BENG 221

Mathematical Model for Protein Diffusion Through a Biodegradable Polymer

Shayan Aftab, Sinead Hawker, Sung Hwang, Raeeun Chung

October 31, 2014

Table of Contents

Introduction

Biodegradable polymers are widely used for drug delivery due to their versatility and non-toxic properties. Their applications range from microparticles for drug release to drug-loaded stents and grafts. For example, the biodegradable polymer poly(D,L,-Lactide-co-Glycolide) (PLG) is used in the delivery of osteotropic factors promoting bone regrowth, since the polymer provides a scaffold to support the bone as well as pores to store and then release the factors[1]. As the polymer degrades the osteotropic factors release more quickly and the bone regrows to fill the area where the scaffold had been providing support. This system improves upon previous delivery systems as it prevents the growth factors from dispersing shortly after implantation in vivo[1]. The porosity of PLG also serves as a scaffold for cell proliferation with a sufficiently high diffusion rate for the transportation of nutrients in and wastes out[1]. Figure 1 shows the pores formed in PLG over time as the polymer degrades. These pores increase the diffusivity of the osteotropic factors out and allows the cells to migrate in. The key to the success of this treatment is the controlled release of the osteotropic factors. A mathematical model for the release of the osteotropic factors would allow for greater control over their release. This provides an example for how a mathematical model for diffusion through a biodegradable polymer will be of great interest.

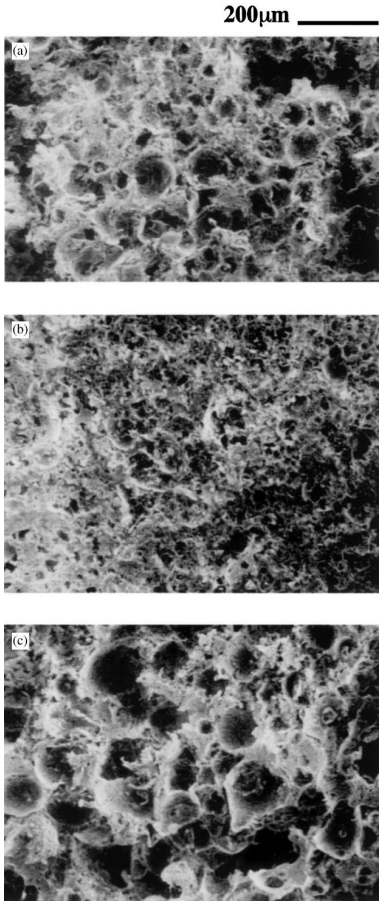

Figure 1. Pores in the PLG scaffold increase in size as the polymer degrades. This allows cells to migrate into the scaffold and the osteotropic factors to diffuse out[1].

In this case, as in many others, the rate of drug release and the amount of total drug release are vital in patient treatment, making the accuracy of mathematical models for drug release critical. An accurate model allows exact release rates over time to be determined before administration for a variety of polymers and drugs, allowing for the prediction of clinical results without needing to perform trial and error experiments. Drug release rates for drug-loaded polymers are dependent on the rate of diffusion of the drug through the polymer. The diffusivity for the drug through these polymers is often treated as constant; however, biodegradable polymers are unique in that diffusivity actually increases with time. As biodegradable polymers degrade the pores within their matrix grow in size and number. This opens up paths for the diffusion of drugs through the matrix leading to an increase in the diffusivity constant. Treating the diffusivity as constant is an approximation that does

not take into account the effect of the degradation of the polymer on diffusion rate. However, in order to take into account all of the processes that affect diffusion including polymer swelling, osmotic effects, adsorption, and drug dissolution the mathematical model would have to be extremely complicated[2]. In order to simplify the model and make it usable, only the forces that play the largest role in the drug release rate will be accounted for in the mathematical model that we will be working with.

In order to develop a model and test its efficacy, we will be using the diffusion of human growth hormone (hGH) in PLG for our constants. PLG was chosen as it is both biodegradable and nontoxic, making it a good example of a polymer used for biomedical applications (Fredenberg). hGH was chosen as its diffusion through PLG has been well studied and experimentally modeled, allowing us to compare our mathematical model with the experimentally obtained results (Fredenberg). For these reasons a mathematical model for the diffusion of hGH through PLG is relevant to the bioengineering community. Figure 2 shows the simplified model we developed for diffusion of hGH through PLG. The boundaries are defined on the x-axis at 0 and L. The growth hormone is shown as a red pentagram, initially uniform throughout the polymer. The PLG pores are initially small and diffusion is slow. Over time the pore size increase and the rate of diffusion is shown to increase accordingly. In order to be able to compare between the models that do not take degradation into account and the model that we have developed, we will be solving both the simple and complex models.

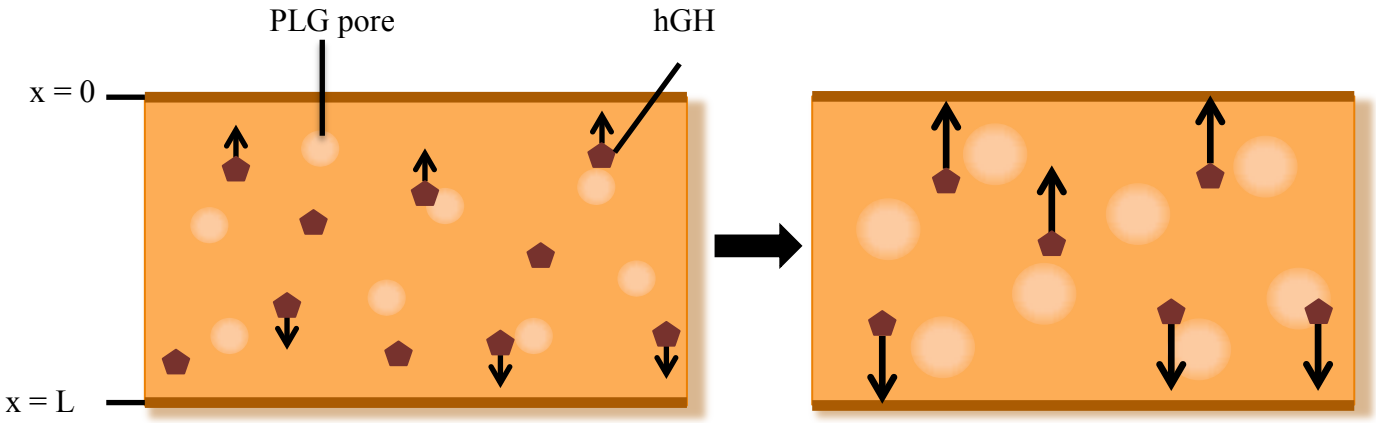

Figure 2. A simplified model demonstrating the diffusion of hGH through PLG. Over time the pore size increases allowing the diffusion rate of hGH to increase. The x-axis values for the boundaries are defined. The magnitude of diffusion is represented by the arrow length attached to the growth hormones.

Mathematical Model

Model Set-Up

Throughout our description of our mathematical model we will be using the following terminology. In order to make our model specific to the diffusion of human growth hormone in PLG, we obtained the following values for our constants from literature resources[2,3,4].

$$C(x,t) = concentration\ profile\ of\ hGH$$
$$C_0 = initial\ hGH\ concentration = 30\ mg/mL$$
$$L = length\ of\ thin\ film = 5\,mm$$
$$D(t) = diffusivity\ of\ hGH\ in\ PLG$$
$$D_0 = initial\ diffusivity\ of\ hGH = 4.32\times10^{-8}\,m^2/day$$
$$k = PLG\ degradation\ rate = 0.044\ day^{-1}$$

We will be modeling the diffusion of the human growth hormone through the PLG by treating the PLG as a thin film with 1-dimensional diffusion. There is no generation factor since there is no synthesis or break down of the hormone. We define the top of the film as x = 0 and the bottom of the film as x = L. This gives allows us to model the diffusion with the following equation.

$$\frac{\partial C}{\partial t} = D(t)\frac{\partial^2 C}{\partial x^2}$$

From literature we found that diffusion in a biodegradable polymer is exponentially dependent on time and polymer degradation rate over the time scale with which we are concerned, giving us the following equation[2].

$$D(t) = D_0 e^{kt}$$

Initially, the hGH concentration is uniformly distributed throughout the polymer, making it a constant value before diffusion begins. This corresponds to the following initial condition.

$$IC: C(x,0) = C_0$$

Because the hGH is assumed to instantly diffuse away from the boundaries without any adsorption, the concentration of hGH would then be 0 mg/mL at the boundaries. This leads to the following two boundary conditions.

$$BCs: C(0,t) = C(L,t) = 0$$

This defines the model, which we will solve and analyze through the rest of the paper. In order to provide a comparison between the less accurate time-independent diffusivity model and the more complex time-dependent diffusivity model, we will solve and analyze both models.

Assumptions

In this model we made the assumptions outlined below:

- hGH is dispersed uniformly throughout the polymer.
- The polymer membrane is thin enough to assume that diffusion only occurs in one dimension; i.e. the polymer is assumed to be infinitely long is dimensions x and z.
- The polymer degrades at a constant rate uniformly over time and throughout the bulk of the polymer.
- hGH diffuses out of the surface of the polymer at the same rate as it diffuses to the surface; i.e. there is no adsorption and the drug diffuses instantly away from the boundary.
- The diffusion of hGH is independent of the diffusion of water and the side products from the polymer degradation.
- The diffusion rate increases exponentially over the time scale we are concerned with.

Analytical Solution

Diffusion Equation Solution

We began with our defined equation for 1-D diffusion with time dependent diffusivity. This gave us the following partial differential equation.

$$\frac{\partial C}{\partial t} = D(t)\frac{\partial^2 C}{\partial x^2}, \; where \; D(t) = D_0 e^{kt} \quad (1)$$

Again, we had the following initial conditions and boundary conditions.

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

With the problem properly setup, we then used separation of variables to solve the partial differential equation. By dividing the concentration profile into a function of x and a function of t, we were able to plug Equation (2) into Equation (1) to form two separate equations that could now be solved.

$$C(x,t) = \Phi(x)G(t) \quad (2)$$

$$\Phi(x)\frac{dG}{dt} = D(t)G(t)\frac{d^2\Phi}{dx^2} = -\lambda$$

$$\frac{\frac{d^2\Phi}{dx^2}}{\Phi(x)} = -\lambda \,,\, \frac{\frac{dG}{dt}}{D(t)G(t)} = -\lambda$$

$$\frac{d^2\Phi}{dx^2} + \lambda\Phi(x) = 0 \quad (3), \frac{dG}{dt} = -\lambda D(t)G(t) \quad (4)$$

Here is where our model deviated from the previous models where diffusivity is treated as constant over time. Solving Equation (4) gave an exponential to an exponential, as seen below. Plugging in the initial conditions also allowed us to find the integration constant G_0.

$$G(t) = G_0 e^{-\frac{\lambda D_0}{k}e^{kt}} \quad (5)$$

$$G(0) = G_0 e^{-\frac{\lambda D_0}{k}} = C_0$$

$$G_0 = C_0 e^{\frac{\lambda D_0}{k}} \quad (6)$$

Then we needed to solve Equation (3) to find the value of λ. This was done using the three different possible values of λ.

$$\lambda < 0 \rightarrow trivial\ solution$$

$$\lambda = 0 \rightarrow trivial\ solution$$

$$\lambda > 0 \rightarrow \Phi(x) = A\cos(\sqrt{\lambda}x) + B\sin(\sqrt{\lambda}x) \quad (7)$$

We only found a non-trivial solution when λ > 0, so the next step was to plug in the boundary conditions.

$$\Phi(0) = A = 0$$

$$\Phi(L) = B\sin(\sqrt{\lambda}L) = 0$$

Because A = 0, B ≠ 0 otherwise we would have had another trivial solution. This meant that the sine term must be equal to zero. Using this, we could then solve for λ.

$$\sin(\sqrt{\lambda}L) = 0$$

$$\sqrt{\lambda} = \frac{n\pi}{L}\,,\ n = 1,2,3..$$

Plugging these results back into Equation (7) and then Equation (2) gave the following:

$$\Phi(x) = \sum_{n=1}^{\infty} B_n \sin(\frac{n\pi}{L}x)$$

$$C(x,t) = \sum_{n=1}^{\infty} B_n \sin(\frac{n\pi}{L}x)\cdot e^{-\frac{\left(\frac{n\pi}{L}\right)^2 D_0}{k}e^{kt}} \quad (8)$$

We then need to solve for the constant B_n, which included the integration constant G_0 from the G(t) function in it.

$$B_n = \frac{2}{L}\int_0^L G_0 \sin(\frac{n\pi}{L}x)dx$$

$$B_n = -\frac{2G_0}{n\pi}\cos(\frac{n\pi}{L}x)\Big|_0^L$$

$$B_n = -\frac{2G_0}{n\pi}\left[\cos(n\pi) - \cos(0)\right]$$

$$B_n = \frac{2G_0}{n\pi}(1-\cos(n\pi)) \quad (9)$$

Plugging Equations (9) and (6) into Equation (8) gave us our final analytical solution:

$$C(x,t) = \sum_{n=1}^{\infty} \frac{2C_0 e^{\frac{\left(\frac{n\pi}{L}\right)^2 D_0}{k}}}{n\pi}(1-\cos(n\pi))\cdot\sin(\frac{n\pi}{L}x)\cdot e^{-\frac{\lambda D_0}{k}e^{kt}} \quad (10)$$

Graphical Representation

After finding our analytical solution, we used MATLAB to plot a 3-dimensional graph of our results. We plotted from n=1 to n=42 to give us a close approximation to the analytical solution, though the oscillations can still be seen at the initial time. As can be seen from the plot below (Figure 3), initially the hormone is uniformly dispersed throughout the polymer. Over time it quickly diffuses through the boundaries, eventually reaching a concentration of 0 mg/mL over the entire length of the polymer. This is what we would expect to see for a protein diffusing out of a polymer with no synthesis or insulation.

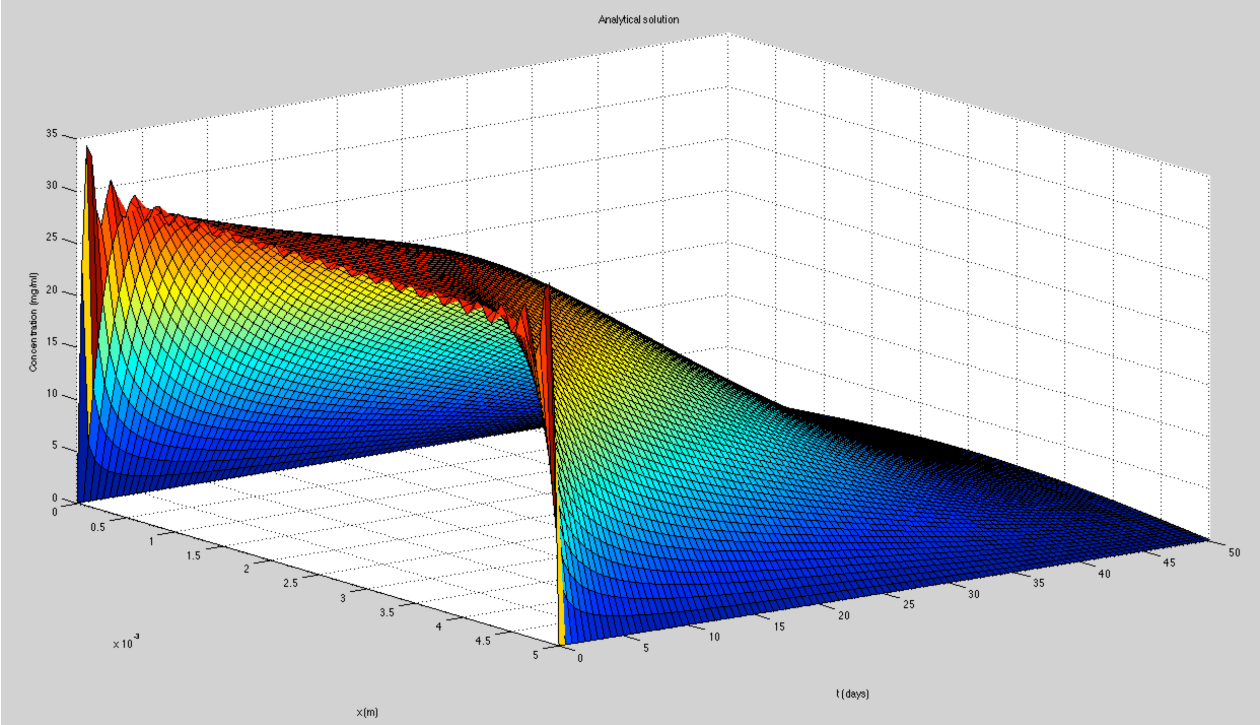

Figure 3. A surf plot of the analytical solution with 42 terms. The plot shows a uniform distribution of the hormone at the initial condition, which quickly diffuses out of the value-value boundaries.

MATLAB Model

Complex Time-Dependent Diffusivity Model

In order to confirm that our analytical solution was correctly solved and plotted, we used the MATLAB *pdepe* function to provide a surf plot of the exact solution. In this case, the graph will no longer be an approximation. The following plot (Figure 4) shows that our analytical solution provided a close approximation to the exact solution. The oscillations are no longer present and the graph is smoother, but the shape of the graph and rate of diffusion are a close match between the graphs. Again, the uniform distribution of the

protein at the initial condition can be seen, followed by its diffusion out of the boundaries bringing the final concentration to 0 mg/mL.

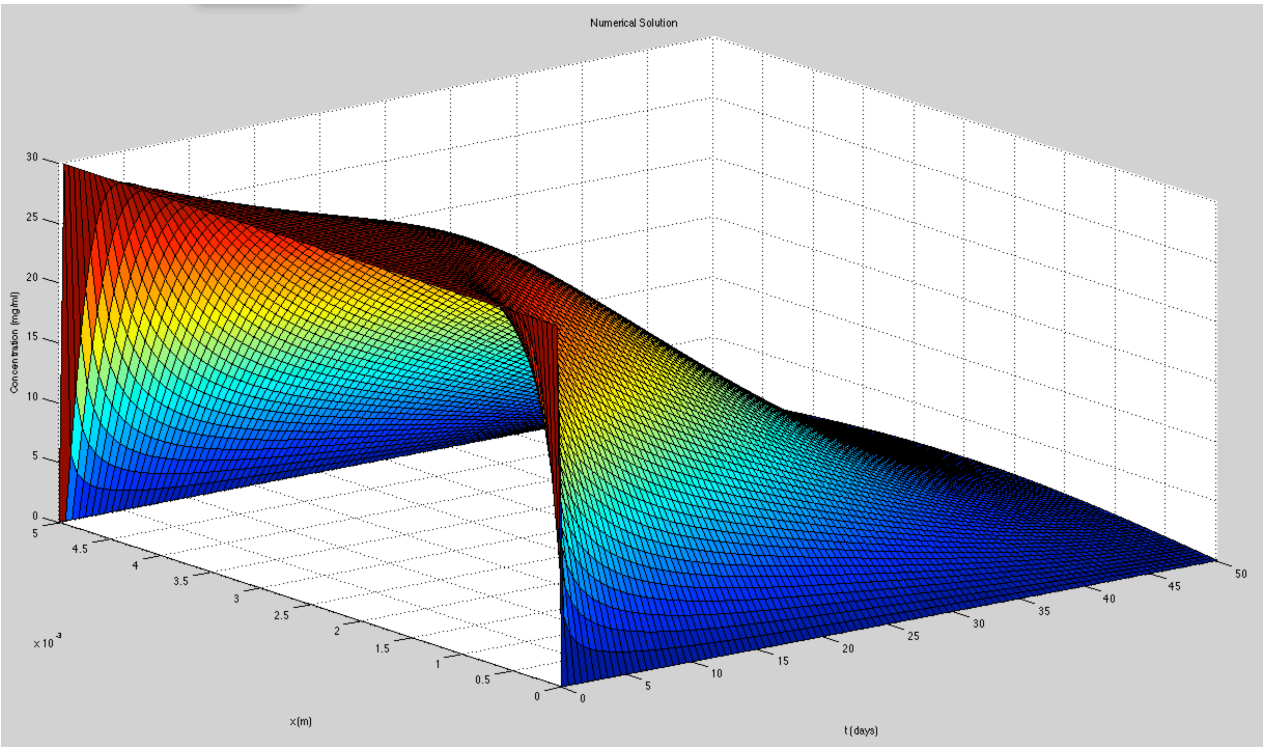

Figure 4. A surf plot produced by the *pdepe* function of MATLAB. It provides an exact solution to our mathematical model. The plot closely resembles our analytical solution's approximation. Confirming it is correctly solved.

Simplified Time-Independent Diffusivity Model

In order to determine whether our model is a significant improvement upon previous models, we solved the same diffusion model, except without the polymer degradation taken into account. In other words, with this model it is assumed that there is no increase in pore size and therefore no exponential increase in diffusivity. Therefore, the diffusivity remains constant over time ($D = D_0$). As a result, there is no exponential term in the diffusivity to account for the degradation of the polymer, and the analytical solution for time dependent function, G(t), becomes much simpler. It is now only an exponential, rather than an exponential to the exponential. Therefore, the analytical solution of the simplified diffusivity model is the equation shown below.

$$C(x,t) = \sum_{n=1}^{\infty} \frac{2C_0}{n\pi}(1-\cos(n\pi)) \cdot \sin(\frac{n\pi}{L}x) \cdot e^{-D_0\lambda t}$$

Since this solution no longer has an exponential to the exponential term, we predicted that the diffusion of the drug would take much longer. This makes sense intuitively, since without the polymer degradation the diffusivity would remain relatively slow. In

order to see if our prediction was correct, we used the MATLAB *pdepe* function again to visualize the slower diffusion rate. Figure 5 shows the diffusion profile of hGH through a non-biodegradable polymer over the same time scale as our previous plots. The initial condition is again the uniform distribution of hormone that we would expect. While hGH still diffuses out of the boundaries, the diffusion rate is much lower than with our more accurate model. Approximately half of the hGH has diffused out from the scaffold after 50 days, whereas, almost all of the hGH has diffused out when the polymer degrades.

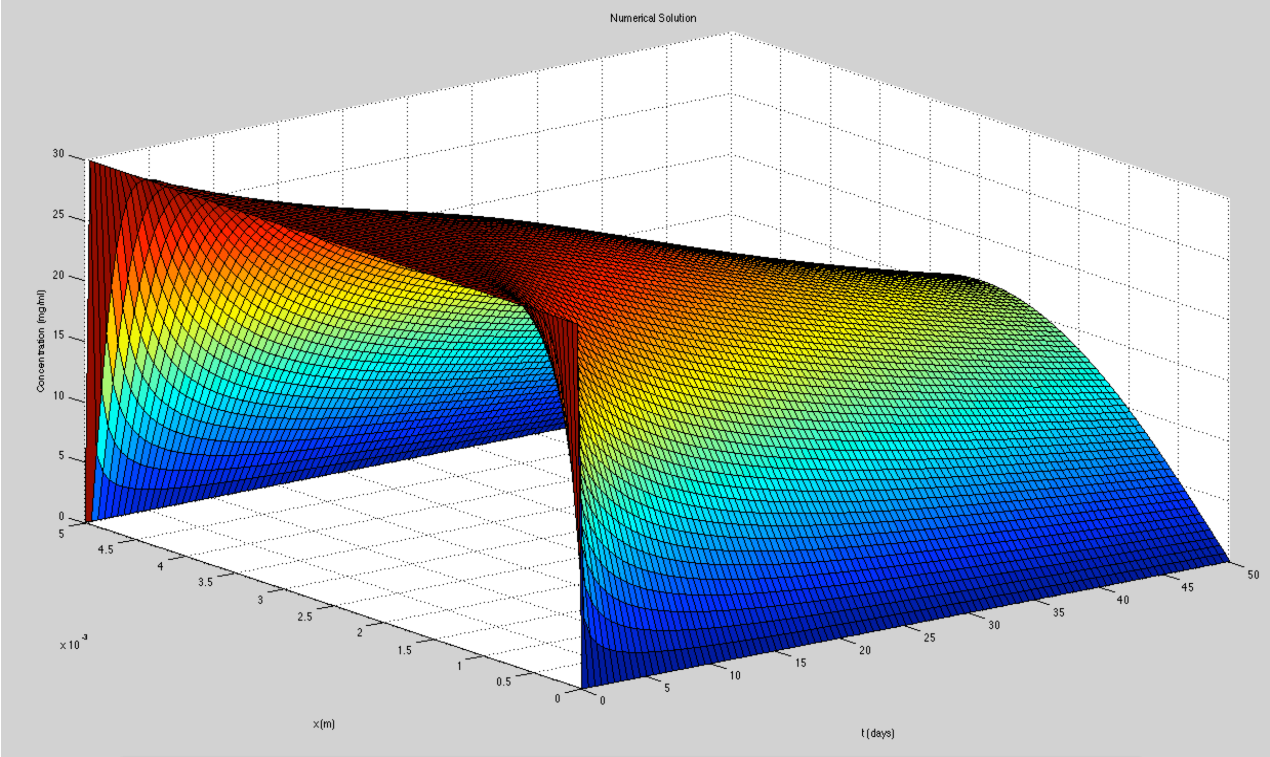

Figure 5. A surf plot made by the MATLAB pdepe function of the time-dependent diffusivity model. It shows slower diffusion than the model that takes degradation into account.

From this we determined that our model was a significant improvement on time-independent diffusivity models for the modeling of diffusion through a biodegradable polymer.

Comparison of Models

We took a slice along each surf plot by holding x constant and looking at the diffusion with respect to time. This allowed us to compare the effect of biodegradation on protein diffusion more easily. The following graphs (Figure 6) show the concentration profile over 50 days and 150 days respectively.

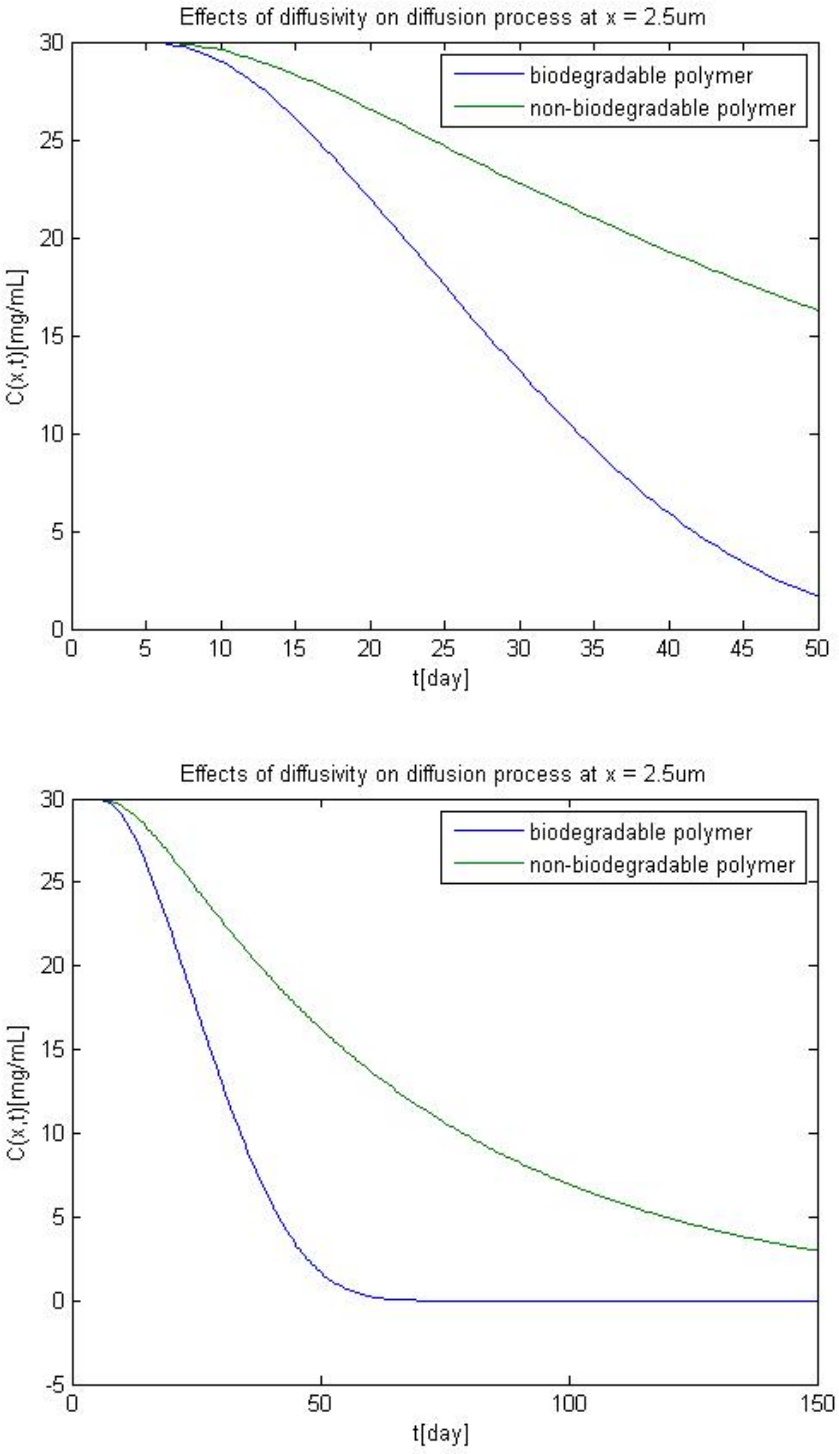

Figure 6. Diffusion over 50 days and 150 days respectively, while holding x constant. The plots show more clearly that the polymer degradation increases the diffusivity. Over time the effect of the polymer degradation grows more pronounced.

Since we know from our mathematical model that diffusivity increases exponentially with relation to time due to polymer degradation, we expected the difference in diffusion between the two models to increase over time. Figure 6 clearly demonstrates the faster diffusion due to polymer degradation, as well as confirming our prediction that the exponential dependence of the diffusivity would increase the differences in the models over time.

Conclusion

Mathematical Solution for Diffusion of hGH in Decaying Polymer Scaffold

In this study we solved the model diffusion equation using two approaches; an analytical approximation and an exact solution. We used the separation of variable method in order to find the analytical solution. The resulting approximation gave us the concentration of the human growth hormone in terms a position-dependent sine wave and a time-dependent exponential term. Due to the sine wave term, the analytical solution yields an oscillatory profile on the graph, especially near t = 0, where the exponential decay term has little effect on the overall solution. Multiple iterations of the summation function yield a smoother approximation. However, MATLAB has limit to its matrix size and calculability, limiting the number of iterations we can take into account. In order to try achieve the closest approximation possible, we performed the maximum number of iterations allowed (n = 42). Although the resulting graph (Figure 3) still showed oscillation near the initial condition, the overall graph showed a contour we could expect from a diffusion system with the conditions we set in place.

In order to verify our analytical solution and to obtain a more accurate surface plot, we used the *pdepe* function in MATLAB. The *pdepe* function yields an exact solution allowing us to plot a corresponding graph to the partial differential equation. As anticipated, the resulting 3-D graph (Figure 4) is much smoother, and the initial condition (C_0 = 30 mg/ml between x = 0 mm and x = .5 mm) no longer has the oscillation approximations. By comparing this graph to the graph from the analytical method, we concluded that our analytical solution was correct, and that if we further increased the number summation terms we would have the exact same graph for both methods. From both graphs we observed that hGH trapped within the .5mm polymer scaffold initially had a uniform concentration of 30 mg/ml within the film. The hormone then diffused out through both boundaries of the film, as expected since there was no adsorption or insulation. By day 50, almost all of the hormone present in the film had diffused out of the polymer scaffold. This depletion time is within a reasonable range of previous works[4] and we are able to say with confidence that our modeling equation appropriately represents a close approximation to the diffusion of a protein through a biodegradable polymer. To further substantiate our model, we compared it to a constant diffusivity model.

Comparison to Constant Diffusivity Model

Our diffusion model took into account the linear decay of the polymer scaffold, which as we found greatly affect the diffusion of hGH. To do this we used a time-dependent diffusivity, instead of the more commonly used constant diffusivity. We believed that such modeling would provide a better representation of an actual system, since polymers degrade in slow, yet steady, manner. It was difficult, however, to observe the effect of having time-dependency in diffusivity without a comparison.

To do this, we solved a similar diffusion model that uses the same constants and assumptions; however this equation does not take into account the time-dependent linear decay of the scaffold polymer. When we used MATLAB to create a surf plot of this simpler model, the diffusion profile appeared similar. However, the total depletion in this model took more than 150 days (Figure 6). This was expected, as lack of scaffold decay would result in a constant and low diffusivity. Without the degradation of the polymer scaffold, the hGH molecules would have more difficulty escaping the polymer film. Compared to this model, our time-dependent diffusivity model shows a rapid diffusion period after day 10 due to the increase in pore size in the polymer scaffold, providing easier diffusion route for the hGH.

Although a constant diffusivity model represents a common diffusion profile, it was not a good representation of drug diffusion through decaying polymer scaffold. The resulting 150 days depletion time was much longer than the experimented value. Thus, we concluded that our model more realistically represented the hGH diffusion through PLG scaffold film.

Future Studies

In order to simplify our mathematical model enough to be solved analytically, we initially made several assumptions. Some of these assumptions may not have been justified, and could affect the diffusion profile significantly. This could mean our model is a less accurate approximation.

To begin with, we assumed that our diffusion was only in one dimension. In a real system, the film is not infinitely long, meaning that diffusion also occurs in the other dimensions. This added diffusion could significantly change the diffusion profile, as the molecules would diffuse more quickly out if they were not insulated in two dimensions. Furthermore, if the film were attached to a surface, the diffusion rate difference between the attached surface and the open surface could be significant enough to change the diffusion profile. That being said, accounting for these boundary condition issues would not be too difficult as long as the interactions between the film and the attached surface were well understood.

Secondly, we assumed that the polymer degradation is linear, or has constant degradation rate. Although polymer degradation might appear linear in a short time frame, in an extended time frame polymer degradation is exponential. This is for the

same reason that the diffusivity has an exponential term; the increase in scaffold pore size also facilitates polymer degradation. In other words, as the polymer breaks down it exposes more surface area leading to further degradation. A more precise modeling of polymer degradation would result in a more accurate hGH diffusion model.

Lastly, we assumed that the hGH diffusion was independent of interaction/diffusion of other molecules. In an *in vitro* system, this assumption might be safe. However, once the film is applied to *in vivo* system, there are countless molecules that hGH could come into contact with, possibly hindering its ability to diffuse out of the polymer. These interactions are difficult to take into account, since developing a model that took into account every interaction would be almost impossible, and not likely very usable. However, isolating a few molecules that have significant effect on hGH diffusion via interaction with hGH and accounting for their effect could greatly enhance the accuracy of our model. These improvements should be looked into for future models in order to obtain more accurate mathematical models for drug release.

References

[1] Whang, K., Goldstick, T.K., Healy, K.E. “A biodegradable polymer scaffold for delivery of osteotropic factors.” *Biomaterials*. Volume 21: 2545-2551. 2000.

[2] Siepmann, J., Gopferich, A. “Mathematical modeling of bioerodible, polymeric drug delivery systems.” *Advanced Drug Delivery Reviews*. Volume 48, Issues 2-3: 229-247. June 2001.

[3] Fredenburg, S., Reslow, M., Axelsson, A. “Measurement of Protein Diffusion Through Poly(d,l-Lactide-Co-Glycolide).” *Pharmaceutical Development and Technology*. Volume 10, Issue 2: 299-307. 2005.

[4] Tracy, M. A., Ward, K.L., Firouzabadian, L., Wang, Y., Dong, N., Qian, R., Zhang, Y. “Factors affecting the degradation rate of poly(lactide-co-glycolide) microspheres in vivo and in vitro.” *Biomaterials*. Volume 20, Issue 11: 1057-1062. June 1999.

Appendix

```
% BENG 221 Group Project
function project_final

global Co L k Do

Co = 30; %mg/ml
L = .005; %m
k = .044; %/day
Do = 4.32e-08; %m^2/day

tmesh = 0:50/100:50 ; %in day
xmesh = 0:L/100:L;


pdefuns = @pdefun;
pdefuns2 = @pdefun2;
ics = @ic;
bcs = @bc;

sol_pdepe = pdepe(0,pdefuns,ics,bcs,xmesh,tmesh);

figure(1)
surf(tmesh,xmesh,sol_pdepe');
title('PDEPE Solution')
xlabel('t[day]')
ylabel('x[m]')
zlabel('C(x,t)[mg/ml]')

%PDEPE for simple diffusivity constant model

sol_pdepe_2 = pdepe(0,pdefuns2,ics,bcs,xmesh,tmesh);
```

```
figure(2)
plot(tmesh,[sol_pdepe(:,51),sol_pdepe_2(:,51)])
title('Effects of diffusivity on diffusion process at x =
2.5um')
ylabel('C(x,t)[mg/mL]');
xlabel('t[day]');
legend('biodegradable polymer','non-biodegradable polymer');


% Analytical Solution for biodegradable polymer

% domain

nx = length(xmesh); % number of points in x dimension
nt = length(tmesh); % number of points in t dimension

u_xt = zeros(nt,nx);

for n = 1:42
    lam = n*pi/L;
    An = 2.*Co./(n*pi*(exp(-lam^2.*Do./k))).*(1-cos(n*pi));
    u_xt = u_xt + An.*sin(n*pi/L*xmesh)'*exp(-
lam.^2./k.*Do.*exp(k.*tmesh));
end

figure(3)
surf(xmesh,tmesh,u_xt')
title('Analytical solution with 42 terms')
xlabel('x[m]')
ylabel('t[day]')
zlabel('C(x,t)[mg/mL]')

%Analytical solution for simple diffusivity model

u_x2t = zeros(nt,nx);
```

```
for n = 1:42
    lam2 = n*pi/L;
    Bn = 2.*Co./(n*pi).*(1-cos(n*pi));
    u_x2t = u_x2t + Bn.*sin(n*pi/L*xmesh)'*exp(-
lam2.^2.*Do.*tmesh);
end

figure(4)
surf(xmesh,tmesh,u_x2t')
title('Analytical solution of constant diffusivity with 42
terms')
xlabel('x[m]')
ylabel('t[day]')
zlabel('C(x,t)[mg/mL]')

end

function u0 = ic(x)
% Initial conditions
global Co

u0 = Co;
end

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

pl = ul;
ql = 0;
pr = ur; % right boundary
qr = 0; %right flux
end

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

```
% PDE coefficients
global Do k

c = 1;
f = Do .* exp(k.*t) .* DuDx; % diffusion
s = 0;
end

function [c, f, s] = pdefun2(x, t, u, DuDx)
% PDE coefficients
global Do

c = 1;
f = Do .* DuDx; % diffusion
s = 0;
end
```