Insulin Diffusion from a Pancreatic Islet

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Introduction

Diabetes mellitus is classified as either type I (T1DM) or type II (T2DM) and affects nearly 26 million people in the United States [1]. The symptoms of T1DM usually develop over a short period of time and include polydipsia, polyuria, polyphagia, weight loss, blurred vision, and extreme fatigue. The symptoms of T2DM, albeit similar, develop more gradually and in some patients may not develop at all. Although the pathogenesis of T1DM differs from T2DM, patients of either type, if left untreated, will experience hyperglycemia, a result of the body's inability to process intake glucose, causing it to build up in the bloodstream. Patients suffering from prolonged hyperglycemia can develop diabetic ketoacidosis, a potentially fatal medical emergency if left untreated. In addition, prolonged hyperglycemia can also have detrimental effects on many organs of the body.

The pancreas is comprised of approximately 1 million clusters of α, β, γ, and pancreatic polypeptide (PP) islet cells. Each islet consists of approximately 1400 cells based on total β-cell mass [2], islet cluster numbers, and islet composition [3]. One of the principle functions of the pancreas is to secrete the anabolic hormone insulin. The main metabolic function of insulin is to increase the rate of glucose transport into cells.

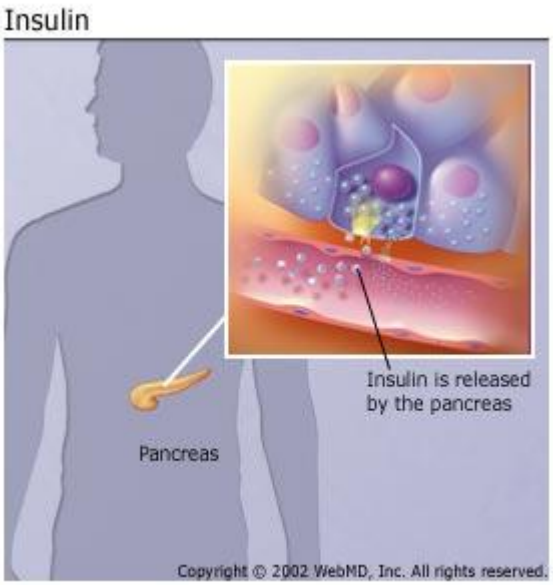

Figure 1: Schematic of insulin release to the blood stream.

The most common conventional therapy is exogenous insulin, which is difficult for patients to self-administer and does not mimic the body's natural pattern of insulin production in response to blood glucose levels; therefore, several tissue engineering (TE) strategies are being developed. Current TE strategies involve immunoisolating insulin-producing islet cells in an unmodified alginate that are implanted into the body. The encapsulated cells secrete insulin in a more biomimetic fashion, acting as a better glucose control system for diabetic patients. Since the synthetic capsules fail to vascularize, clusters of islets must be within 185 μm from a capillary in order for nutrients and oxygen to diffuse properly.

A single islet, encapsulated in alginate, secretes insulin in response to blood glucose fluctuations over the period of one day. In this problem we intend to model the diffusion of insulin through tissue from an islet cell to the bloodstream. A model of insulin diffusion from the islet through tissue will determine the concentration profile over 24 hours throughout the tissue. Results from this study will provide insight into whether or not this process is diffusion limited in order to understand limitations of encapsulating islet cells.

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Problem Setup

The islet and surrounding pancreatic tissue were modeled as concentric spheres, with literature values yielding a typical islet radius of 10μm, and surrounding tissue between vasculature radius of 50μm [2].

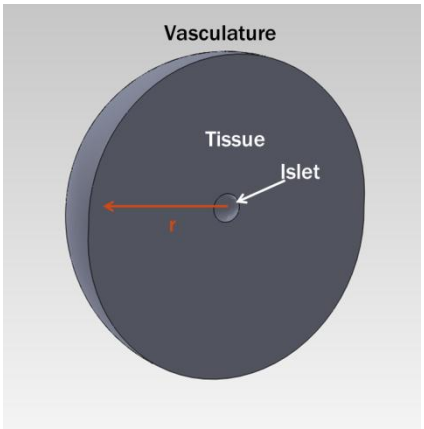

Figure 2: Model of islet (inner sphere) and surrounding tissue (outer sphere) with radius, r, labeled.

A model of insulin production and secretion responding to fluctuating glucose concentrations was then determined. We assumed that glucose concentration could be modeled as a sinusoid reaching a maximum after a meal and a minimum between meals. From average values for glucose concentration, we assumed that the maximum and minimum concentrations were 6 and 4 mM, respectively. Additionally, we assumed that meals occurred eight hours apart. Therefore, the following equation was used to model glucose fluctuations over 24 hours:

$$[G] = \sin\left(\frac{5t}{2\pi}\right) + 5\ mM \qquad (1)$$

This corresponded to the figure 3 over a 24 hour timespan.

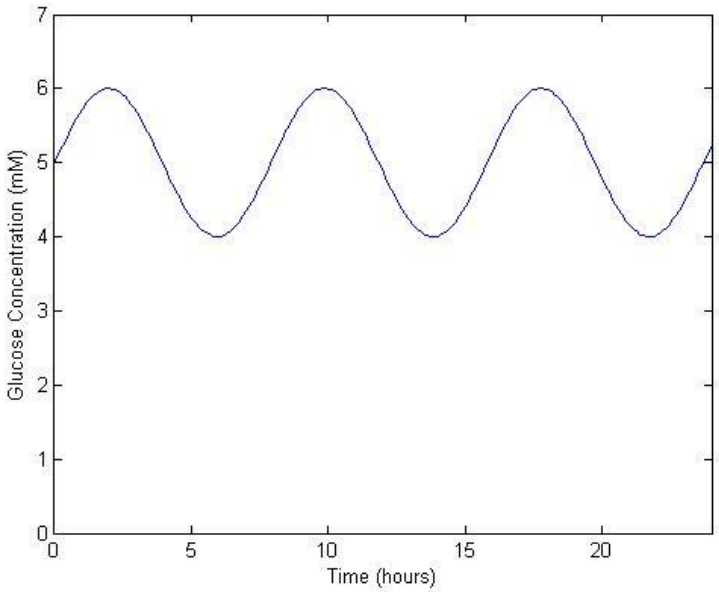

Figure 3: Glucose concentration fluctuations over the period of 24 hours

From the literature, we found that insulin production as a function of glucose concentration can be modeled using Michaelis-Menten kinetics [4]. We used the following equation to model insulin production in response to fluctuating glucose concentration. Values for I_{max}, K_m, and n were found from [4] and are listed in Table 1.

$$[I] = \frac{I_{\max}[G]^n}{[G]^n + K_m^n} \tag{2}$$

Table 1: Values used in Equation (2) adapted from [4].

I_{max}	$3x10^{-5}$ mol/m^3s
Km	7 mmol/L
n	2.5

In order to simplify the model for easier use, we manually fit the graph with a sinusoid of the same period used in modeling glucose concentration. A graph showing insulin production obtained using equation (2) is shown below (Fig. 4) along with the manual fit equation (Eqn. 3).

$$[I]_{fit} = 3\times10^{-6}\sin\left(\frac{5t}{2\pi}\right) + 9\times10^{-6}\ mM \tag{3}$$

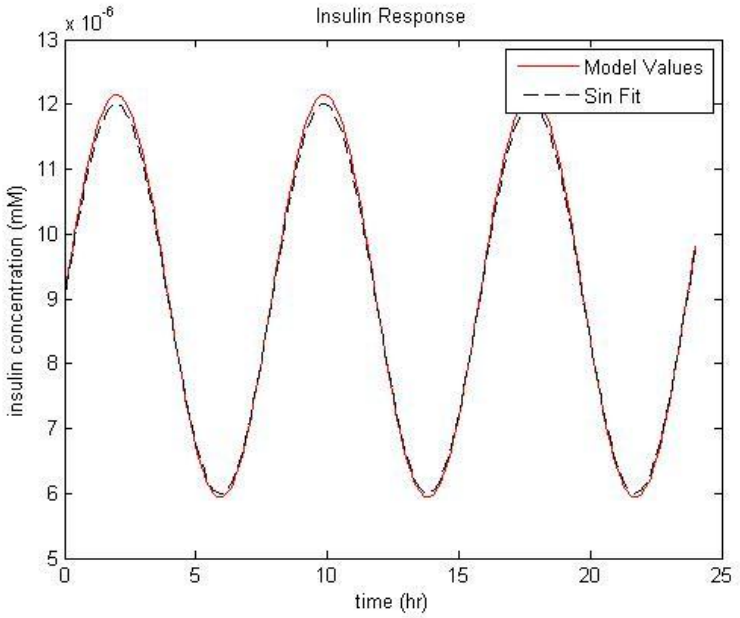

Figure 4: Insulin production from (a) Eq. 2 shown in red solid line and (b) our manual fit (Eq. 3) shown in dotted black line.

From the literature, it was found that the diffusion constant for insulin in pancreatic tissue is the following [4].

$$D = 1.8\times10^{5}\ \mu m^2 / hr \tag{4}$$

Diffusion Problem Setup

For setting up the diffusion problem, we started with the diffusion equation in spherical coordinates.

$$\frac{\partial I}{\partial t} = D\left(\frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2\frac{\partial I}{\partial r}\right) + \frac{1}{r^2\sin\varphi}\frac{\partial}{\partial \varphi}\left(\sin\varphi\frac{\partial I}{\partial \varphi}\right) + \frac{1}{r^2\sin^2\varphi}\frac{\partial^2 I}{\partial \theta^2}\right) + Q(r,\theta,\varphi,t) \tag{5}$$

Where I is the concentration of insulin, r is the radius of the sphere, θ is the polar angle, and φ is the azimuthal angle. Since we assumed there is symmetry around the polar and azimuthal angles, the diffusion equation reduced down to a 1-D radial spherical diffusion equation

$$\frac{\partial I}{\partial t} = D\frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2\frac{\partial I}{\partial r}\right) + Q(r,t) \tag{6}$$

Where the source term is

$$Q(r,t) = 3\times10^{-6}\sin\left(\frac{5t}{2\pi}\right) + 9\times10^{-6} \qquad \text{with } 0 \le r \le d \tag{7}$$

Where d is the radius of the islet source sphere. The mixed homogenous boundary conditions were

$$\frac{\partial I}{\partial r}(0,r) = 0$$
$$I(R,t) = 0 \tag{8,9}$$

Where R is the outer radius of the sphere. Homogenous initial conditions are given by

$$I(r,0) = 0 \tag{10}$$

Analytical Solution

Homogeneous Solution

To solve this nonhomogeneous diffusion problem, the homogenous solution was first solved for by separation of variables

$$I = f(r)\phi(t) \tag{11}$$

$$\frac{\frac{1}{D}\frac{\partial\phi}{\partial t}}{\phi} = \frac{\frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2\frac{\partial f}{\partial r}\right)}{f} = -\lambda \tag{12}$$

Where λ is a constant. Solving for the time-varying solution

$$\frac{\frac{1}{D}\frac{\partial\phi}{\partial t}}{\phi} = -\lambda \tag{13}$$

$$\frac{1}{\phi}\frac{\partial\phi}{\partial t} = -D\lambda \tag{14}$$

$$\int\frac{1}{\phi}\partial\phi = -\int D\lambda\partial t \tag{15}$$

$$\ln\phi = -D\lambda t + c \tag{16}$$

$$\phi = ce^{-D\lambda t} \tag{17}$$

Solving for the boundary value problem

$$\frac{\frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2\frac{\partial f}{\partial r}\right)}{f} = -\lambda \tag{18}$$

Rearranging the equation yields

$$\frac{\partial}{\partial r}\left(r^2\frac{\partial f}{\partial r}\right) + \lambda f r^2 = 0 \tag{19}$$

This equation is the general form of a radial spherical Bessel function given by the equation

$$\frac{\partial}{\partial r}\left(r^2\frac{\partial f}{\partial r}\right) + \left(\lambda r^2 - n(n+1)\right)f = 0 \tag{20}$$

Where is our case, $n=0$. For a radial spherical Bessel function, the value of the variable f is given by

$$f(r)=r^{-1/2}J_{n+1/2}\left(\sqrt{\lambda}r\right) \tag{21}$$

Which is our case of $n=0$ is

$$f(r)=r^{-1/2}J_{1/2}\left(\sqrt{\lambda}r\right) \tag{22}$$

Where J is a Bessel function of the first kind, and λ is the eigenvalue. Plugging in for our value boundary condition of $f\left(R,t\right)=0$,

$$f(R)=0=R^{-1/2}J_{1/2}\left(\sqrt{\lambda}R\right) \tag{23}$$

Which can be simplified to

$$J_{1/2}\left(\sqrt{\lambda}R\right)=0 \tag{24}$$

If we set the root of the Bessel function, $\sqrt{\lambda}R$, to z

$$J_{1/2}\left(z\right)=0 \tag{25}$$

Then our eigenvalue can be defined as

$$\lambda=\left(\frac{z}{R}\right)^2 \tag{26}$$

General Solution

Combining the time-varying and boundary value problem solutions, we formed the general homogenous solution

$$I_H\left(r,t\right)=\sum_{i=1}^{\infty}A_i\frac{J_{1/2}\left(\sqrt{\lambda_i}r\right)}{\sqrt{r}}e^{-D\lambda_i t} \tag{27}$$

Where A_i is a constant term. Solving for A_i using the orthogonality of spherical Bessel functions yields

$$\iiint_V A_i\left(\frac{J_{1/2}\left(\sqrt{\lambda_i}r\right)}{\sqrt{r}}\right)^2\sin\theta r^2 dr d\varphi d\theta=\iiint_V\frac{J_{1/2}\left(\sqrt{\lambda_i}r\right)}{\sqrt{r}}g(r)\sin\theta r^2 dr d\varphi d\theta \tag{28}$$

Since the diffusion problem is 1-D, the volume integrals was solved to single integrals

$$4\pi\int_0^R A_i\left(\frac{J_{1/2}\left(\sqrt{\lambda_i}r\right)}{\sqrt{r}}\right)^2 r^2dr = 4\pi\int_0^R \frac{J_{1/2}\left(\sqrt{\lambda_i}r\right)}{\sqrt{r}}g(r)r^2dr \tag{29}$$

$$A_i = \frac{\int_0^R \frac{J_{1/2}\left(\sqrt{\lambda_i}r\right)}{\sqrt{r}}g(r)r^2dr}{4\pi\int_0^R\left(\frac{J_{1/2}\left(\sqrt{\lambda_i}r\right)}{\sqrt{r}}\right)^2 r^2dr} \tag{30}$$

Where $g(r)$ is the negative of the source term. We set the bottom side of the rhs to the constant c_i

$$C_i = 4\pi\int_0^R\left(\frac{J_{1/2}\left(\sqrt{\lambda_i}r\right)}{\sqrt{r}}\right)^2 r^2dr \tag{31}$$

$$C_i = 4\pi\int_0^R J_{1/2}^2\left(\sqrt{\lambda_i}r\right)rdr \tag{32}$$

To solve for the spherical Bessel functions, we used the half-order Bessel identity:

$$x^{-1/2}J_{n+1/2}(x) = x^n\left(-\frac{1}{x}\frac{d}{dx}\right)^n\left(\frac{\sin x}{x}\right) \tag{33}$$

Which simplifies for $n=0$ to

$$J_{1/2}(x) = \frac{\sin x}{x^{1/2}} \tag{34}$$

Where $x=\sqrt{\lambda_i}r$, yielding

$$J_{1/2}(\sqrt{\lambda_i}r) = \frac{\sin\left(\sqrt{\lambda_i}r\right)}{\left(\sqrt{\lambda_i}r\right)^{1/2}} \tag{35}$$

Plugging in for the Bessel functions in the homogenous solution, eqn. (27)

$$I_H(r,t) = \sum_{i=1}^{\infty} A_i \frac{1}{r} \frac{\sin\left(\sqrt{\lambda_i} r\right)}{\lambda_i^{1/4}} e^{-D\lambda_i t} \tag{36}$$

With the constant c_i

$$c_i = 4\pi \int_0^R \frac{\sin^2\left(\sqrt{\lambda_i} r\right)}{\sqrt{\lambda_i} r} r dr \tag{37}$$

Green's Function

We can find Green's formula from the homogenous solution

$$G(r,t;r_o,t_o) = \sum_{i=1}^{\infty} \frac{1}{c_i} \frac{1}{r} \frac{1}{r_o} \frac{1}{\sqrt{\lambda_i}} \sin\left(\sqrt{\lambda_i} r\right) \sin\left(\sqrt{\lambda_i} r_o\right) e^{-D\lambda_i (t-t_o)} \tag{38}$$

Where c_i was found in the homogenous solution and substituted for the Bessel function identities

$$c_i = 4\pi \int_0^R \frac{\sin^2\left(\sqrt{\lambda_i} r\right)}{\sqrt{\lambda_i}} dr \tag{39}$$

Which simplifies to

$$c_i = \frac{4\pi}{\sqrt{\lambda_i}} \int_0^R \sin^2\left(\sqrt{\lambda_i} r\right) dr \tag{40}$$

We can then solve for c_i using the integral trig identity for $\sin^2(x)$

$$c_i = \frac{4\pi}{\sqrt{\lambda_i}} \left[\frac{r}{2} - \frac{\sin\left(2\sqrt{\lambda_i} r\right)}{4\sqrt{\lambda_i}} \right]_{r=0}^{R} \tag{41}$$

$$c_i = \frac{4\pi}{\sqrt{\lambda_i}} \left[\frac{R}{2} - \frac{\sin\left(2\sqrt{\lambda_i} R\right)}{4\sqrt{\lambda_i}} \right] \tag{42}$$

Green's Formula

We can then solve for the overall solution by using Green's formula. Since we have zero boundary conditions and zero initial conditions, only one term is non-zero, corresponding to the contribution of the source term.

$$I(r,t)=\int_0^t\int_0^b Q(r_o,t_o)G(r,r_o;t,t_o)4\pi {r_o}^2 dr_o dt_o \tag{43}$$

Plugging $Q(r_o,t_o)$ and $G(r,r_o;t,t_o)$ into Green's formula

$$I(r,t)=\int_0^t\int_0^b\left(3\times10^{-6}\sin\left(\frac{5t}{2\pi}\right)+9\times10^{-6}\right)\sum_{i=1}^{\infty}\frac{1}{c_i}\frac{1}{r}\frac{1}{r_o}\frac{1}{\sqrt{\lambda_i}}\sin\left(\sqrt{\lambda_i}r\right)\sin\left(\sqrt{\lambda_i}r_o\right)e^{-D\lambda_i(t-t_o)}4\pi {r_o}^2 dr_o dt_o \tag{44}$$

Plugging in c_i

$$I(r,t)=\int_0^t\int_0^b\left(3\times10^{-6}\sin\left(\frac{5t}{2\pi}\right)+9\times10^{-6}\right)\sum_{i=1}^{\infty}\frac{1}{\frac{4\pi}{\sqrt{\lambda_i}}\left[\frac{R}{2}-\frac{\sin\left(2\sqrt{\lambda_i}R\right)}{4\sqrt{\lambda_i}}\right]}\frac{1}{r}\frac{1}{r_o}\frac{1}{\sqrt{\lambda_i}}\sin\left(\sqrt{\lambda_i}r\right)\ldots$$

$$\times\sin\left(\sqrt{\lambda_i}r_o\right)e^{-D\lambda_i(t-t_o)}4\pi {r_o}^2 dr_o dt_o \tag{45}$$

Simplifying this down to

$$I(r,t)=\frac{\sin\left(\sqrt{\lambda_i}r\right)}{r\left[\frac{R}{2}-\frac{\sin\left(2\sqrt{\lambda_i}R\right)}{4\sqrt{\lambda_i}}\right]}\sum_{i=1}^{\infty}\int_0^t\int_0^b\left(3\times10^{-6}\sin\left(\frac{5t}{2\pi}\right)+9\times10^{-6}\right)\sin\left(\sqrt{\lambda_i}r_o\right)e^{-D\lambda_i(t-t_o)}r_o dr_o dt_o \tag{46}$$

By separating the integrals for the variables r_o and t_o

$$I(r,t)=\frac{\sin\left(\sqrt{\lambda_i}r\right)}{r\left[\frac{R}{2}-\frac{\sin\left(2\sqrt{\lambda_i}R\right)}{4\sqrt{\lambda_i}}\right]}\sum_{i=1}^{\infty}\int_0^t\left(3\times10^{-6}\sin\left(\frac{5t}{2\pi}\right)+9\times10^{-6}\right)e^{-D\lambda_i(t-t_o)}dt_o\int_0^b\sin\left(\sqrt{\lambda_i}r_o\right)r_o dr_o \tag{47}$$

Symbolically solving the integrals separately using Wolfram Alpha (Wolfram, Champaign, IL)

$$\int_0^t\left(3\times10^{-6}\sin\left(\frac{5t}{2\pi}\right)+9\times10^{-6}\right)e^{-D\lambda_i(t-t_o)}dt_o=\frac{6\pi\left(5e^{-D\lambda_i t}+2\pi D\lambda_i\sin\left(\frac{5t}{2\pi}\right)-5\cos\left(\frac{5t}{2\pi}\right)\right)}{4\times10^6\pi^2D^2\lambda_i^2+25}+\frac{9-9e^{-D\lambda_i t}}{D\lambda_i} \tag{48}$$

$$\int_0^b \sin\left(\sqrt{\lambda_i} r_o\right) r_o dr_o = \frac{\sin\left(b\sqrt{\lambda_i}\right) - b\sqrt{\lambda_i}\cos\left(b\sqrt{\lambda_i}\right)}{\lambda_i} \tag{49}$$

Plugging these solved integrals (48,49) into the general solution equation (47) yields the final solution

$$I(r,t) = \frac{\sin\left(\sqrt{\lambda_i} r\right)}{r\left[\frac{R}{2} - \frac{\sin\left(2\sqrt{\lambda_i} R\right)}{4\sqrt{\lambda_i}}\right]} \sum_{i=1}^{\infty} \left(\frac{6\pi\left(5e^{-D\lambda_i t} + 2\pi D\lambda_i \sin\left(\frac{5t}{2\pi}\right) - 5\cos\left(\frac{5t}{2\pi}\right)\right)}{4\times 10^6 \pi^2 D^2 \lambda_i^2 + 25} + \frac{9 - 9e^{-D\lambda_i t}}{D\lambda_i} \right) \ldots$$
$$\times \left(\frac{\sin\left(b\sqrt{\lambda_i}\right) - b\sqrt{\lambda_i}\cos\left(b\sqrt{\lambda_i}\right)}{\lambda_i} \right) \tag{50}$$

Analytical Results

The analytical solution was evaluated in MATLAB (Mathworks, Natick, MA) using the values presented in the introduction. The resulting insulin concentration surface plots are shown in Figure 5 and Figure 6. At the origin, the insulin concentration follows the expected sinusoidal generation term in the temporal dimension. Based on the steep slope in insulin concentration, it appears that insulin rapidly diffuses through the tissue, which avoids an accumulation of insulin at the source. Interestingly, the analytical concentration profile exhibits an oscillatory characteristic in the radial direction. We expect that these oscillations arise from our approximation of the Bessel functions.

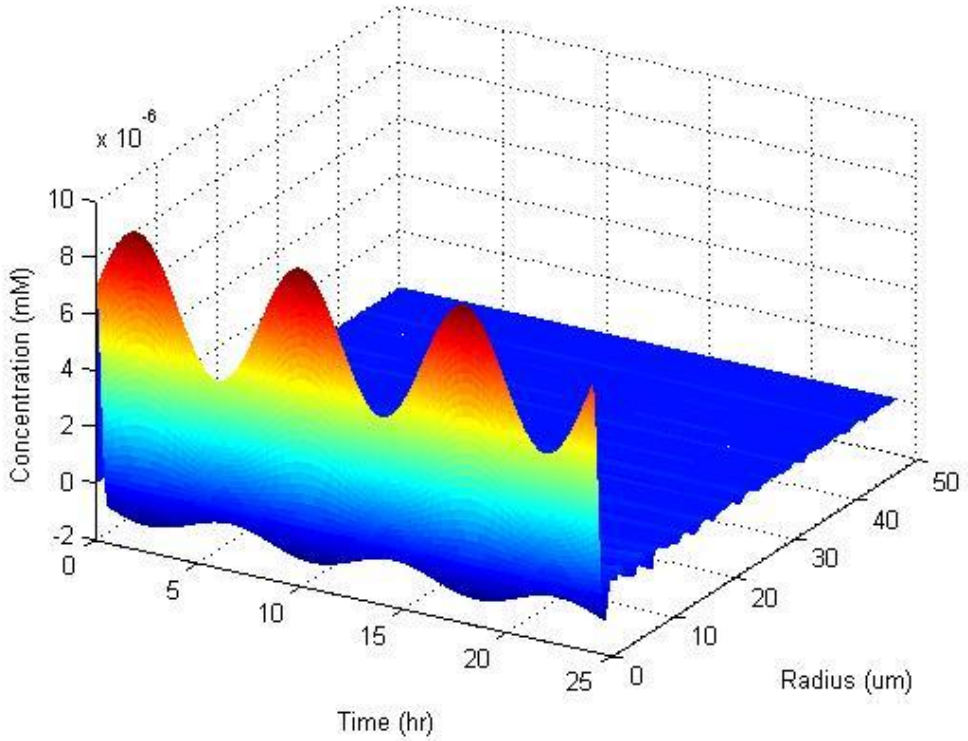

Figure 5: Analytical solution, view one.

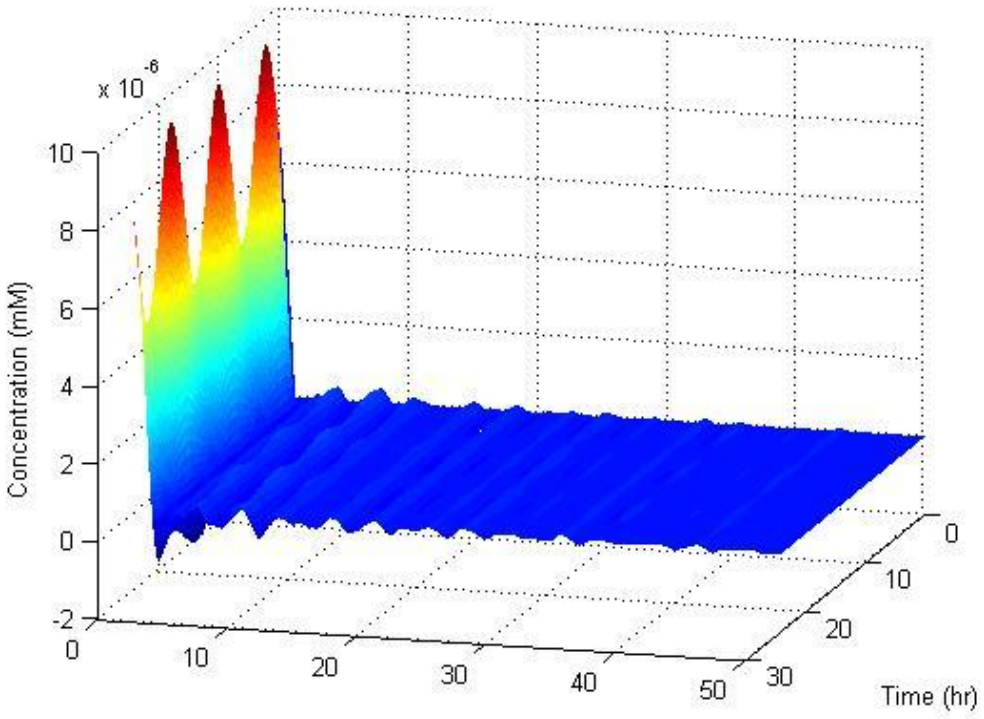

Figure 6: Analytical solution, view two.

Numerical Results

The insulin diffusion equation was solved using the pdepe function in MATLAB. The resulting concentration surface plot is shown in Figure 7. The plot shows a sinusoidal variation in the temporal dimension, as expected with the sinusoidal source term. In the 24 hour timespan plotted, the insulin concentration peaks 3 times, corresponding to the 3 daily meals incorporated into our model. In the radial dimension, the concentration decays from the peak value at the origin to the zero value at the outer radius. A rapid decay is seen in the insulin concentration outside of the source term radius.

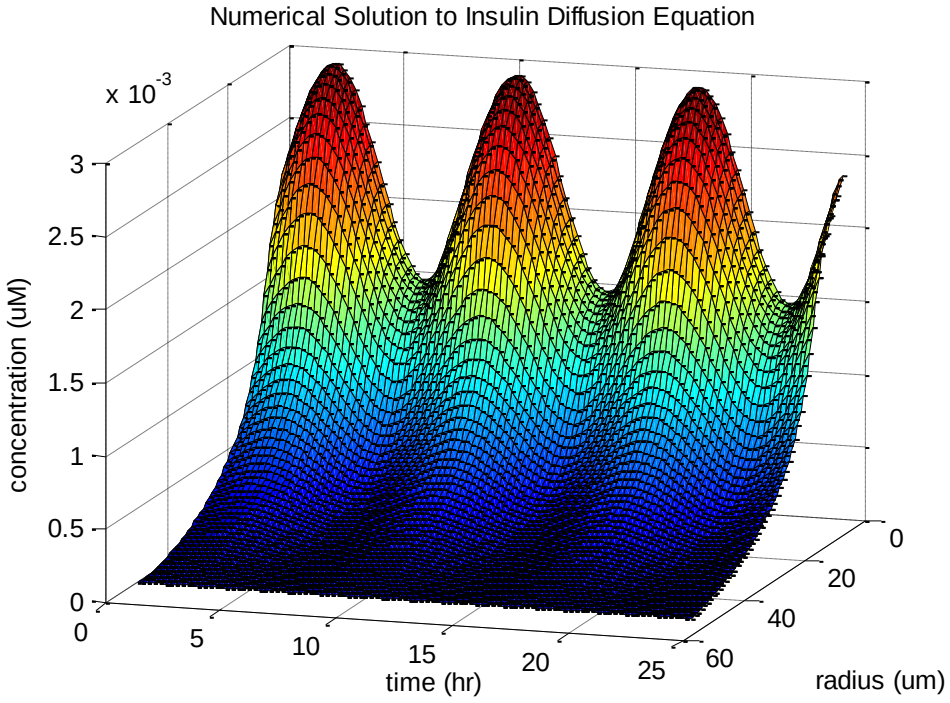

Figure 7: Numerical solution to insulin diffusion equation using pdepe.

Conclusions

The behavior of the numerical solution matches the behavior of the analytical solution in the temporal dimension, with a sinusoid of similar frequency and amplitudes. Both solutions exhibit a rapid decay in concentration in the radial dimension. These results suggest that insulin can effectively diffuse to the bloodstream at the diffusion coefficient found. Therefore, we conclude that insulin secretion is not diffusion limited. This is an important property of this system, as insulin should not accumulate in excess amounts in the tissues near the islet. Instead, it is rapidly distributed to other tissues in the body to regulate metabolic processes, through facilitating glucose uptake, for example. Extensive vascularization is an important feature in the pancreas that minimizes the distance between islets and vessels and enables this effective distribution of insulin and other hormones.

The values of local insulin concentration near the islet are also reasonable as evidenced by the results of a similar study [4]. Models of islet cells, such as this simplified model, can be valuable for understanding the details of islet cell function and how it is affected. Understanding how individual islets respond to changes in glucose levels and other important factors, such as oxygen, can provide a fundamental knowledge for extension to an organ or organism-wide level. By first understanding how islets respond in normal and diseased states, treatments that target diseases at the cellular level can be designed in a more quantitative fashion.

Future Work

The model presented here involves insulin secretion and diffusion in a normal, healthy individual. This model could be further developed to model insulin diffusion in individuals suffering from either Type I or Type II diabetes. In order to accomplish this, a more comprehensive model of glucose concentration that includes exogenous input and endogenous consumption must be developed. For the Type I case, insulin production would be stunted due to the autoimmune rejection of islet cells, causing a decrease in endogenous consumption and an overall accumulation of glucose. For the Type II case, endogenous consumption would decrease because cells become resistant to insulin. Consequently, islet cells would increase production of insulin in response to the increasing levels of glucose.

References

[1] National diabetes statistics, 2011.(Accessed November 15, 2011, at http://diabetes.niddk.nih.gov/dm/pubs/statistics)
[2] In't Veld P, Marichal M. Microscopic Anatomy of the human islet of Langerhans. Adv Exp Med Biol 2010;654:1-19.
[3] Kumar, V. et. al. Robbins basic pathology. 8 ed. 2007
[4] P. Buchwald. A local glucose-and oxygen concentration-based insulin secretion model for pancreatic islets. Theor Biol Med Model 2011;8:20.

Appendix A: Analytical Solution MATLAB Code

```
function BENG221Project_Analytical

R = 50;        %50 microns
D = 0.05E-9*3600*(1E6)^2;    %in um2/hr
b = 10;          % radius of the islet (for source term)
T_max = 24;         %in hours

t_vect = 0:(T_max/R/20):T_max;
x_vect = 0:0.05:R;
F = zeros(length(x_vect),length(t_vect));

%Bessel zeros
BesZero=besselzero(1/2,100,1);

for x=0:0.05:R
    X = round(x*20 + 1);

    for t=0:(T_max/R/20):T_max
        T = round(t*(R*20)/T_max + 1);

        for j=1:1:20    %number of terms for bessel series expansion

            sqbes = sqrt(BesZero(j));
            F(X,T) = F(X,T) - 1/(4*pi/sqbes*(R/2 - ...
sin(2*sqbes*R)/(4*sqbes)))/x/sqbes*sin(sqbes*x)*4*pi*((6*pi*(5*exp(-...
D*BesZero(j)*t) + 2*pi*D*BesZero(j)*sin(5*t/(2*pi)) - ...
5*cos(5*t/(2*pi))))/(4*pi^2*D^2*(BesZero(j))^2 + 25) + (9 - 9*exp(-...
D*BesZero(j)*t))/(D*BesZero(j)))*((sin(b*sqbes)) - ...
b*sqbes*cos(b*sqbes))/BesZero(j);
        end

    end
end

figure
surf(t_vect,x_vect,F,'EdgeColor','none')
xlabel('Time (hr)')
ylabel('Radius (um)')
zlabel('Concentration (mM)')

end
```

```
function x=besselzero(n,k,kind)

%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
%
% besselzero.m
%
% Find first k positive zeros of the Bessel function J(n,x) or Y(n,x)
% using Halley's method.
%
% Written by: Greg von Winckel - 01/25/05
% Contact: gregvw(at)chtm(dot)unm(dot)edu
%
%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%

k3=3*k;

x=zeros(k3,1);

for j=1:k3

    % Initial guess of zeros
    x0=1+sqrt(2)+(j-1)*pi+n+n^0.4;

    % Do Halley's method
    x(j)=findzero(n,x0,kind);

    if x(j)==inf
        error('Bad guess.');
    end

end

x=sort(x);
dx=[1;abs(diff(x))];
x=x(dx>1e-8);

x=x(1:k);

function x=findzero(n,x0,kind)

n1=n+1;     n2=n*n;

% Tolerance
tol=1e-12;

% Maximum number of times to iterate
MAXIT=100;

% Initial error
err=1;

iter=0;
```

```
while abs(err)>tol & iter<MAXIT

    switch kind
        case 1
            a=besselj(n,x0);
            b=besselj(n1,x0);
        case 2
            a=bessely(n,x0);
            b=bessely(n1,x0);
    end

    x02=x0*x0;

    err=2*a*x0*(n*a-b*x0)/(2*b*b*x02-a*b*x0*(4*n+1)+(n*n1+x02)*a*a);

    x=x0-err;
    x0=x;
    iter=iter+1;

end

if iter>MAXIT-1
    warning('Failed to converge to within tolerance. ',...
            'Try a different initial guess');
    x=inf;
end
```

Appendix B. Numerical Solution MATLAB Code

```
function BENG221Project_Numerical

% initialize variables
global C1 C2 R D T A b

D = 0.05E-9*3600*(1e6)^2; %in um2/hr
C1 = 9; % initial basal insulin concentration
A = 3; %amplitude of insulin oscillation

C2 = 0; % insulin concentration at blood vessel
R = 50; % outer radius of tissue (um)
b = 10; % radius of islet (um)
T = 24; %final time

dx = R/50; % step size in x dimension
dt = T/100;  % step size in t dimension
xmesh = 0:dx:R; % domain in x (m)
tmesh = 0:dt:T;  % domain in t (hr)

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

%Matlab pdepe
sol_pdepe = pdepe(2,@pdefun,@ic,@bc,xmesh,tmesh,odeset('Abstol',1e-12));

figure
surf(xmesh,tmesh,sol_pdepe)
title('Numerical Solution to Insulin Diffusion Equation');
xlabel('radius (um)');
ylabel('time (hr)');
zlabel('concentration (mM)');

function [c, f, s] = pdefun(x, t, u, DuDx)
% PDE coefficients functions
global C1 C2 R D T A b
c = 1;
f = D*DuDx; % diffusion

%finite volume source term
if x < b
s = (A*sin(2.5*(t/pi))+C1);
else
s = 0;
end
% ---------------------------------------------------------------

function u0 = ic(x)
% Initial conditions function
global C1 C2 R D T
u0 = 0;
% ---------------------------------------------------------------
```

```
function [pl, ql, pr, qr] = bc(xl, ul, xr, ur, t)
% Boundary conditions function
global C1 C2 R D T A
pl = 0; % inner boundary condition
ql = 1;
pr = ur-C2;
qr = 0;  %  flux outer boundary condition
```