

Diffusion of dexamethasone from a PLGA-wrapped suture

By Sandeep Adem, Chiyuan Cheng, and Norman Luong
BENG 221 Fall 2016

Table of Contents

Introduction
.....
2

Mathematical Models
.....3

Analytical Solution Approximation
 Model I
.....6
 Model II
.....7

PDEPE solver Approximation
 Model I
.....7
 Model II
.....8

Results
.....8

Future Models
.....13

Discussion
.....14

References
.....15

Appendix (MATLAB Code)
 A: Analytical Solution Approximation
.....16

B: PDEPE Solution Model I	
.....	17
C: PDEPE Solution Model II	
.....	20

Introduction:

Inflammation is a natural defense mechanism in our body to protect itself after trauma. Although it is a necessary signaling process for the body, it interferes with healing. This is especially apparent during surgery when inflammation at an incision or wound site is prevalent and must be controlled for proper healing in patients. Anti-inflammatory drug delivery is a crucial to help alleviate this problem. This paper aims to explore the diffusion of drug from a coated-suture drug delivery system. This is widely applicable for medical procedures that require localized drug delivery to internal wound sites or surgical incisions [3].

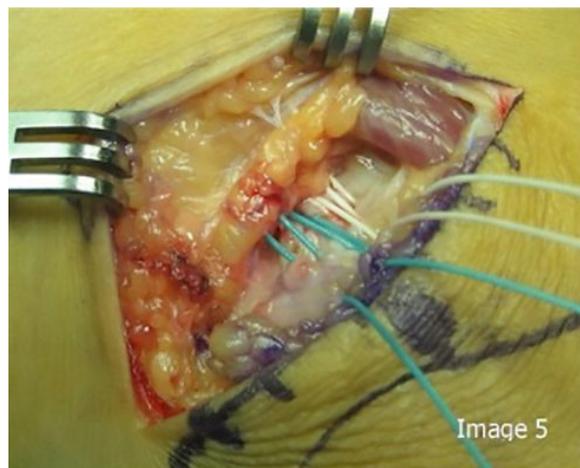


Figure 1. Internal sutures are used in surgery to stabilize and close ankle incision [1]

For our model, the drug of interest is the glucocorticoid steroid drug dexamethasone. It is one of the most well known anti-inflammatory drugs (WHO list of essential medicine) [9]. It is a strong immunosuppressant and works by blocking inflammatory mediators that induce enzymes involved in pain [10]. This drug is very versatile and can be taken orally, subcutaneously, or intravenously. This means it can be delivered directly into the wound site for immediate anti-inflammatory effects [10].

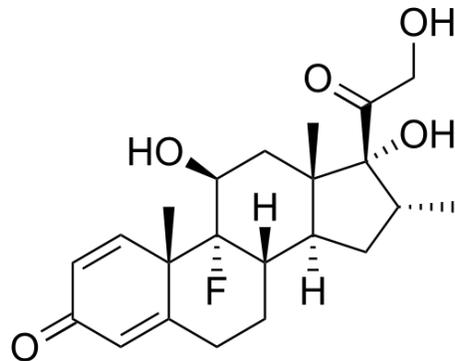


Figure 2. Dexamethasone Molecular Structure [2]

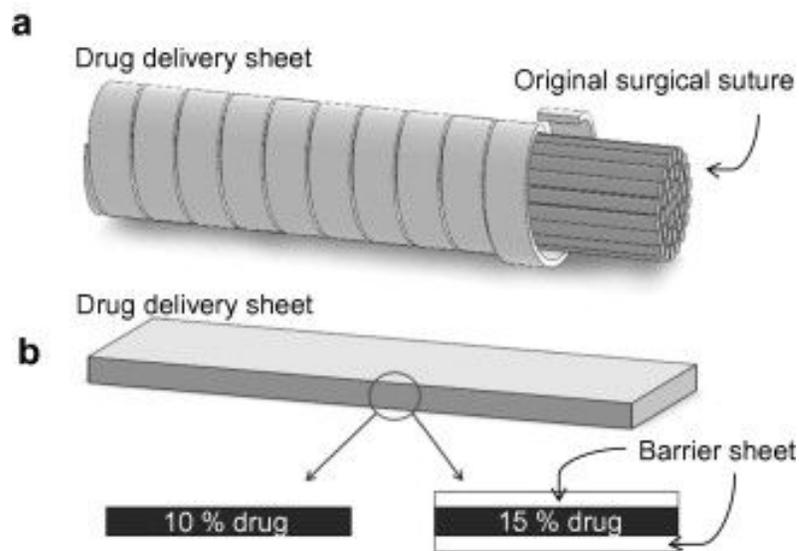


Figure 3. Suture Drug Delivery System [3]

Sutures that are coated with drugs can solve the problem of controlling inflammation at wound or incision sites. These sutures are loaded with drugs by wrapping a drug-delivery sheet made of biocompatible polymer called poly lactic-co-glycolic acid (PLGA) which is then doped with a drug of interest [3]. PLGA breaks down by hydrolysis of its ester linkages once exposed to the body's interstitial fluid. During a surgical operation,

this means the PLGA+drug composite sheet breaks down in the tissue where the suture is being placed, allowing for the drug to then diffuse and interact with the affected target tissue. We will model diffusion of dexamethasone from the PLGA sheet to the surrounding tissue. From this, we can then predict the area of tissue that will receive adequate concentration of dexamethasone and also predict the drug lifetime for a given dosage.

Mathematical Models:

We developed two models to simulate drug diffusion, in which we make some common assumptions. We assume that the suture is sufficiently deep within surface and the tissue surrounding it is homogeneous. In this case, our model is independent with θ . Another assumption we make is that the suture’s length is much longer than suture’s radius. As a result, our model is independent of the z direction as well. By making these assumptions, we can simplify our model as one-dimensional cylindrical diffusion:

$$\frac{\partial u}{\partial t} = \frac{D}{r} \frac{\partial}{\partial r} (r \frac{\partial u}{\partial r})$$

In our model, the suture’s radius is denoted as a , and the outer radius of PLGA is denoted as b . The illustration is shown in Fig. 4.

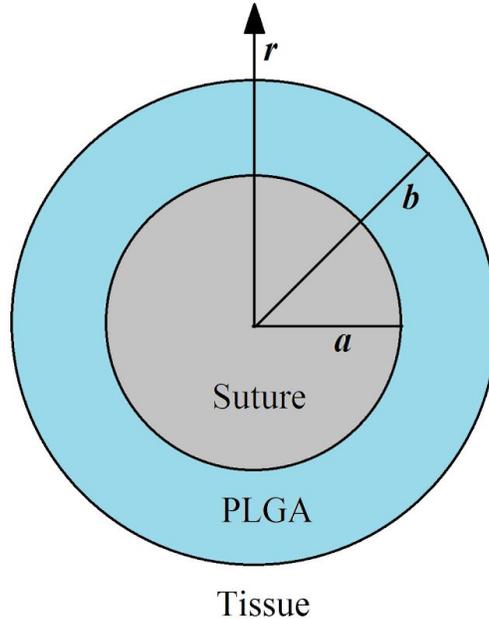


Figure 4. Cross-section of suture

We assume that the suture is impermeable so the boundary condition at a is zero flux condition. Initially, the drug is localized within the PLGA layer. Another boundary condition we set is zero value at infinity because the depth of tissue is much longer than the suture's radius.

In Model I, we assume that PLGA degradation is fast in comparison with the diffusion of DEX in PLGA. As a result, we set our initial condition as $u(r, 0) = C_0$ for r from a to b , where C_0 is the given drug concentration. We then have the following boundary condition and initial condition:

$$\begin{aligned}\frac{\partial u(a,t)}{\partial r} &= 0 \\ u(\infty, t) &= 0 \\ u(r, 0) &= C_0 \text{ for } r \text{ from } a \text{ to } b\end{aligned}$$

In this model, the PLGA degrades quickly, so we can assume that the diffusivity of DEX in the $r:(a, \infty)$ space is the diffusivity in tissue. The diffusivity we use here is 4.11×10^{-5} mm²/s, which is based on a rat study.[4] We set $a = 0.1$ mm as our suture radius and a PLGA sheet thickness of $b - a = 0.04$ mm, based on typical dimensions used.[3] We use $C_0 = 0.33$ M as our initial drug concentration, which is based on the loading capacity of DEX in PLGA.[5][6]

In Model II, we let our drug release rate be limited by PLGA hydrolysis. We do this by letting drug release occur over a course of $T = 30$ days, which is based on the time it takes for complete degradation-limited drug release from a 50:50 lactic acid-glycolic acid polymer [8]. Although drug release from PLGA follows a sigmoidal curve (Fig. 5), we initially wanted to approximate this with a constant release rate boundary condition. A more accurate model is discussed in Future Models. A finite amount of DEX is released over a fixed duration based on the amount that can be loaded onto PLGA, C_0 , the lifetime of the PLGA layer, T , the cross-sectional area of the PLGA sheet, and the circumference of the release boundary. This release ends when $t > T$ due to complete release of the drug, and can be represented by the piecewise flux boundary condition at $r = b$. Our resulting boundary and initial conditions are:

$$\begin{aligned}-D \frac{\partial u(b,t)}{\partial r} &= \frac{C_0(b^2 - a^2)}{2bT}; \quad t < T \\ -D \frac{\partial u(b,t)}{\partial r} &= 0; \quad t \geq T \\ u(\infty, t) &= 0 \\ u(r, 0) &= 0\end{aligned}$$

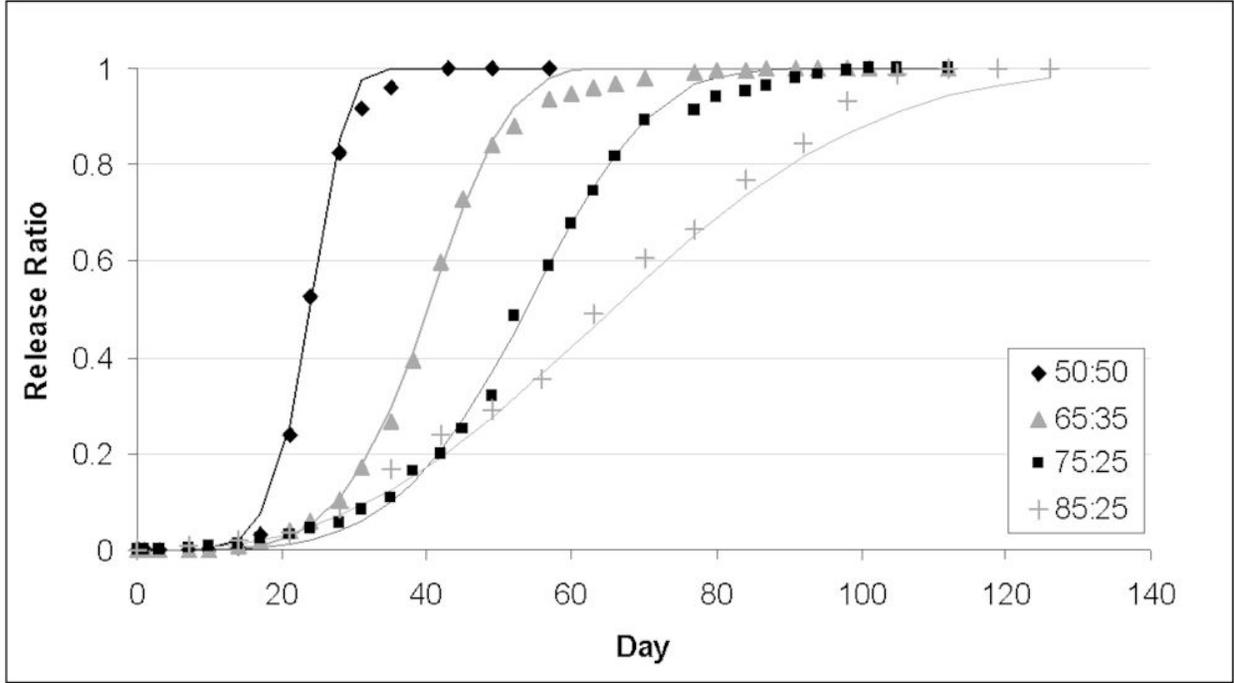


Figure 5. Drug release ratios for various PLGA compositions (lactic acid:glycolic acid). [8]

Analytical solution approximation (Model I):

We start with the Green's function for an infinite body with a hole in radial coordinates [7]:

$$G(r, t; r_0, t_0) = \frac{1}{2\pi a^2} \int_0^\infty e^{-\frac{\beta^2 D(t-t_0)}{a^2}} \frac{\beta R(r)R(r_0)}{J_1(\beta)^2 + Y_1(\beta)^2} d\beta$$

where $R(r) = J_0\left(\frac{\beta r}{a}\right)Y_1(\beta) - Y_0\left(\frac{\beta r}{a}\right)J_1(\beta)$

Since we have a zero-flux boundary condition and no generation term, the only contribution to the solution comes from the IC term:

$$u(r, t) = \iint_{a, 0}^{\infty, 2\pi} u_0(r_0, \theta_0) \cdot G(r, \theta, t; r_0, \theta_0, 0) \cdot r_0 dr_0 d\theta_0$$

We are working with a 1-D Green's function, which is independent of θ_0 . This allows the integral over $d\theta_0$ to be factored out. The initial condition u_0 is zero everywhere except $r_0=a$ to b , where it is C_0 . The integral limits for dr_0 become a to b :

$$u(r, t) = \int_0^{2\pi} d\theta_0 \int_a^b C_0 r_0 \cdot G(r, t; r_0, 0) dr_0$$

After pulling out C_0 , plugging in our Green's function, and evaluating the integral over $d\theta_0$, we obtain the following equation:

$$u(r, t) = \frac{C_0}{a^2} \int_0^\infty \int_a^b r_0 e^{-\frac{\beta^2 D(r-t_0)}{a^2}} \frac{\beta R(r) R(r_0)}{J_1(\beta)^2 + Y_1(\beta)^2} dr_0 d\beta$$

With our current knowledge of Bessel function integration, we were not able to evaluate this integral further and had to resort to numerical approximation. We decided to use the trapezoidal integration method since it provides decent accuracy and is not as computationally demanding as higher order methods such as Simpson's or Boole's rules.

First integration along β :

$$u(r, t) =$$

$$\frac{C_0 \Delta\beta}{a^2 2} \sum_{j=1}^n \int_a^b r_0 e^{-\frac{(\beta_j^2 + \beta_{j+1}^2) D(r-t_0)}{a^2}} \left(\frac{\beta_j R(r, \beta_j) R(r_0, \beta_j)}{J_1(\beta_j)^2 + Y_1(\beta_j)^2} + \frac{\beta_{j+1} R(r, \beta_{j+1}) R(r_0, \beta_{j+1})}{J_1(\beta_{j+1})^2 + Y_1(\beta_{j+1})^2} \right) dr_0$$

Second integration along r_0 :

$$u(r, t) =$$

$$\frac{C_0 \Delta\beta}{a^2 2} \frac{\Delta r_0}{2} \sum_{j=1}^n \sum_{i=1}^k (r_{0,i} + r_{0,i+1}) e^{-\frac{(\beta_j^2 + \beta_{j+1}^2) D(r-t_0)}{a^2}} \left(\frac{\beta_j R(r, \beta_j) R(r_{0,i}, \beta_j)}{J_1(\beta_j)^2 + Y_1(\beta_j)^2} + \frac{\beta_{j+1} R(r, \beta_{j+1}) R(r_{0,i}, \beta_{j+1})}{J_1(\beta_{j+1})^2 + Y_1(\beta_{j+1})^2} + \frac{\beta_j R(r, \beta_j) R(r_{0,i+1}, \beta_j)}{J_1(\beta_j)^2 + Y_1(\beta_j)^2} + \frac{\beta_{j+1} R(r, \beta_{j+1}) R(r_{0,i+1}, \beta_{j+1})}{J_1(\beta_{j+1})^2 + Y_1(\beta_{j+1})^2} \right)$$

Note that the end index of the sum along discrete points β_j is n rather than infinity. This is another approximation we make in order to make the solution computable. Despite this approximation, we can see that this will still be computationally demanding since each point computed in the (r, t) space requires its own double summation in the (r_0, β) space. The Matlab code used to do this computation can be found in Appendix A.

Analytical solution (Model II):

In Model II, the only non-zero term is constant flux boundary condition at $r = b$:

$$u(r, t) = \iint_{0,0}^{t, 2\pi} D \frac{\partial}{\partial t_0} u(b, t_0) G(r, \theta, t; b, \theta_0, t_0) \cdot b dt_0 d\theta_0$$

We can substitute our boundary condition in. Since this model is also independent of θ_0 . The integral over $d\theta_0$ can be factored out as well:

$$u(r, t) = \frac{DC_0}{2T} (b^2 - a^2) \int_0^{2\pi} d\theta_0 \int_0^t G(r, t; b, t_0) dt_0$$

$$u(r, t) = \frac{DC_0}{2T} (b - a) (2\pi) \int_0^t G(r, t; b, t_0) dt_0$$

After plugging in the same Green's function as for Model I, we obtain the equations shown below. Because there will be no drug release after time greater than PLGA livetime, the constant flux boundary condition will become 0. Instead, we will have a new diffusion function with initial condition as the concentration at $t = T$:

$$u(r, t) = \frac{DC_0(b-a)}{2T} \frac{1}{a^2} \int_0^{\infty} \int_0^{\infty} e^{-\frac{\beta^2 D(t-t_0)}{a^2}} \frac{\beta R(r, \beta) R(b, \beta)}{J_1(\beta)^2 + Y_1(\beta)^2} d\beta dt_0; \quad t < T$$

$$u(r, t) = \iint_{b,0}^{\infty, 2\pi} u_b(r_0, T) \cdot \frac{1}{2\pi a^2} \int_0^{\infty} e^{-\frac{\beta^2 D(t-T)}{a^2}} \frac{\beta R(r) R(r_0)}{J_1(\beta)^2 + Y_1(\beta)^2} d\beta \cdot r_0 dr_0 d\theta_0; \quad t \geq T$$

$$\text{where } u_b(r_0, T) = \frac{DC_0(b-a)}{2T} \frac{1}{a^2} \int_0^{\infty} \int_0^{\infty} e^{-\frac{\beta^2 D(T-t_0)}{a^2}} \frac{\beta R(r, \beta) R(b, \beta)}{J_1(\beta)^2 + Y_1(\beta)^2} d\beta dt_0;$$

Similar to Model I, these equations can be numerically solved in Matlab. However, we chose to use a PDEPE based solver due to its shorter computational time and simpler implementation.

PDE solver approximation (Model I):

The PDE solver we are using is the pdepe function from MATLAB. Since the pdepe function cannot have an infinity boundary condition, we reset our boundary condition at $u(10, t) = 0$. This is a reasonable boundary condition since 10 mm is relatively large compared with 0.04 mm, the thickness of the drugged PLGA layer. The MATLAB code used can be found in Appendix B.

PDE solver approximation (Model II):

The simulation time for model II is 90 days due to the slow degradation rate of PLGA. We expand our right boundary condition to $u(100, t) = 0$ to approximate a semi-infinite system. The MATLAB code used can be found in Appendix C.

Results:

Fig. 6, Fig. 7, and Fig. 8 show the results of analytical solution approximation and PDE solver approximations, respectively. We can see that they only have a slight difference, which may be due to the trapezoidal integration parameters used when approximating the analytical solution. At $t = 600$ seconds, the concentration in the pdepe solution at 0.1 mm is a little higher than the analytical solution. This is because pdepe's boundary condition cannot be at infinity, resulting in less space for the drug to diffuse over.

For Model II, the drug concentration increases when time is smaller than 30 days due to the constant flux condition. After 30 days, the drug is depleted and the concentration near the suture begins to decrease. The reason why the diffusion distance is much greater than model I is because the drug flux comes into tissue through left boundary condition over an extended time, which gives the drug more time to diffuse.

Fig. 6 and Fig. 7 only show r in range 0 mm to 1 mm which the area we are interested in. For Fig. 8, the range is from 0 mm to 60 mm.

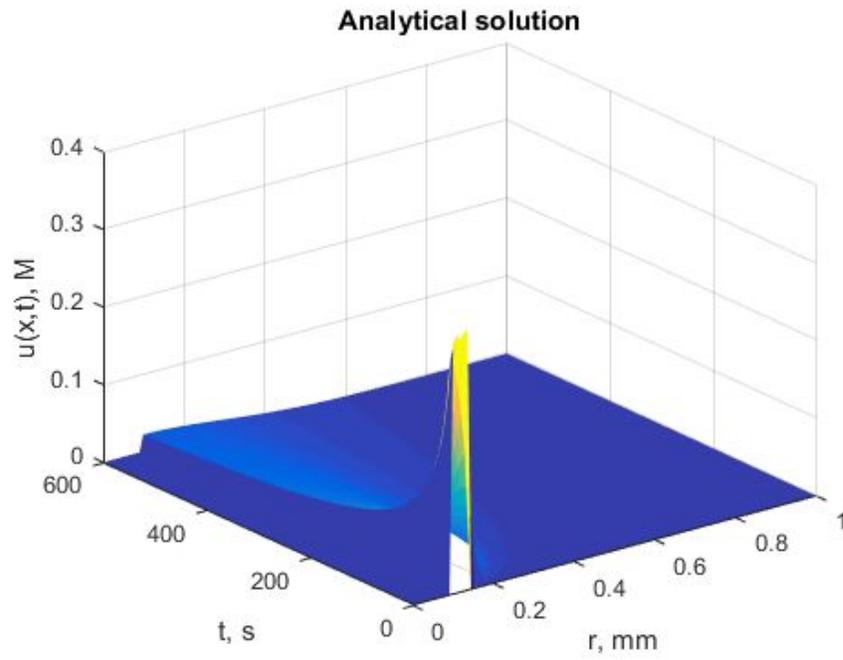


Figure 6. Analytical solution approximation

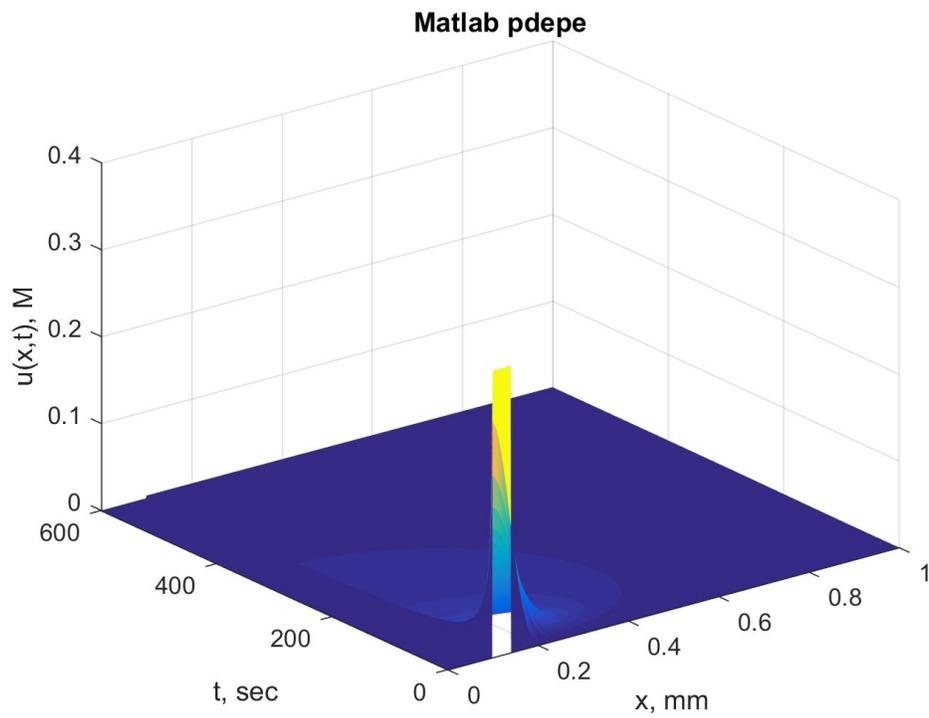


Figure 7. PDE solver approximation (Model I)

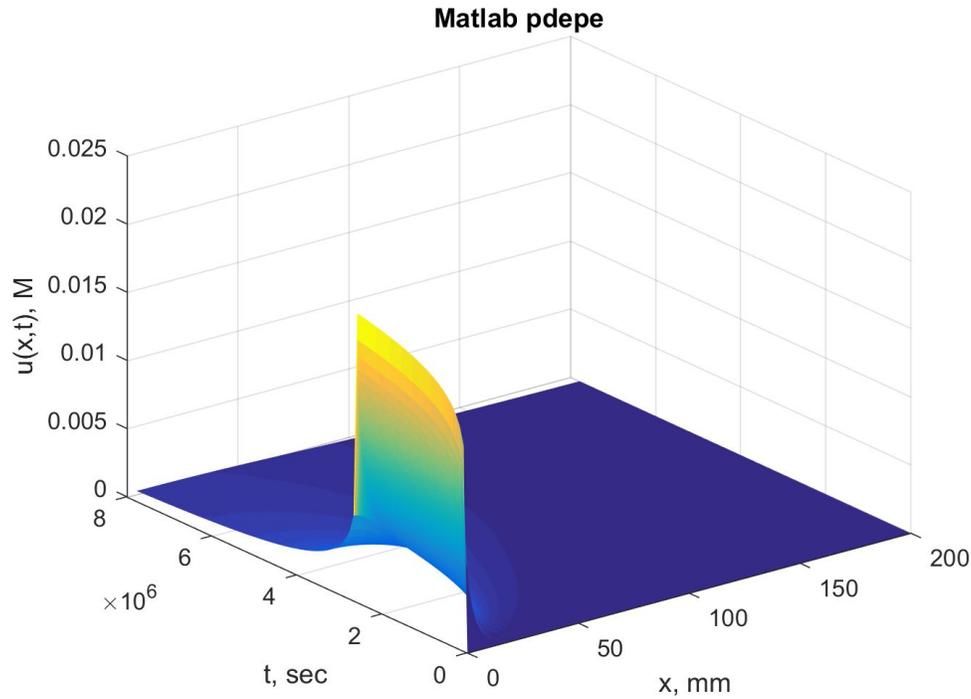


Figure 8. PDE solver approximation (Model II)

With this model, we can discuss two important factors of drug delivery: drug lifetime and effective area. The drug's concentration has to be above a certain level to be functional, so finding the maximum distance at which the concentration remains above this threshold is essential. We define this distance as r_{min} . Since the concentration profile is time-dependent, r_{min} not only depends on given concentration but also time. Our model shows an example of the r_{min} for a given concentration as the yellow curve in Fig. 9. The method to find r_{min} in our algorithm is to compare the absolute difference between given concentration and solution. In Fig. 10 and 11, we demonstrate two r_{min} with different given concentrations of Model I and Model II.

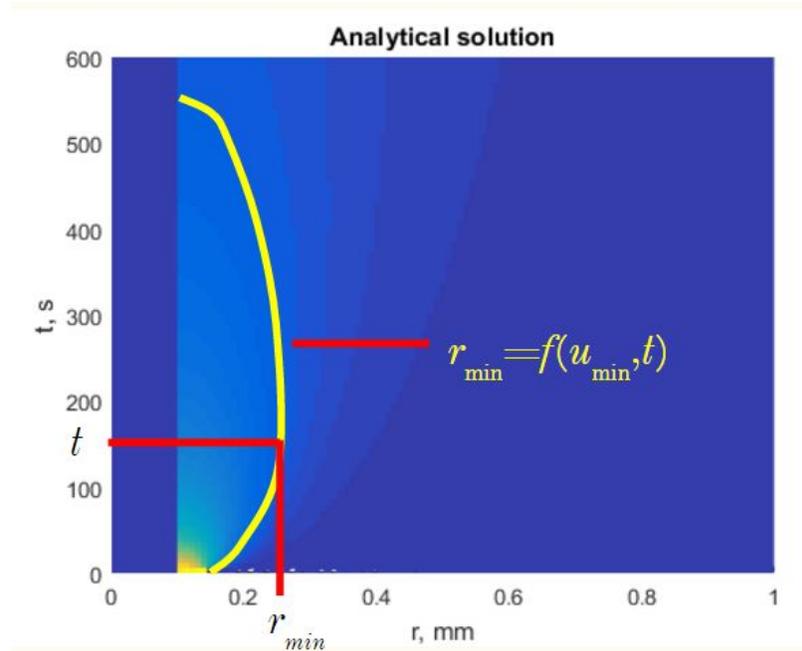


Figure 9. r_{\min} as a function of minimum concentration and time

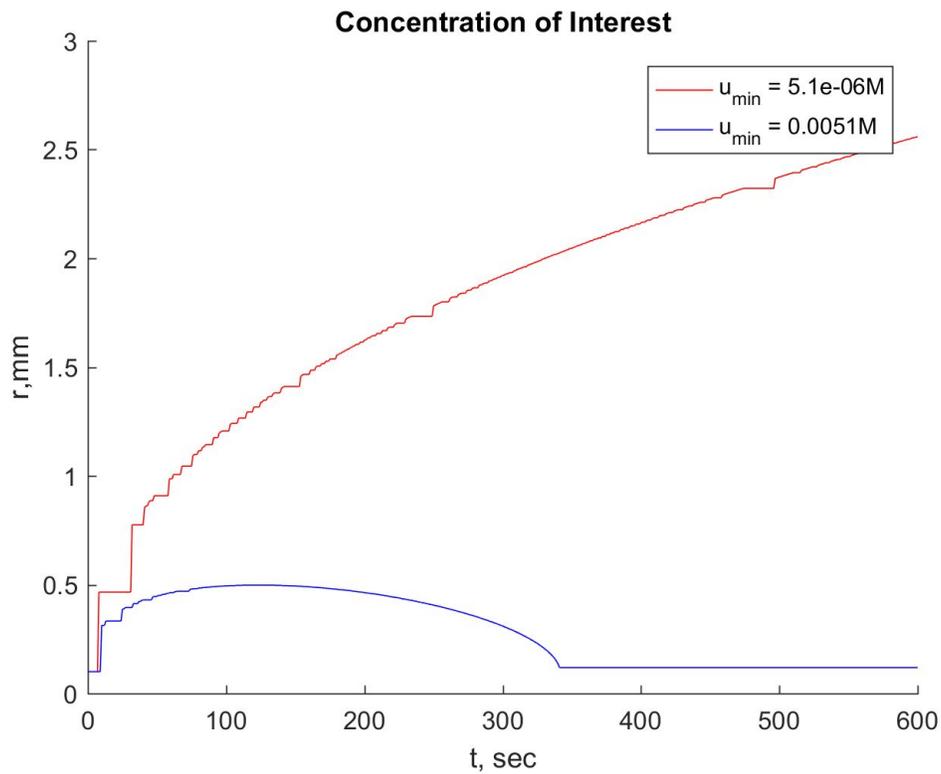


Figure 10. r_{\min} of two given concentrations in Model I.

The concentration we choose for the red curve is a rough estimate of the drug concentration necessary to be functional based on an IV dosage that was found to be effective and the total blood volume of the human body.[4] We can see that r_{min} increases with time at the beginning as the drug diffuses away from the suture, followed by a gradual decrease after peaking at a certain value. If we extend our observed time, we expect the red curve have the same tendency as the blue curve. We can also see there is a flat part at the end of blue curve. This shows that there is no concentration higher than the given concentration so r_{min} will be the same as the radius of suture.

The r_{min} of Model II is similar to Model I but with a longer diffusion range and longer lifetime. When the simulation time for Model I is extended to $8e+06$ s, r_{min} for $u_{min} = 5.1e-06$ M has a maximum at 7 mm before decreasing (plot not shown). This may be due to the prolonged release of DEX in Model II having a positive effect on diffusion-length.

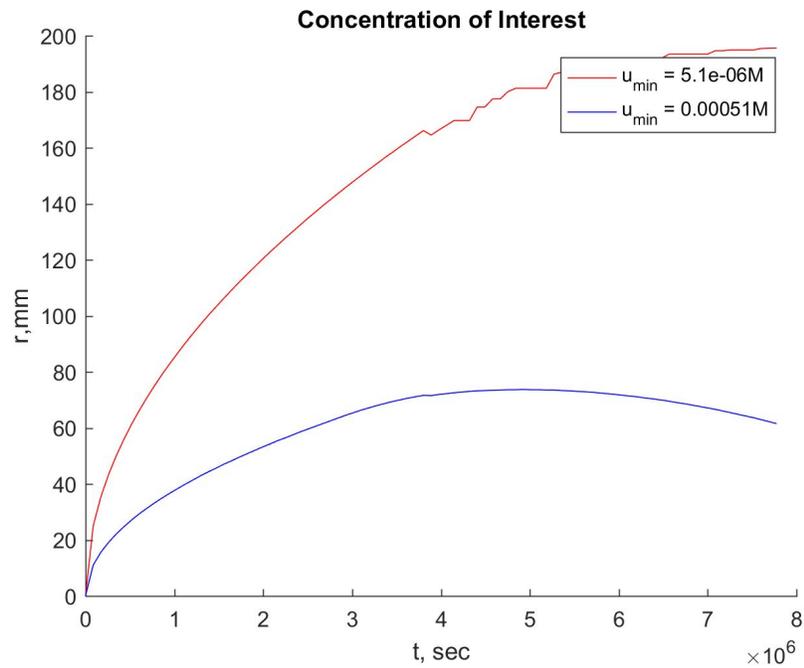


Figure 11. r_{min} of two given concentrations in Model II.

Different drugs have different diffusivity in tissue depending on their size and hydrophobicity. To investigate how drug diffusivity affects our model, we compare r_{min} with different diffusivities. In Fig.12 and 13, we can see that the higher the diffusivity, the farther drug can diffuse.

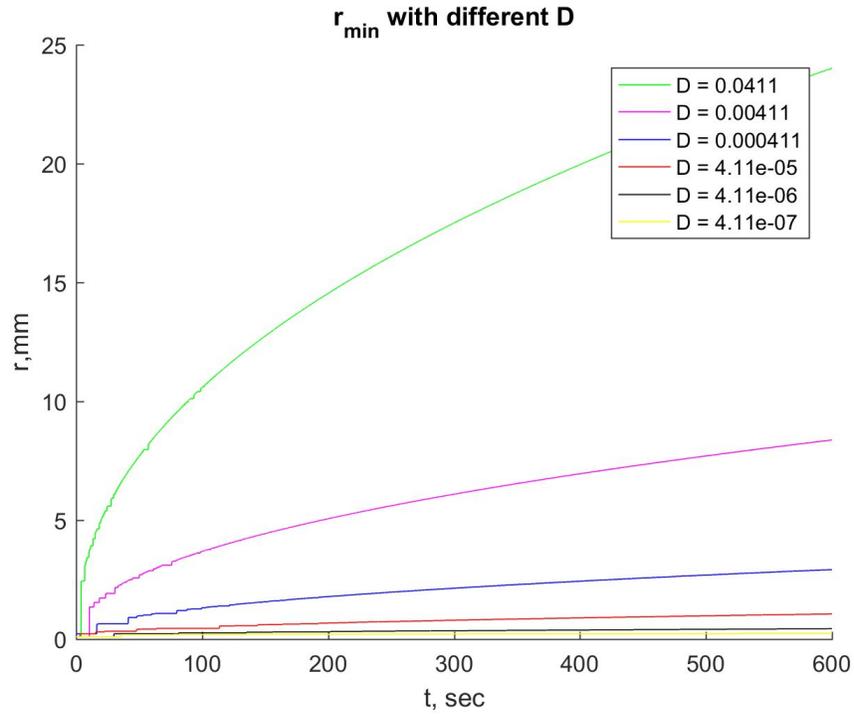


Figure 12. r_{\min} with different D in Model I.

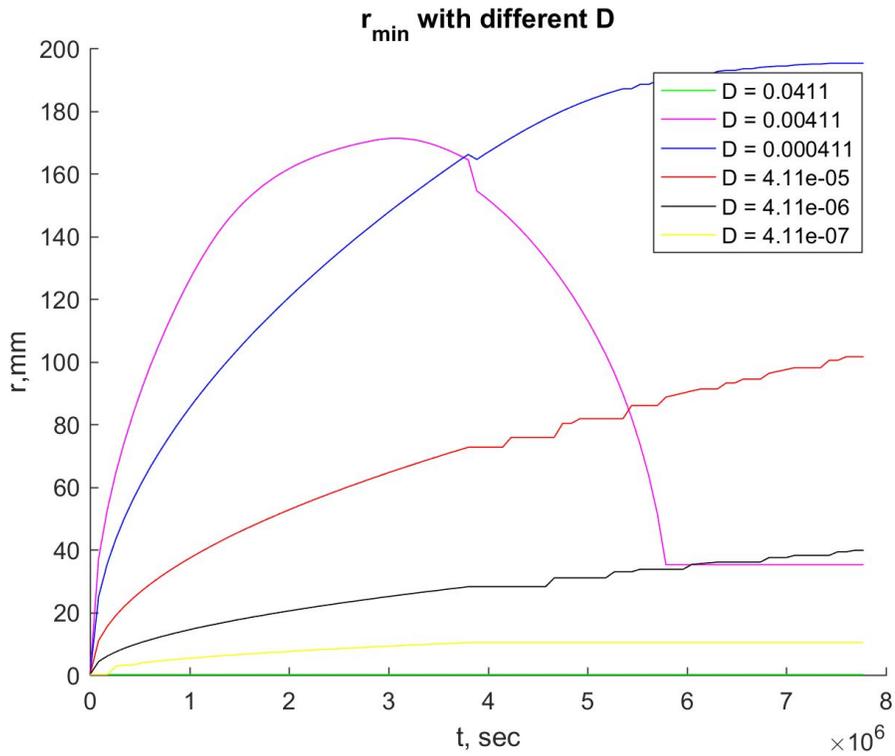


Figure 13. r_{\min} with different D in Model II.

The reason why the flat part of blue curve is not equal to radius of suture is because our resolution (dx, dt) and threshold of comparison is still not small enough. As a result, we

will lose the information when the concentration changes slightly. Also, the result of $D = 0.0411$ remains near the suture is because the diffusion is so fast the concentration immediately drops below the effective threshold.

Future models:

Though our model performs well, it can still be further improved. The first thing to consider is sigmoidal release of DEX from PLGA as the polymer undergoes hydrolysis. Instead of using a constant rate boundary condition, we use a rate corresponding to the time derivative of the release curve in Fig. 5. This rate would be in the form of a Gaussian function:

$$-D \frac{\partial u(b,t)}{\partial r} = \frac{C_0(b^2-a^2)}{2b} \frac{1}{\sigma\sqrt{2\pi}} e^{-\frac{(t-t_{0.5})^2}{2\sigma^2}}$$

Where $t_{0.5}$ is the time at which half of the total drug is released. σ is a time constant inversely proportional to the slope of the linear segment of the release curve and can be found by fitting the release curve to a cumulative normal distribution function.

This model can also be improved by considering different diffusivities in PLGA and tissue. In this case, we will have to separate our diffusion equation into two parts and the boundary condition at $r = b$ will become time-dependent.

$$\text{In PLGA: } \frac{\partial u_{PLGA}}{\partial t} = \frac{D}{r} \frac{\partial}{\partial r} \left(r \frac{\partial u_{PLGA}}{\partial r} \right)$$

$$\text{BC: } \frac{\partial u_{PLGA}(a,t)}{\partial r} = 0$$

$$\frac{\partial u_{PLGA}(b,t)}{\partial r} = \frac{\partial u_{Tissue}(b,t)}{\partial r}$$

$$\text{In Tissue: } \frac{\partial u_{Tissue}}{\partial t} = \frac{D}{r} \frac{\partial}{\partial r} \left(r \frac{\partial u_{Tissue}}{\partial r} \right)$$

$$\text{BC: } \frac{\partial u_{Tissue}(b,t)}{\partial r} = \frac{\partial u_{PLGA}(b,t)}{\partial r}$$

$$\frac{\partial u_{Tissue}(\infty,t)}{\partial r} = 0$$

Assuming high drug-target affinity, consumption of the drug can be modeled by irreversible binding with its target. This reaction is dependent on the concentration of drug and a rate constant k :

$$\frac{\partial u}{\partial t} = \frac{D}{r} \frac{\partial}{\partial r} \left(r \frac{\partial u}{\partial r} \right) - ku(r, t)$$

Moreover, if the target is a uniformly generated substance, we have to consider the concentration profile of the target when we calculate the elimination rate of the drug.

$$\frac{\partial u}{\partial t} = \frac{D}{r} \frac{\partial}{\partial r} \left(r \frac{\partial u}{\partial r} \right) - ku(r, t)u_{target}(r, t)$$

Discussion:

Sutures that are coated with anti-inflammatory drugs can help alleviate pain through local drug delivery at wound or incision site during and after surgery. We modeled

diffusion of dexamethasone from the PLGA sheet in two cases: i) PLGA hydrolysis is fast and releases drug instantly, ii) PLGA hydrolysis is slow and releases drug at a constant rate over an extended time. In the first case, we found solutions using an analytical approximation and the Matlab pdepe function. In the second case, we only used the pdepe function to find the solution. Based on the time it takes for PLGA to degrade (several weeks), the latter model is more relevant to our suture-PLGA system. For degradation-limited release, effective drug radius and dosage peak time are 73 mm and 58 days for a minimum drug concentration of 5.1×10^{-4} M. This minimum effective concentration is two orders of magnitude larger than the value we estimated, so we expect the actual effective drug radius and dosage peak time to be larger for 5.1×10^{-6} M. We also expect these parameters to decrease significantly when DEX elimination rate is factored in. Based the results from our current model, DEX is effective on a large length scale and does not need to be considered to determine the minimum suture spacing. In addition, the duration that the drug remains above effective concentration means that it is unlikely that additional painkillers need to be administered during recovery.

These models can also be applied to other suture and drug types to predict drug lifetime and effective area, which is essential in planning proper drug delivery in surgical operations. In a clinical setting a physician can observe the postoperative drug effectiveness through these models. For example, if the wound is more serious and needs immediate treatment, a suture would need to be coated with a Model I biomaterial that hydrolyzes quickly for fast drug delivery. If a wound needs to be controlled with anti-inflammatory over a longer period of time, a PLGA suture is more applicable because of its longer lifetime.

References (needs cleanup - harmonization with document)

1. Oster, D.P.M. Jeffrey A. "Ankle Sprains | Causes and Treatment Options." *MyFootShop.com*. Myfootshop.com, L.L.C., n.d. Web. 23 Nov. 2016.
2. "File:Dexamethasone Structure.svg." File:Dexamethasone Structure.svg - Wikimedia Commons. N.p., n.d. Web. 23 Nov. 2016.
3. Lee, Ji Eun, et al. "Surgical suture assembled with polymeric drug-delivery sheet for sustained, local pain relief." *Acta biomaterialia* 9.9 (2013): 8318-8327.
4. Moussy, Yvonne, Lawrence Hersh, and Paul Dungal. "Distribution of [3H] dexamethasone in rat subcutaneous tissue after delivery from osmotic pumps." *Biotechnology progress* 22.3 (2006): 819-824.
5. Ju, Young Min, et al. "A dexamethasone-loaded PLGA microspheres/collagen scaffold composite for implantable glucose sensors." *Journal of Biomedical Materials Research Part A* 93.1 (2010): 200-210.
6. Liu, K., C. C. Hsu, and Y. Y. Chia. "Effect of dexamethasone on postoperative emesis and pain." *British journal of anaesthesia* 80.1 (1998): 85-86.
7. "Green's Function Library." Green's Function Library. University of Nebraska, Lincoln, n.d. Web. 23 Nov. 2016.

8. Makadia, Hirenkumar K., and Steven J. Siegel. "Poly lactic-co-glycolic acid (PLGA) as biodegradable controlled drug delivery carrier." *Polymers* 3.3 (2011): 1377-1397.
9. "19th WHO Model List of Essential Medicines (April 2015)". WHO. April 2015.
10. AHFS drug information 2004. McEvoy GK, ed. Dexamethasone. Bethesda, MD: American Society of Health-System Pharmacists; 2004:2906-8.

Appendix A: Matlab code for analytical solution approximation

```

% function inf_hole2
% solution for infinite body with circular hole, 1-D
% 11/15/16nl

global D a b C0
D = 4.11e-5; % diffusion constant, mm^2/s
a = 0.1; % radius of hole, mm
b = a + 0.04; % outer radius of PLGA, mm
C0 = 0.33; % initial condition, M = mol/L = umol/uL

B = 100; % upper bound of bessel integration
L = 100; % simulation length
T = 3600*24; % simulation time

% double integration domain
db = 0.1; % integration step size KEEP SMALL
bmesh = db:db:B; % integration domain
dr0 = (b-a)/10; % dummy var integration step size
r0mesh = a:dr0:b; % dummy var domain

% space-time domain
dr = (L-a)/100; % step size in r dimension
dt = T/100; % step size in t dimension
rmesh = a:dr:L; % domain in space dim1
tmesh = 0:dt:T; % domain in t
nr = length(rmesh); % number of points in space dim1
nt = length(tmesh); % number of points in t dimension

% besselr definition
besselr = @(r,b) besselj(0,b.*r./a).*bessely(1,b)-bessely(0,b.*r./a).*besselj(1,b);

% Integrand definition
fun = @(t,r,r0,b)
exp(-b.^2.*D.*t./a.^2).*b.*besselr(r,b).*besselr(r0,b)./(besselj(1,b).^2+bessely(1,b).^2).*r0;

[X,Y,Z,W] = ndgrid(tmesh,rmesh,r0mesh,bmesh);
F = fun(X,Y,Z,W);
sol = C0/a^2*dr0*trapz(db*trapz(F,4),3);

```

```

suture = zeros(nt,floor(a/dr));
sol = [suture, sol]; % append zeros

rmesh2 = 0:dr:L;

figure(2)
surf(rmesh2,tmesh,sol,'edgecolor','none')
title(['Analytical solution'])
ylabel('t, s')
xlabel('r, mm')
zlabel('u(x,t), M')

```

Appendix B: Matlab code for pdepe solution Model I

```

clear all
clc

global D a b C0
D = 4.11e-5; % diffusion constant
a = 0.1; % radius of hole
b = a+0.04; % outer radius of fabric
C0 = 0.33; % initial condition

dx = 0.001;
dt = 0.1; % sec
obtime = 10; % min

x = a:dx:10;
t = 0:dt:obtime*60; % sec
nt = length(t);
suture = zeros(nt,a/dx);

sol = pdepe(0,@pdefun,@ic,@bc,x,t);
new_sol = [suture, sol];

x2 = 0:dx:10;

figure(1)
surf(x2,t,new_sol,'edgecolor','none')
title('Matlab pdepe')
caxis([0 0.25])
xlabel('x, mm')
ylabel('t, sec')
zlabel('u(x,t), M')
xlim([0,1])

```

```

%%
% time of interest

Cs = 5.1e-6;
Cs2 = 5.1e-2;
zth = 1e-8; % threshold to find zero
zth2 = 1e-3;
ri = 0;
ri2 = 0;
rsiall=ones(1,length(t))*a;
rsiall2=ones(1,length(t))*a;

for j = 1:length(t)
    sol_s = new_sol(j, :);
    k=1;
    k2=1;
    for i = 1:length(x2)
        if abs(sol_s(i)-Cs) < zth
%         rsa(k) = x2(i);
            ri = i;
            k=k+1;
        end

        if abs(sol_s(i)-Cs2) < zth2
%         rsa(k) = x2(i);
            ri2 = i;
            k2=k2+1;
        end
    end
    rs = mean(rsa);
    if any(ri)
        rsiall(j) = x2(ri);
    end
    if any(ri2)
        rsiall2(j) = x2(ri2);
    end
end

figure(3)
hold on
plot(t, rsiall, 'r-', 'DisplayName', ['u_{min} = ',num2str(Cs), 'M'])
plot(t, rsiall2, 'b-', 'DisplayName', ['u_{min} = ',num2str(Cs2), 'M'])
title('Concentration of Interest')
xlabel('t, sec')
ylabel('r,mm')

```

```

hold off
legend('show')
%%
% % Polar Coord.
% tclick = 1;
% r = 0:dx:1;
% theta = 0:0.1:2*pi+0.1;
% [rmesh, thetamesh] = meshgrid(r,theta);
% %change into cartesian Coord.
% X = rmesh.*cos(thetamesh);
% Y = rmesh.*sin(thetamesh);
% Z = new_sol(tclick,:)*(theta >=0);
%
% figure(3)
% surf(X, Y, Z')
% caxis([0 0.4])
% title('Suture_{not pass}')
% xlabel('concentration')

%%
% % Animation
% tlen = 5*60/dt; % in min
%
% vid = VideoWriter('Suture_not_pass_bes.avi');
% open(vid);
%
% axis tight equal
% set(gca,'nextplot','replacechildren');
%
% for k = 1:tlen-1 % in sec
%     Zt = new_sol(k,:)*(theta >=0);
%     caxis([-0.01 0.05])
%     surf(X,Y,Zt')
%     title('Suture_{not pass}    Bes')
%     text(1,-1,max(max(Zt)),[sprintf('%0.2f',k*dt/60),'
(min)'],'FontSize',12,'Color','red','HorizontalAlignment','right');
%     M = getframe(gcf);
%     writeVideo(vid, M);
% end
%
% close(vid);

%%
% function definitions for pdepe:

```

```

% -----
function [c, f, s] = pdefun(x, t, u, DuDx)
% PDE coefficients functions
% form: c(x,t,u,dudx)*dudt = x^-m * d/dx(x^m * f(x,t,u,dudx) +
% s(x,t,u,dudx)

```

```

global D
c = 1;
f = D * DuDx; % diffusion
s = -3.6e-5*u;
% s = 0;
end

```

```

% -----

function u0 = ic(x)
% Initial conditions function
global C0 a b
u0 = C0*(x>=a)*(x<=b);
% u0 = 0;
end
% -----

```

```

function [pl, ql, pr, qr] = bc(xl, ul, xr, ur, t)
% Boundary conditions function
% pl(x,t,u) + ql(x,t,u) * f(x,t,u,dudx) = 0 at x = xl
% pr(x,t,u) + qr(x,t,u) * f(x,t,u,dudx) = 0 at x = xr
global C0 D b a
pl = 0;
ql = 1; %
pr = ur;
qr = 0; %
end

```

Appendix C: Matlab code for pdepe solution Model II

```

clear all
clc

global D a b C0
D = 4.11e-5; % diffusion constant
a = 0.1; % radius of hole
b = a+0.04; % outer radius of fabric
C0 = 0.33; % initial condition

```

```

dx = 0.01;
dt = 1*60*60*24; % sec
obtime = 90; % min

x = b:dx:100;
t = 0:dt:obtime*60*60*24; % sec
nt = length(t);
suture = zeros(nt,a/dx);

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

figure(1)
surf(x,t,sol,'edgecolor','none')
title('Matlab pdepe')
xlabel('x, mm')
ylabel('t, sec')
zlabel('u(x,t), M')
xlim([0,60])

%%
% time of interest

Cs = 5.1e-6;
Cs2 = 5.1e-4;
zth = 1e-8; % threshold to find zero
zth2 = 1e-6;
ri = 0;
ri2 = 0;
rsiall=ones(1,length(t))*b;
rsiall2=ones(1,length(t))*b;

for j = 1:length(t)
    sol_s = sol(j, :);
    k=1;
    k2=1;
    for i = 1:length(x)
        if abs(sol_s(i)-Cs) < zth
%            rsa(k) = x2(i);
            ri = i;
            k=k+1;
        end

        if abs(sol_s(i)-Cs2) < zth2
%            rsa(k) = x2(i);
            ri2 = i;

```

```

        k2=k2+1;
    end
end
% rs = mean(rsa);
if any(ri)
    rsiall(j) = x(ri);
end
if any(ri2)
    rsiall2(j) = x(ri2);
end
end

figure(3)
hold on
plot(t, rsiall, 'r-', 'DisplayName', ['u_{min} = ', num2str(Cs), 'M'])
plot(t, rsiall2, 'b-', 'DisplayName', ['u_{min} = ', num2str(Cs2), 'M'])
title('Concentration of Interest')
xlabel('t, sec')
ylabel('r, mm')
ylim([0 70])
hold off
legend('show')
%%
% function definitions for pdepe:
% -----

function [c, f, s] = pdefun(x, t, u, DuDx)
% PDE coefficients functions
% form: c(x,t,u,dudx)*dudt = x^-m * d/dx(x^m * f(x,t,u,dudx) +
% s(x,t,u,dudx)

global D
c = 1;
f = D * DuDx; % diffusion
% s = -3.6e-5*u;
s = 0;
end

% -----

function u0 = ic(x)
% Initial conditions function
global C0 a b

```

```

% u0 = C0*(x>=a)*(x<=b);
u0 = 0;
end
% -----

function [pl, ql, pr, qr] = bc(xl, ul, xr, ur, t)
% Boundary conditions function
% pl(x,t,u) + ql(x,t,u) * f(x,t,u,dudx) = 0 at x = xl
% pr(x,t,u) + qr(x,t,u) * f(x,t,u,dudx) = 0 at x = xr
global C0 D b a
pl = C0*(b-a)/(30*3600*24)*(t<=30*3600*24);
ql = 1; %
pr = ur;
qr = 0; %
end

```