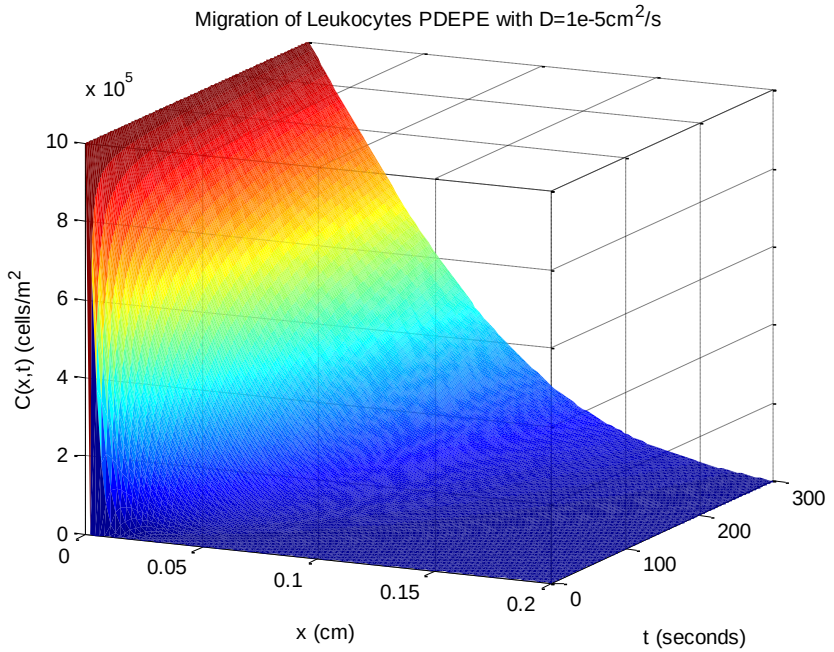


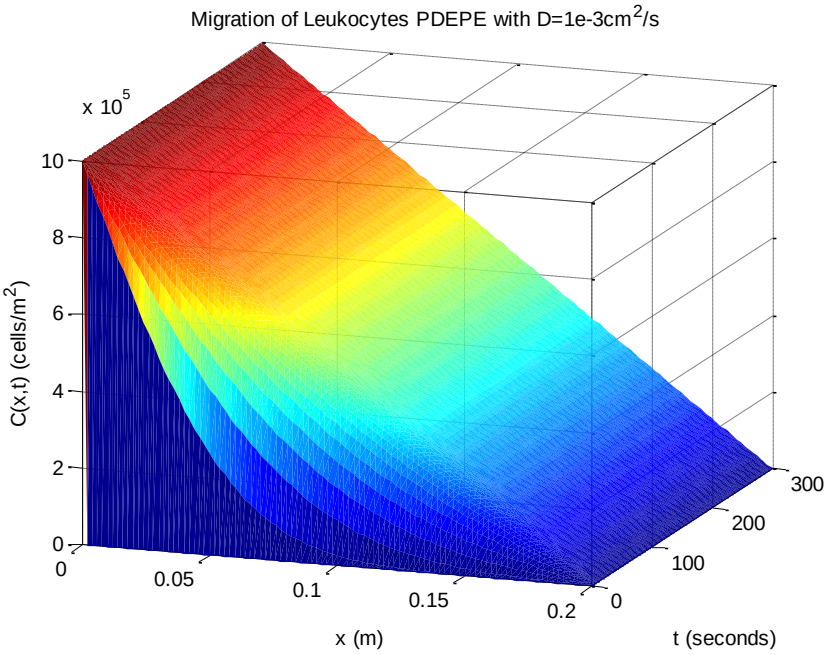
The next plot shows more cleary what the steady state concentration profile is for this equation at the different values of Veff.



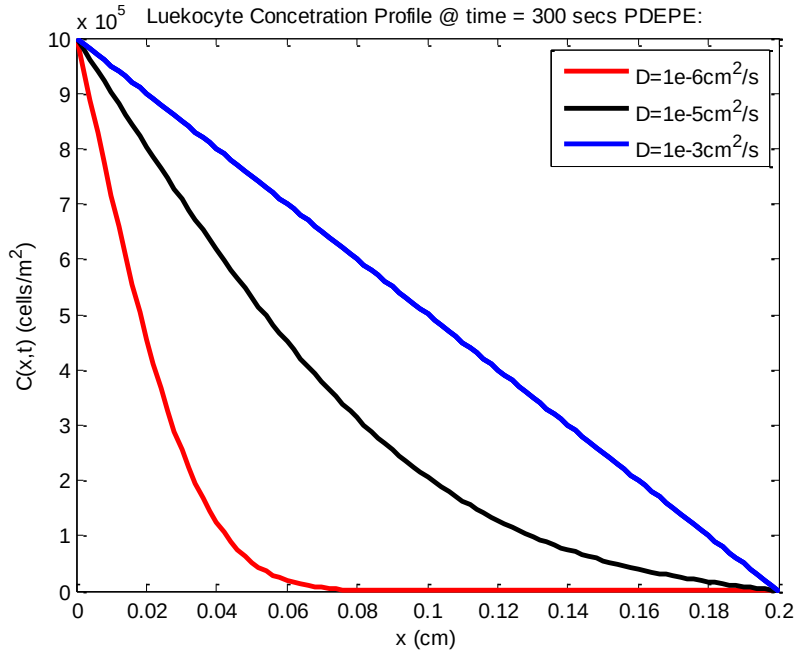
Along with seeing the effects of Veff has on the equation, it is also important to understand how the diffusion constant plays a role in the leukocyte concetration. For all of the following plots, Veff is 0 in order to make the effects of diffusion more clear. Also, take note that all diffusion constants, although at different magnitudes, are all positive. This is because is the definition of diffusion is the act of spreading out, the postive case, and not retracting, the negative case. By comparing the next three suraface plots to each other it is evident that the main effect of the diffusion constant is on the time it takes for the system to reach steady state.


Migration of Leukocytes PDEPE with D=1e-6cm2/s
x 10^5
10
8
6
4
2
0
C(x,t) (cells/m2
0
0.05
0.1
0.15
0.2
x (cm)
0
100
200
300
t (seconds)


Migration of Leukocytes PDEPE with D=1e-5cm2/s
x 10^5
10
8
6
4
2
0
C(x,t) (cells/m2
0
0.05
0.1
0.15
0.2
x (cm)
0
100
200
300
t (seconds)



Given enough time the first two plots would eventually have the same linear profile as the last plot. To get a cleaer view of the role of the diffusion constant, a plot of the concentration profile for all all three values at time = 300seconds is shown below. Clearly as the diffusion constant increases in magnitude, the faster the concentration profile will reach steady state.



CONCLUSIONS AND FUTURE WORK

Convection has a very important effect over the form of the solution of the Diffusion Equation and, thus, over the motion of leukocytes while they migrate towards the implantation site of a vascular graft. In order to prevent infection in prosthetic vascular grafts, one must understand this behavior of leukocytes and use mathematical models to predict the time it takes to get a desirable concentration of these cells in the point of interest. Also, several assays should be performed with different conditions in order to be able to optimize immune response and infection resistance during implantation of this prosthetics.

Future work in modeling the migration of leukocytes towards the implantation site of a vascular prosthetic material can be more accurate by modifying the assumptions we made. For instance, one assumption made was that the concentration of leukocytes at the left boundary is constant (C_0) and zero at the right boundary. However, in a more realistic model the concentration of leukocytes at the boundaries would behave more like a function of time due to blood flow and random collisions of leukocytes with other types of cells in the blood stream.

Another important characteristic of our model that must be taken into consideration is that it was chosen to be one-dimensional. A future (and more complex) model will have to be a two-dimensional system in z (position) and θ (angle with respect to the center of the cylindrical vascular graft). The model would be two-dimensional because radius R of prosthetic vascular grafts is usually constant. Finally, the rate of chemo-attractant molecules (released at the infection site, the right boundary) is of massive importance for modeling leukocytes migration since these molecules greatly determine the level of the immune response and their motion should be included as a function of position and time.

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APPENDIX: MATLAB CODE

```
%% Simplified Model - Finite difference method
% diffusion constant
clear all
global D
D = 1*10^-4; % cm^2/s

global C0
C0 = 1*10^6;

global V
V = 0; % cm/s

% domain
dx = 0.005; % step size in x dimension cm
dt = .1; % step size in t dimension weeks
xmesh = 0:dx:.2; % domain in x cm
tmesh = 0:dt:150; % domain in t weeks

% solution using finite differences (see Week 1 class notes)
nx = length(xmesh); % number of points in x dimension
nt = length(tmesh); % number of points in t dimension
stepsize = D * dt / dx^2; % stepsize for numerical integration
sol_fd = zeros(nt, nx);
sol_fd(:, 1) = C0; % left boundary conditions; constant value
sol_fd(:, nx) = 0; % left boundary conditions; zero value
sol_fd(1, :) = 0;  % initial conditions; zero

for t = 1:nt-1
    for x = 2:nx-1
        sol_fd(t+1, x) = sol_fd(t, x) + stepsize * ...
            (sol_fd(t, x-1) - 2 * sol_fd(t, x) + sol_fd(t, x+1)) -
(V*dt/dx) * ...
            (sol_fd(t, x+1) - sol_fd(t, x));
    end
end

figure(1)
surf(tmesh,xmesh,sol_fd','EdgeColor','none')
title('Luekocyte Migration Finite differences: Simplified Model Veff =
0cm/s')
xlabel('t(secs)')
ylabel('x (cm)');
zlabel('C(x,t) (cells/m^2)')

A= sol_fd(1500, :)';

%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
%%%%%%%%%%%%%%%%%%
%% General Model - Finite difference method
% diffusion constant
global D
D = 1*10^-4; % cm^2/s
```

```
global C0
C0 = 1*10^6;

global V
V = -1.5*10^-3; % cm/s

% domain
dx = 0.005; % step size in x dimension cm
dt = .1; % step size in t dimension weeks
xmesh = 0:dx:.2; % domain in x cm
tmesh = 0:dt:150; % domain in t weeks

% solution using finite differences (see Week 1 class notes)
nx = length(xmesh); % number of points in x dimension
nt = length(tmesh); % number of points in t dimension
stepsize = D * dt / dx^2; % stepsize for numerical integration
sol_fd = zeros(nt, nx);
sol_fd(:, 1) = C0; % left boundary conditions; constant value
sol_fd(:, nx) = 0; % left boundary conditions; zero value
sol_fd(1, :) = 0;  % initial conditions; zero

for t = 1:nt-1
    for x = 2:nx-1
        sol_fd(t+1, x) = sol_fd(t, x) + stepsize * ...
            (sol_fd(t, x-1) - 2 * sol_fd(t, x) + sol_fd(t, x+1)) -
(V*dt/dx) * ...
            (sol_fd(t, x+1) - sol_fd(t, x));
    end
end

figure(2)
surf(tmesh,xmesh,sol_fd','EdgeColor','none')
title('Luekocyte Migration Finite differences: General Model Veff = V = -
1.5*10^-3cm/s')
xlabel('t(secs)')
ylabel('x (cm)');
zlabel('C(x,t) (cells/m^2)')

A1= sol_fd(1500, :)';
%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
%%%%%%%%%%%%%%%%%%
%% General Model - Finite difference method
% diffusion constant
global D
D = 1*10^-4; % cm^2/s

global C0
C0 = 1*10^6;

global V
V = 1.5*10^-3; % cm/s

% domain
dx = 0.005; % step size in x dimension cm
dt = .1; % step size in t dimension weeks
```

```
xmesh = 0:dx:.2; % domain in x cm
tmesh = 0:dt:150; % domain in t weeks

% solution using finite differences (see Week 1 class notes)
nx = length(xmesh); % number of points in x dimension
nt = length(tmesh); % number of points in t dimension
stepsize = D * dt / dx^2; % stepsize for numerical integration
sol_fd = zeros(nt, nx);
sol_fd(:, 1) = C0; % left boundary conditions; constant value
sol_fd(:, nx) = 0; % left boundary conditions; zero value
sol_fd(1, :) = 0;  % initial conditions; zero

for t = 1:nt-1
    for x = 2:nx-1
        sol_fd(t+1, x) = sol_fd(t, x) + stepsize * ...
            (sol_fd(t, x-1) - 2 * sol_fd(t, x) + sol_fd(t, x+1)) -
(V*dt/dx) * ...
            (sol_fd(t, x+1) - sol_fd(t, x));
    end
end

figure(3)
surf(tmesh,xmesh,sol_fd','EdgeColor','none')
title('Luekocyte Migration Finite differences: General Model Veff =
1.5*10^-3cm/s')
xlabel('t(secs)')
ylabel('x (cm)');
zlabel('C(x,t) (cells/m^2)')

A2= sol_fd(1500, :)';
figure(4)
plot(xmesh, A, 'r', 'linewidth', 2.5);
hold on
plot(xmesh, A1, 'k', 'linewidth', 2.5);
plot(xmesh, A2,  'linewidth', 2.5);
title('Luekocyte Concetration Profile @ t=150secs Finite differences')
xlabel('x (cm)');
ylabel('C(x,t) (cells/m^2)')
legend('Veff = 0cm/s','Veff = -1.5*10^-3cm/s','Veff = 1.5*10^-3cm/s')
%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
%%%%%%%%%%%%%%%%%%


%Migration of Leukocytes with "pdepe"

function leukocytemig
global miuD
global Co
global veff
global L

Co = 1e6; %cells/cm^2
miuD = 1e-6; %cm^2/s
L = 0.2; %cm
veff = 1e-5; %cm/s
```

```
x = 0:0.01*L:L;
t = 0:1:300;

sol_pdepe = pdepe(0,@pdefun,@ic,@bc,x,t);

A= sol_pdepe(300, :)';
figure(4)
plot(x, A, 'r', 'linewidth', 2.5);
hold on
figure(1)
surf(t,x,sol_pdepe','EdgeColor','none')
title('Migration of Leukocytes PDEPE with D=1e-6cm^2/s')
xlabel('t (seconds)')
ylabel('x (cm)')
zlabel('C(x,t) (cells/m^2')
% function definitions for pdepe:
% --------------------------------------------------------------
function [c, f, s] = pdefun(x, t, u, DuDx)
% PDE coefficients functions
global miuD
global veff
c = 1;
f = miuD * DuDx; % diffusion
s = -veff * DuDx; % convection
% --------------------------------------------------------------
function u0 = ic(x)
global Co

% Initial conditions function
u0 = (x==0);


% --------------------------------------------------------------
function [pl, ql, pr, qr] = bc(xl, ul, xr, ur, t)
% Boundary conditions function

global Co

pl = ul-Co; % value left boundary condition
ql = 0; % flux left boundary condition
pr = ur; % value right boundary condition
qr = 0; % flux right boundary condition



%Migration of Leukocytes with "pdepe"

function leukocytemig1
global miuD
global Co
global veff
global L

Co = 1e6; %cells/cm^2
```

```
miuD = 1e-5; %cm^2/s
L = 0.2; %cm
veff = 1e-5; %cm/s
x = 0:0.01*L:L;
t = 0:1:300;

sol_pdepe1 = pdepe(0,@pdefun2,@ic2,@bc2,x,t);
A1= sol_pdepe1(300, :)';
figure(4)
plot(x, A1, 'k', 'linewidth', 2.5);
hold on
figure(2)
surf(t,x,sol_pdepe1','EdgeColor','none')
title('Migration of Leukocytes PDEPE with D=1e-5cm^2/s')
xlabel('t (seconds)')
ylabel('x (cm)')
zlabel('C(x,t) (cells/m^2')
% function definitions for pdepe:
% --------------------------------------------------------------
function [c, f, s] = pdefun2(x, t, u, DuDx)
% PDE coefficients functions
global miuD
global veff
c = 1;
f = miuD * DuDx; % diffusion
s = -veff * DuDx; % convection
% --------------------------------------------------------------
function u0 = ic2(x)
global Co

% Initial conditions function
u0 = (x==0);


% --------------------------------------------------------------
function [pl, ql, pr, qr] = bc2(xl, ul, xr, ur, t)
% Boundary conditions function

global Co

pl = ul-Co; % value left boundary condition
ql = 0; % flux left boundary condition
pr = ur; % value right boundary condition
qr = 0; % flux right boundary condition




%Migration of Leukocytes with "pdepe"

function leukocytemig2
global miuD
global Co
global veff
global L
```

```
Co = 1e6; %cells/cm^2
miuD = 1e-3; %cm^2/s
L = 0.2; %cm
veff = 1e-5; %cm/s
x = 0:0.01*L:L;
t = 0:1:300;

sol_pdepe2 = pdepe(0,@pdefun3,@ic3,@bc3,x,t);
A2= sol_pdepe2(300, :)';
figure(3)
surf(t,x,sol_pdepe2','EdgeColor','none')
title('Migration of Leukocytes PDEPE with D=1e-3cm^2/s')
xlabel('t (seconds)')
ylabel('x (m)')
zlabel('C(x,t) (cells/m^2)')

figure(4)
plot(x, A2, 'b', 'linewidth', 2.5);
hold on

title('Luekocyte Concetration Profile @ time = 300 secs PDEPE:')
xlabel('x (cm)');
ylabel('C(x,t) (cells/m^2)')
legend('D=1e-6cm^2/s','D=1e-5cm^2/s','D=1e-3cm^2/s')
% function definitions for pdepe:
% -----------------------------------------------------------------
function [c, f, s] = pdefun3(x, t, u, DuDx)
% PDE coefficients functions
global miuD
global veff
c = 1;
f = miuD * DuDx; % diffusion
s = -veff * DuDx; % convection
% -----------------------------------------------------------------
function u0 = ic3(x)
global Co

% Initial conditions function
u0 = (x==0);


% -----------------------------------------------------------------
function [pl, ql, pr, qr] = bc3(xl, ul, xr, ur, t)
% Boundary conditions function

global Co

pl = ul-Co; % value left boundary condition
ql = 0; % flux left boundary condition
pr = ur; % value right boundary condition
qr = 0; % flux right boundary condition
```