Modeling the Diffusion of TGF-β1 from a Fibrin Scaffold through Alveolar Bone

Martin Barrio and Sindhu Raghunandan

10/28/2011

BENG221

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I. Background

Periodontitis is defined as infection and inflammation of the primary tissues surrounding one or more teeth [5]. While the initial stages involve the infection and inflammation of the coronal gingival tissue (or the tissue surrounding each tooth) as seen in Figure 1, more extreme cases are characterized by degradation of ligaments and bones that support teeth. The condition is perpetuated by the buildup of plaque in the coronal and apical gingival sulcus (which is the gap between the tooth and the surrounding tissue) leading to chronic and recurring infection and inflammation [6]. Once plaque reaches the interface between the gingival tissue and the alveolar bone, the bacterial cells begin to degrade the bone. A complication that can arise after this stage is that the gingival tissue cells infiltrate the gap in the alveolar bone and begin to inhibit bone regeneration ultimately leading to insufficient mechanical support for teeth.

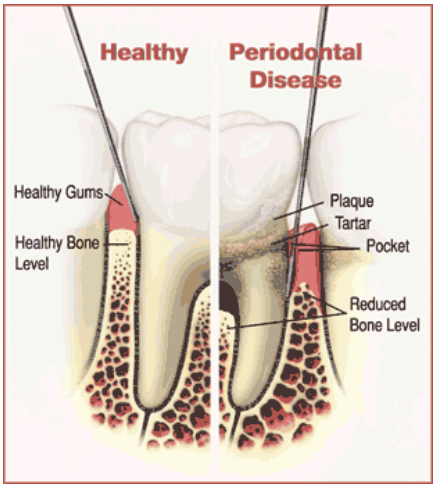

Figure 1. A visual juxtaposition of periodontal tissue and healthy tissue.

Conventional treatments can be broken up into the initial and surgical categories. If initial treatments do not facilitate regression of periodontitis then more substantial measures are taken to prevent alveolar bone and tooth loss. The surgeries that are most commonly applied to these cases are open-flap debridement, osseous surgery, and guided tissue regeneration and bone grafting [4]. The goal of these surgeries is to create a space for bone and ligaments to regenerate around the tooth after periodontal surgery. Without this barrier faster growing soft tissue, such as epithelium and gingival tissue, would fill in the space around the tooth. Generally, surgical treatment and post treatment maintenance prevents tooth loss for 85% of patients [4, 7].

One avenue for guided tissue regeneration is the development of synthetic polymer scaffolds infused with bone regenerating growth factors. The properties of both the scaffold and growth factors can be controlled in order to elute a certain concentration of the growth factor into the tissue intended for regeneration. Furthermore, the use of mathematical models can be used to examine any combination of available scaffolds and growth factors to generate the most efficient delivery of growth factors to the alveolar bone. The motivation for this study is to generate a model that will plot the diffusion of the growth factor into the bone over time with hypothetical boundary conditions and initial conditions. The accuracy with which the

model matches physiological circumstances will then be assessed and further improvements to the model will be proposed.

II. Design Concept

The goal of this project is to model the diffusion of transforming growth factor (TGF-β1, a cell proliferation associated growth factor) from a fibrin scaffold into the alveolar bone to regenerate degraded bone tissue due to periodontitis. The physiological system relevant to periodontitis is shown in the figures below. The image to the left shows the actual layering of the gingival tissue, alveolar bone, and mandibular canal. The simplified representation used for this project is shown to the right.

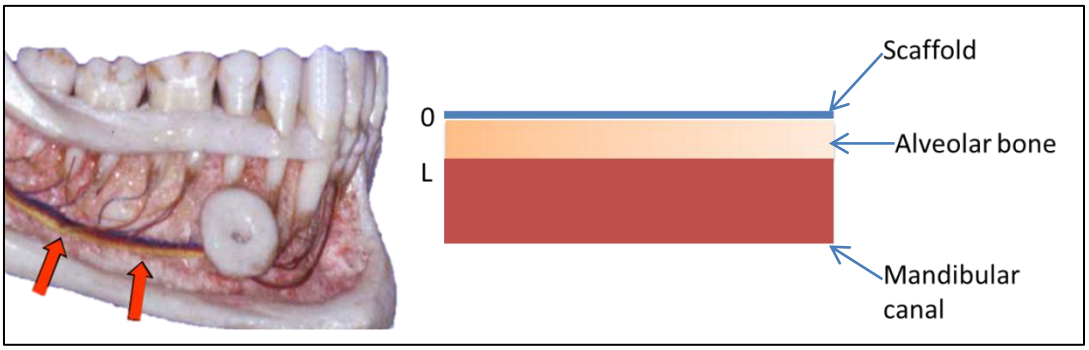

Figure2. The physiological system and the simplified model.

This study assumes that the progression of periodontitis is at a point where the gingival tissue has degraded and there is a small cavity in the alveolar bone. The scaffold employed will, therefore, be placed inside of the cavity against the surface of the bone to regenerate this bone before gingival tissue infiltration.
Before deriving an analytical or numerical solution, a set of assumptions were established to guide the solution.

- First, the initial concentration of the growth factor was chosen to be 2mM. Since the initial concentration is tailored to the degree of regeneration required, this value was somewhat arbitrarily chosen.
- Second, a study by Leddy et.al suggested that the diffusion of dextrans through various scaffolds is comparable to the diffusion of growth factors through those same scaffolds. So, by making the same assumption, the diffusivity of generic growth factors through a fibrin scaffold is approximately 115μm^2/s [3].
- Third, the thickness of the alveolar bone (the layer through which the growth factors are diffusing) is ~2.06mm [1] as indicated by another study.
- It was also assumed that no other factors in the matrix or the surrounding tissues affect the diffusion or uptake of TGF-β1. While this assumption significantly limits the physiological relevance of the model, this was a necessary simplification to isolate a model of diffusion of a specific growth factor through a specific scaffold.
- Fourth, looking at the scaffold and mandibular canal boundaries shown in figure 2, it was assumed that no growth factors can escape from the scaffold away from the bone (no flux boundary condition).
- Fifth, we assumed that the osteocytes that make up the alveolar bone will consume the growth factor at a constant rate 1.86E-5 M/s. [2]

- Sixth, we assumed that the application of the scaffold to the alveolar bone can be modeled as an impulse at t = 0.
- Finally, it was assumed that once the growth factors diffuse through the alveolar bone into the mandibular channel, the vessels present in that canal will instantly uptake the growth factors (zero boundary condition).

III. Analytical solution

Diffusion Equation	$\frac{du}{dt} = D\frac{d^2u}{dx^2} - Q$
Boundary and Initial Conditions	$\frac{du}{dx}(0,t) = 0$ $u(L,t) = 0$ $u(x,0) = C_0\delta(x)$ = g(x)

The most generic analytical solution for any system with any initial and boundary conditions can be written as follows.

$$u(x,t) = \int_0^L g(x_0)G(x,t;x_0,0)dx_0 - \int_0^L \int_0^t Q(x_{0,},t_0)G(x,t;x_0,t_0)dx_0\,dt_0 - \int_0^L D\frac{du}{dx}(0,t)G(x,t;0,t_0)dt_0 - \int_0^L Du(L,t)\frac{d}{dx_0}G(x,t;L,t_0)dt_0$$

However, based on the boundary and initial conditions as well as the nature of the source term, $Q(x_{0,},t_0)$, an appropriate Green's function can be chosen and the above statement can be simplified. Since this system involves a flux-value boundary condition, the Green's functions relevant to this problem are shown below:

$$G(x,t;x_0,t_0) = \sum_{n=odd}^{\infty}\frac{2}{L}\cos\left(\frac{n\pi x_0}{2L}\right)\cos\left(\frac{n\pi x}{2L}\right)e^{-D\left(\frac{n\pi}{2L}\right)^2(t-t_0)}$$

$$G(x,t;x_0,0) = \sum_{n=odd}^{\infty}\frac{2}{L}\cos\left(\frac{n\pi x_0}{2L}\right)\cos\left(\frac{n\pi x}{2L}\right)e^{-D\left(\frac{n\pi}{2L}\right)^2 t}$$

Since the boundary conditions are both zero, the last two integrals in the entire general solution can be eliminated and the general solution rewritten as follows:

$$u(x,t) = \int_0^L C_0\delta(x_0) \sum_{n=odd}^{\infty} \frac{2}{L}\cos\left(\frac{n\pi x_0}{2L}\right)\cos\left(\frac{n\pi x}{2L}\right) e^{-D\left(\frac{n\pi}{2L}\right)^2 t} dx_0$$
$$-\int_0^L \int_0^t Q \sum_{n=odd}^{\infty} \frac{2}{L}\cos\left(\frac{n\pi x_0}{2L}\right)\cos\left(\frac{n\pi x}{2L}\right) e^{-D\left(\frac{n\pi}{2L}\right)^2 (t-t_0)} dx_0\, dt_0$$

The solution to the first integral is shown below. Since we are taking the integral of the impulse function, the solution can be represented as the cosine function evaluated at zero.

$$\int_0^L C_0\delta(x_0) \sum_{n=odd}^{\infty} \frac{2}{L}\cos\left(\frac{n\pi x_0}{2L}\right)\cos\left(\frac{n\pi x}{2L}\right) e^{-D\left(\frac{n\pi}{2L}\right)^2 t} dx_0 = \boxed{\sum_{n=odd}^{\infty} \frac{2C_0}{L}\cos\left(\frac{n\pi x}{2L}\right) e^{-D\left(\frac{n\pi}{2L}\right)^2 t}}$$

The solution to the second double integral is shown below.

$$\int_0^L \int_0^t -Q \sum_{n=odd}^{\infty} \frac{2}{L}\cos\left(\frac{n\pi x_0}{2L}\right)\cos\left(\frac{n\pi x}{2L}\right) e^{-D\left(\frac{n\pi}{2L}\right)^2 (t-t_0)} dx_0\, dt_0$$

$$= -Q \sum_{n=odd}^{\infty} \frac{2}{L}\cos\left(\frac{n\pi x}{2L}\right) e^{-D\left(\frac{n\pi}{2L}\right)^2 t} \int_0^L \int_0^t \cos\left(\frac{n\pi x_0}{2L}\right) e^{D\left(\frac{n\pi}{2L}\right)^2 t_0} dx_0\, dt_0$$

Rewriting the above statement to exclude all the constant terms from the integral results in the following statement:

$$-Q \sum_{n=odd}^{\infty} \frac{2}{L}\cos\left(\frac{n\pi x}{2L}\right) e^{-D\left(\frac{n\pi}{2L}\right)^2 t} \int_0^L \int_0^t \cos\left(\frac{n\pi x_0}{2L}\right) e^{D\left(\frac{n\pi}{2L}\right)^2 t_0} dx_0\, dt_0$$
$$= -Q \sum_{n=odd}^{\infty} \frac{2}{L}\cos\left(\frac{n\pi x}{2L}\right) e^{-D\left(\frac{n\pi}{2L}\right)^2 t} \left[\frac{2L}{n\pi}\sin\left(\frac{n\pi x_0}{2L}\right)\right]_0^L \int_0^t e^{D\left(\frac{n\pi}{2L}\right)^2 t_0}\, dt_0$$

$$-Q \sum_{n=odd}^{\infty} \frac{2}{L}\cos\left(\frac{n\pi x}{2L}\right) e^{-D\left(\frac{n\pi}{2L}\right)^2 t} \frac{2L}{n\pi}\sin\left(\frac{n\pi}{2}\right) \int_0^t e^{D\left(\frac{n\pi}{2L}\right)^2 t_0}\, dt_0$$
$$= -Q \sum_{n=odd}^{\infty} \frac{2}{L}\cos\left(\frac{n\pi x}{2L}\right) e^{-D\left(\frac{n\pi}{2L}\right)^2 t} \frac{2L}{n\pi}\sin\left(\frac{n\pi}{2}\right) \left[\frac{4L^2}{n^2\pi^2} e^{D\left(\frac{n\pi}{2L}\right)^2 t_0}\right]_0^t$$

$$-Q \sum_{n=odd}^{\infty} \frac{2}{L}\cos\left(\frac{n\pi x}{2L}\right) e^{-D\left(\frac{n\pi}{2L}\right)^2 t} \frac{2L}{n\pi}\sin\left(\frac{n\pi}{2}\right) \left[\frac{4L^2}{n^2\pi^2} e^{D\left(\frac{n\pi}{2L}\right)^2 t_0}\right]_0^t$$

$$= -Q \sum_{n=odd}^{\infty} \frac{2}{L} \cos\left(\frac{n\pi x}{2L}\right) e^{-D\left(\frac{n\pi}{2L}\right)^2 t} \frac{2L}{n\pi} \sin\left(\frac{n\pi}{2}\right) \frac{4L^2}{n^2\pi^2} \left[e^{D\left(\frac{n\pi}{2L}\right)^2 t_0} - 1\right]$$

$$\sum_{n=odd}^{\infty} \frac{-16QL^2}{(n\pi)^2} \cos\left(\frac{n\pi x}{2L}\right) e^{-D\left(\frac{n\pi}{2L}\right)^2 t} \sin\left(\frac{n\pi}{2}\right) \frac{4L^2}{n^2\pi^2} \left[1 - e^{-D\left(\frac{n\pi}{2L}\right)^2 t}\right]$$

The sum of the solutions to the two integral terms yields the final solution:

$$u(x,t) = \sum_{n=odd}^{\infty} \frac{2C_0}{L} \cos\left(\frac{n\pi x}{2L}\right) e^{-D\left(\frac{n\pi}{2L}\right)^2 t} + \frac{-16QL^2}{(n\pi)^2} \cos\left(\frac{n\pi x}{2L}\right) e^{-D\left(\frac{n\pi}{2L}\right)^2 t} \sin\left(\frac{n\pi}{2}\right) \frac{4L^2}{n^2\pi^2} \left[1 - e^{-D\left(\frac{n\pi}{2L}\right)^2 t}\right]$$

IV. Results

Using MATLAB, the analytical solution was graphed. The results indicate an impulse at *x = 0*, and *t = 0*. As *t* and *x* increases, the growth factors diffuse through the alveolar bone as seen by the rapid decay of the impulse to zero with respect to position and time. Figure 3 is a plot of *u(0,t) vs. time* to represent how the diffusion decays at an exponential rate over time.

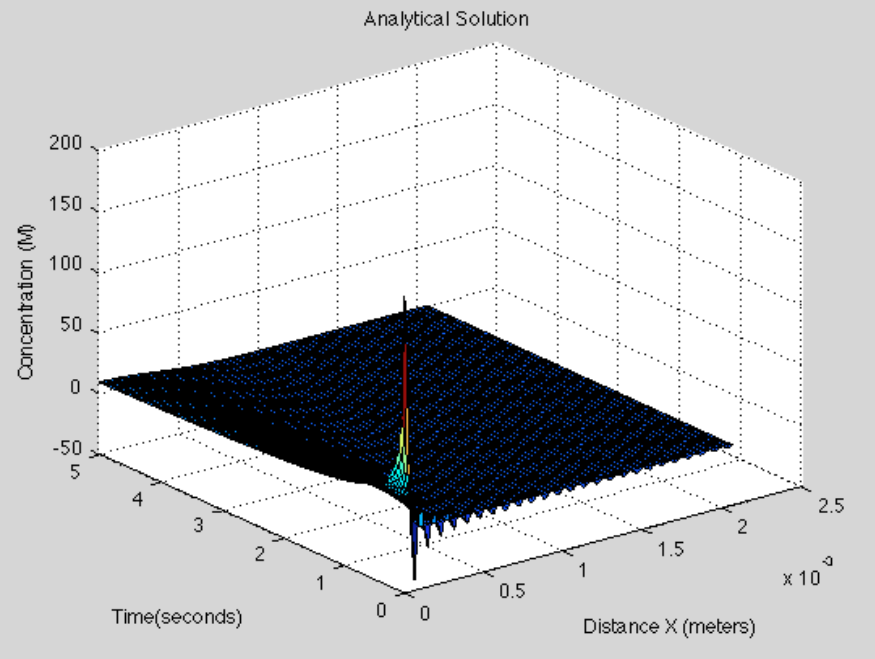

Figure 3a

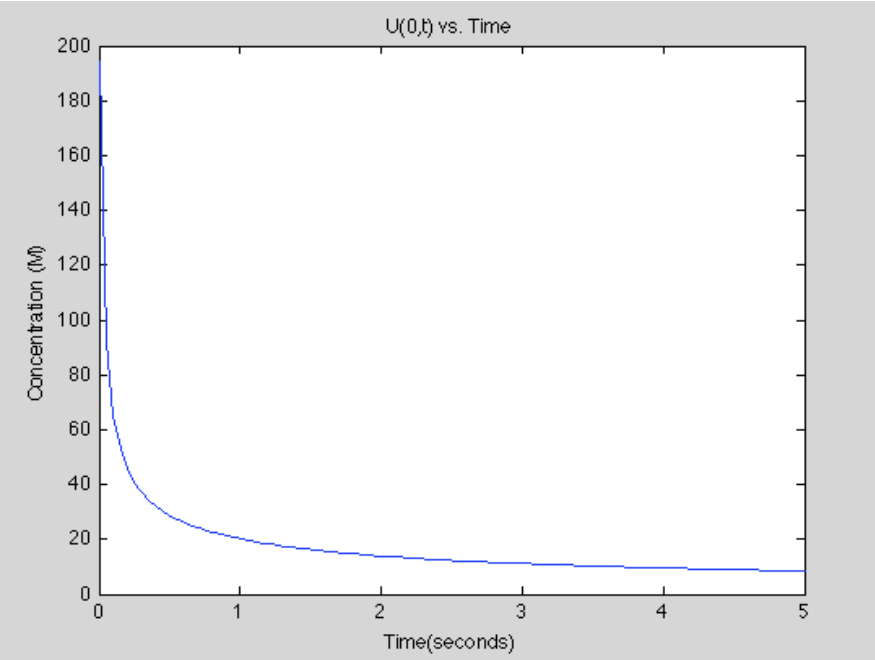

Figure 3b

Figure 3a: the analytical solution. 3b: a concentration vs. time graph to indicate the exponential decay of concentration over time.

Numerical Solution:

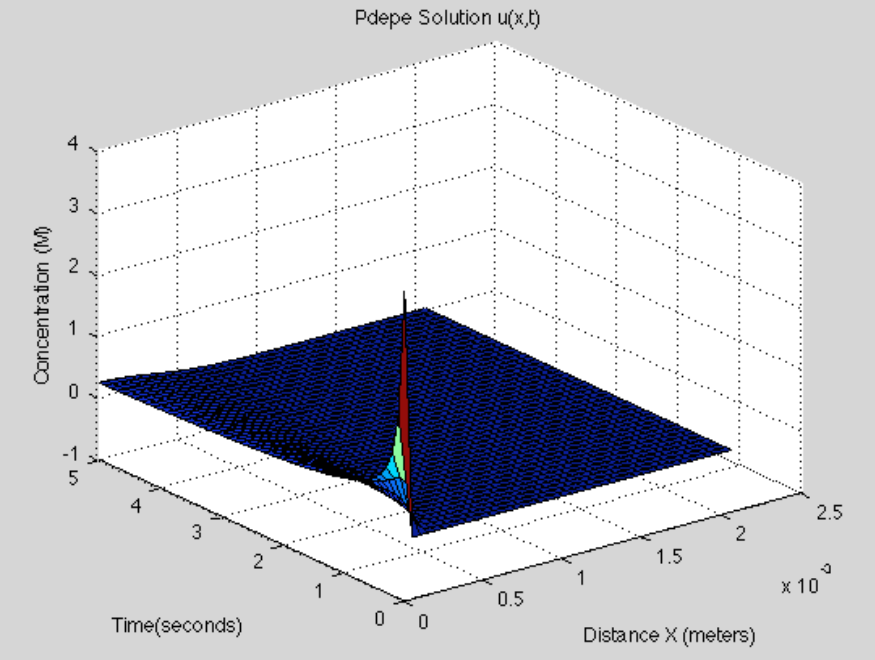

Figure 4a

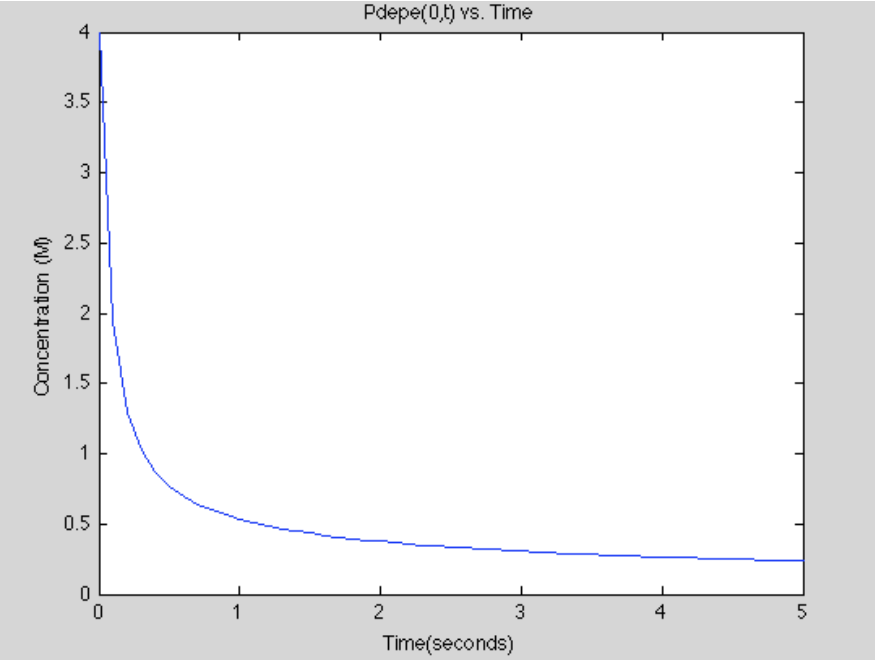

Figure 4b

Figure 4a and 4b are graphs of the numerical solution generated using MATLAB's PDEPE function. Figure 4b is a plot of pdepe(0,t) vs. time that indicates the exponential decay of growth factor concentration over time.

V. Discussion

The results primarily indicate that using the impulse function to model the chosen system is difficult and contributes to physiologically unreasonable diffusion profiles. The following analyses of the analytical and numerical solutions underline the factors that shape this conclusion.

Analytical Solution

As seen in the MATLAB scripts used to derive the analytical and numerical solutions (appendix A), the impulse function was used to generate an acute increase in growth factor concentration at t = 0 and x = 0. As seen in the analytical solutions (Figures 3a) the use of the impulse function results in unreasonable concentrations (on the order of ~150M) when x and t are close to 0. Also, because the system is using an impulse function, the decay (seen in figure 3b and 4b) from t = 0 to t = 1 is very drastic, a feature that is not physiologically realistic. In reality, the growth factors most likely diffuse much more gradually over time and space. Therefore, the impulse function may not be the most effective way to model a physiological "impulse" of concentration of the chosen growth factor.

For the analytical solution the growth factor concentration slowly approaches a negative value at steady state. This is also inaccurate because a negative concentration is physiologically impossible. This inconsistency between the physiological system and the chosen model can be attributed to the nature of the

source term. The mathematical interpretation of setting a constant consumption rate is that the cells will continue to consume the growth factors even when the concentration is zero.

Numerical Solution

The PDEPE solver seemed to better interpret the impulse function as indicated by the much more reasonable values of concentration near zero and throughout the decay. The concentration distribution over time and space were much more physiologically reasonable. However, this solution also indicated that the chosen PDE would converge to a negative value at steady state. Once again, this is unreasonable because cells cannot consume growth factors when they are not present.

Overall, while the analytical solution was confirmed by the numerical solution, this model is not recommended for modeling nonhomogenous flux-value PDEs. Methods of addressing the mentioned inconsistencies are discussed in the next section.

VI. Future Work

Even though the analytical methods are confirmed by numerical methods, the model does not accurately represent what occurs in a physiological environment. The key factor that may have shaped this inconsistency is a source term independent of the concentration of the growth factors present. In such a case, the cells would constantly "consume" growth factors even if the concentration reaches a value equal to zero (driving the analytical and numerical solution to a negative steady state value). Therefore to accurately model our system, we must use the new diffusion equation shown below.

$$\frac{du}{dt} = D\frac{d^2u}{dx^2} - Qu$$

If the source term is based on the present concentration, when the concentration of the growth factor approaches zero, the source term will approach zero as well. The new plots would show an impulse at *x = 0, t = 0,* but the concentration will decay exponentially to zero. Further investigations on an impulse of concentration at t =0 need to be made such that the analytical solution does not yield unreasonably high concentration values, and the both the analytical and numerical solutions do not decay so rapidly. Perhaps including other factors that would impede diffusion would also aid in constructing a more accurate model.

Once the model better represents physiological concentration profiles of TGF-β1 through the alveolar bone, it would be interesting to investigate what factors allow the bone regeneration to occur before tissue infiltration. This would motivate the design and construction of scaffolds that would somewhat slow or even reverse the most severe consequences of periodontitis.

VII. References

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VIII. APPENDIX A:

ANALYTICAL SOLUTION

```
% Constants

C0 = 0.002; %Molar
L = 0.00206; %meters
D = 1.15E-8; %meters per second
Q = 1.86E-5; %molar per second


% Time step

x = linspace(0,L);
t = linspace(0,5);

% Analytical Solution
n = 1:1:20;

F = zeros(length(x),length(t),length(n));
MF = zeros(length(x),length(t));
```

```
for j = 1:length(x)

    for k = 1:length(t)

        for n = 1:100

            A1 = 2*C0/L;

            A2 = ((n*pi)/(2*L));

            A3 = (Q*16*(L^2))/(D*(n*pi)^3);

            A4 = ((n*pi)/2);

            F(j,k,n) = A1*cos(A2*x(j))*exp(-D*(A2^2)*t(k)) -
A3*sin(A4)*cos(A2*x(j))*(1-exp(-D*(A2^2)*t(k)));

            MF(j,k) = MF(j,k) + F(j,k,n);
        end
    end
end


figure(1)
surf(x,t,MF')
figure(2)
plot(t,MF(1,:))
```

NUMERICAL SOLUTION

```
function Projectpdepe

% Constants

global C0 L D Q

C0 = 0.002; %Molar
L = 0.00206; %meters
D = 1.15E-8; %meters per second
Q = 1.86E-5; %molar per second


% Time step

x = 0:0.00005:L;
t = 0:0.1:5;

m = 0;

sol = pdepe(m,@pdex1pde,@pdex1ic,@pdex1bc,x,t);
```

```
up = sol(:,1,1);

% A surface plot is often a good way to study a solution.
figure(1)
plot(t,up)
figure(2)
surf(x,t,sol)
title('Pdepe Solution u(x,t)')
ylabel('Time (s)')
xlabel('Distance (m)')
zlabel('Concentration (M)')

% --------------------------------------------------------------
function [c,f,s] = pdex1pde(x,t,u,DuDx)

D = 1.15E-8;
Q = 1.86E-5; %molar per second

c = 1;
f = DuDx*D;
s = -Q;
% --------------------------------------------------------------
function u0 = pdex1ic(x)

% Constants
global C0 L D Q

C0 = 0.002; %Molar
L = 0.00206; %meters
D = 1.15E-8; %meters per second
Q = 1.86E-5; %molar per second

y = 0;
if x < 0
    y = 0;
end

if x == 0;
    y = 2*C0;
end

if x > 0
    y = 0;
end

u0 = y;
% --------------------------------------------------------------
function [pl,ql,pr,qr] = pdex1bc(xl,ul,xr,ur,t)

pl = 0;
ql = ul;
pr = ur;
qr = 0;
```