Modeling 1-Dimensional Diffusion of TDF via an Intravaginal Ring

BENG221A

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Introduction:

HIV is a sexually transmitted disease that infects an individual's T cells. This slowly cripples the body's ability to fight off invader and eventually leads to immune system failure and death. Condoms are effective at preventing the spread of HIV, but transmission can still occur due to condom failure or other unforeseen circumstances. Current data estimates that there are over one million people in the United States alone with HIV, and the disease has reached near epidemic levels in some African countries where researchers speculate almost half the population may be infected. At the moment, there is no cure.

When HIV enters an individual's system, the retrovirus infects him/her by attaching to their T cells and injecting its own RNA. An enzyme known as reverse transcriptase is involved in the maintenance of genetic material in the cell. It generates double stranded DNA from an RNA template, and it is this function that retroviruses, such as HIV exploit. If the injected HIV RNA undergoes reverse transcription, the resulting DNA may insert itself into the host cell's DNA. Should this happen, the host cell will begin creating more of the retrovirus until the cell inevitably dies and the newly fabricated HIV seek out more T cells to infect.

Tenofovir Disoproxil Fumarate or TDF is a prescription drug that blocks the transmission of HIV. It is currently prescribed as a pill, but other methods of administering it are being explored. One that shows a great deal of promise is the use of intravaginal rings. An intravaginal ring is a polymeric drug device that provides controlled release of a drug over an extended period of time. It has been determined for TDF that "Topical preexposure prophylaxis interrupts HIV transmission at the site of mucosal exposure." With this in mind, a model for the diffusion of TDF in cervicovaginal mucus was created to better understand the process. Additionally, environmental changes were taken into account due to the cyclic nature of the menstrual cycle.

The assumptions used for the model are outlined below:

- The concentration of TDF at the interface between the intravaginal ring and mucus remains stable.
- The concentration at the interface between the mucus and the vaginal wall is zero.
- Diffusion of TDF only travels away from the ring, toward the tissue wall.
- The distance between the ring and the tissue remains fixed.

Analytical Solution:

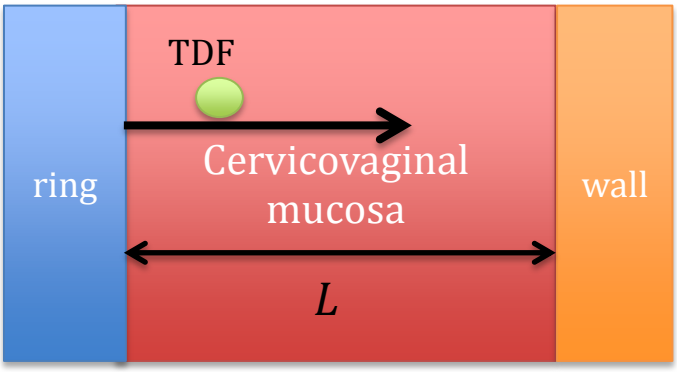

Figure 1: Diagram of Diffusion from Intravaginal Ring into Mucus

Our system is modeled by the partial differential equation (PDE):

$$1)\ \frac{\partial C}{\partial t} = D\frac{\partial^2 C}{\partial x^2}$$

with initial condition (IC) and boundary conditions (BC):

$$2)\ \text{IC: } C(x,0) = 0$$

$$3)\ \text{BC: } \begin{cases} C(0,t) = C_0 \\ C(L,t) = 0 \end{cases}$$

Here, $C(x,t)$ is the concentration of the drug (dependent on time t and length x), L is the distance measured from the ring (from where the drug is released) to the end boundary of the cervicovaginal mucosal layer, its target destination, and D is the diffusion coefficient for the drug as it travels from the ring to the length of the cervicovaginal mucosal layer.

The problem is that we cannot use Separation of Variables to solve this PDE because our boundary conditions are non-homogeneous. Normally, Separation of Variables works if the PDE and BC are both linear and homogeneous.

Now, let's consider the problem from some perspective. There are no sources to basically decrease or increase the drug concentration between the ring and cervicovaginal mucosal layer. Based on our boundary conditions, they are fixed concentrations, thus they cannot change with time and there's no flux on the boundaries to increase or decrease the drug concentration.

This means there is no type of concentrated forcing of drug, so while the drug concentration is flowing out of the ring, eventually, the concentration distribution within the range of the ring and cervicovaginal mucosa should stabilize and no longer be time-dependent.

We define an equilibrium concentration, or steady-state concentration, $C_E(x)$ by the infinite t −limit for $C(x,t)$. In other words,

$$4)\ \lim_{t\to\infty} C(x,t) = C_E(x)$$

$C_E(x)$ will satisfy the diffusion equation and boundary conditions, but not the initial condition because it defines the concentration profile as $t \to \infty$, but the initial condition is for $t = 0$. Instead, it satisfies

$$5)\ \frac{d^2C_E}{dx^2} = 0 \text{ with BC: } \begin{cases} C_E(0,t) = C_0 \\ C_E(L,t) = 0 \end{cases}$$

The solution for this 2nd order ODE is a linear equation: $C_E(x) = Ax + B$ Solving for the values of A and B using the boundary conditions, we get $B = C_0$ and $A = -C_0/L$ and now, we substitute these values.

$$6)\ C_E(x) = C_0 - \frac{C_0}{L}x$$

We define another function $V(x,t)$ in terms of $C(x,t)$ and $C_E(x)$ as the difference between the two and solve for $C(x,t)$ from it:

$$7)\ V(x,t) = C(x,t) - C_E(x)$$
$$\Rightarrow C(x,t) = V(x,t) + C_E(x)$$

Note that the units are still consistent with units of concentration. Compute some partial derivatives in relation to the diffusion equation:

$$8)\ \frac{\partial C}{\partial t} = \frac{\partial V}{\partial t} + \frac{\partial C_E}{\partial t}$$
$$\Rightarrow \frac{\partial C}{\partial t} = \frac{\partial V}{\partial t}$$

$$9)\ \frac{\partial^2 C}{\partial x^2} = \frac{\partial^2 V}{\partial x^2} + \frac{\partial^2 C_E}{\partial x^2}$$
$$\Rightarrow \frac{\partial^2 C}{\partial x^2} = \frac{\partial^2 V}{\partial x^2}$$

We use the fact C_E is the equilibrium concentration, it's time-independent, and is a solution to

$$10)\qquad \frac{d^2C_E}{dx^2} = 0 \text{ with BC: } \begin{cases} C_E(0,t) = C_0 \\ C_E(L,t) = 0 \end{cases}$$

Both $C(x,t)$ and $V(x,t)$ satisfy the equation directly above. Let's define the initial condition and boundary condition by $V(x,t)$:

$$11) V(x,0) = C(x,0) - C_E(x) = 0 - \left(C_0 - \frac{C_0}{L}x\right) = \frac{C_0}{L}x - C_0$$
$$12) V(0,t) = C(0,t) - C_E(0) = C_0 - C_0 = 0$$
$$13) V(L,t) = C(L,t) - C_E(L) = 0 - C_0 + \frac{C_0}{L}(L) = 0$$

Now, even though the initial condition is a bit odd, we now have homogenous boundary conditions!

$V(x,t)$ must satisfy $\frac{\partial V}{\partial t} = D\frac{\partial^2 V}{\partial x^2}$ with IC $V(x,0) = \frac{C_0}{L}x - C_0$ and BC: $\begin{cases} V(0,t) = 0 \\ V(L,t) = 0 \end{cases}$

Solution to the diffusion equation is given by

$$14) V(x,t) = \sum_{n=1}^{\infty} B_n \sin\left(\frac{n\pi x}{L}\right) e^{-D\left(\frac{n\pi}{L}\right)^2 t}$$

This is a Fourier series for sine. The coefficients given by

$$15) B_n = \frac{2}{L}\int_0^L \left(C(x,0) - C_E(x)\right) \sin\left(\frac{n\pi x}{L}\right)\, dx\,, n = 1, 2, 3, \dots$$

We can try to also find an expression for the coefficients of B_n. Substituting that $C(x,0) = 0$ and $C_E(x) = C_0 - \frac{C_0}{L}x$ into the equation:

$$16) \quad B_n = \frac{2}{L}\int_0^L \left(0 - \left(C_0 - \frac{C_0}{L}x\right)\right) \sin\left(\frac{n\pi x}{L}\right)\, dx =$$
$$\frac{2}{L}\int_0^L \left(\frac{C_0}{L}x - C_0\right) \sin\left(\frac{n\pi x}{L}\right)\, dx =$$
$$\frac{2}{L}\int_0^L \left(\frac{C_0}{L}x - C_0\right) \sin\left(\frac{n\pi x}{L}\right)\, dx \ (n = 1, 2, 3, \dots)$$
$$\overset{(*)}{\Rightarrow} -\frac{2C_0}{\pi n} \ (n = 1, 2, 3, \dots)$$

The $(*)$ refers to the evaluation of the integral using integration by parts. The solution makes sense because in the final expression for $C(x,t)$ below, we want units of concentration and since the sine and exponential term are dimensionless, B_n should have units of concentration.

Since $V(x,t) = \sum_{n=1}^{\infty} B_n \sin\left(\frac{n\pi x}{L}\right) e^{-D\left(\frac{n\pi}{L}\right)^2 t}$ and $C(x,t) = C_E(x) + V(x,t)$, we have our final solution.

$$17) C(x,t) = C_0 - \frac{C_0}{L}x + \sum_{n=1}^{\infty} B_n \sin\left(\frac{n\pi x}{L}\right) e^{-D\left(\frac{n\pi}{L}\right)^2 t}$$

Numerical Method:

Recall our equation for diffusion of the drug:

$$18)\frac{\partial C}{\partial t} = D\frac{\partial^2 C}{\partial x^2}$$

We used the Crank Nicolson method to numerically determine concentrations at positions x and times t. Equation 18 must be rewritten in a form that can be solved using Crank Nicolson method.

$$19)\frac{C_i^{n+1}-C_i^n}{\Delta t} = \frac{D}{2(\Delta x)^2}((C_{i+1}^{n+1} - 2C_i^{n+1} + C_{i-1}^{n+1}) + (C_{i+1}^n - 2C_i^n + C_{i-1}^n))$$

Where Δt is the time step, Δx is the size of the x-step, D is the diffusion coefficient, and C_i^n indicates the concentration at time-step n and x-step i. The x-step, t-step, and diffusion constants can be rearranged to give constant a:

$$20) \quad a = \frac{D\Delta t}{2(\Delta x)^2}$$

Allowing equation 19 to be rewritten simply:

$$21) \quad -aC_{i+1}^{n+1} + (1-2a)C_i^{n+1} - aC_{i-1}^{n+1} = -aC_{i+1}^n + (1-2a)C_i^n - aC_{i-1}^n$$

At this point, the equation can be rewritten in matrix form:

$$22) \quad [A]\left[C^{j+1}\right] = [B]\left[C^j\right]$$

Where A and B are tridiagonal matrices as shown below.

$$23) \quad A = \begin{bmatrix} \frac{1}{a}+2 & -1 & 0 \\ -1 & \frac{1}{a}+2 & -1 \\ 0 & -1 & \ddots \end{bmatrix}$$

$$24) \quad B = \begin{bmatrix} \frac{1}{a}-2 & 1 & 0 \\ 1 & \frac{1}{a}-2 & 1 \\ 0 & 1 & \ddots \end{bmatrix}$$

For purposes of solving in Matlab, equation 22 should be rewritten to solve for $[C^{j+1}]$.

$$25) \quad \left[C^{j+1}\right] = [A]\backslash[B]\left[C^j\right]$$

Note that the backslash indicates a left division. Additionally, the time-step and x-step should be chosen such that the ratio between the time-step and the square of the x-step is less than one half:

$$26) \quad \frac{\Delta t}{\Delta x^2} < \frac{1}{2}$$

In the case of a two-layer problem in which the diffusion coefficient is different in the second layer, simply change constant a in matrices A and B at $A(\geq j_{interface}, \geq j_{interface})$ and $B(\geq j_{interface}, \geq j_{interface})$, where $j_{interface}$ is the x node closest to the interface of the two boundaries.

The plots in Figure [2] show how TDF diffuses across the cervicocvaginal mucosa with time. The analytical and the numerical solution plots are virtually the same when the first 100 terms in the series are used for the analytical solution and a time step of 100 seconds is used for Crank-Nicolson (as shown). However, the analytical solution produces a sine wave that disappears with time due to the sine term in the analytical solution equation.

Diffusion is slower when the mucosa has a higher viscosity and quicker when the mucosa has a lower viscosity, as expected. Therefore, at lower viscosity, the system reaches steady state sooner. At steady state, the concentration profile of TDF across the mucosa is linear, from a concentration of 10 μM at distance 0 μm to a concentration of 0 μM at distance 100 μm.

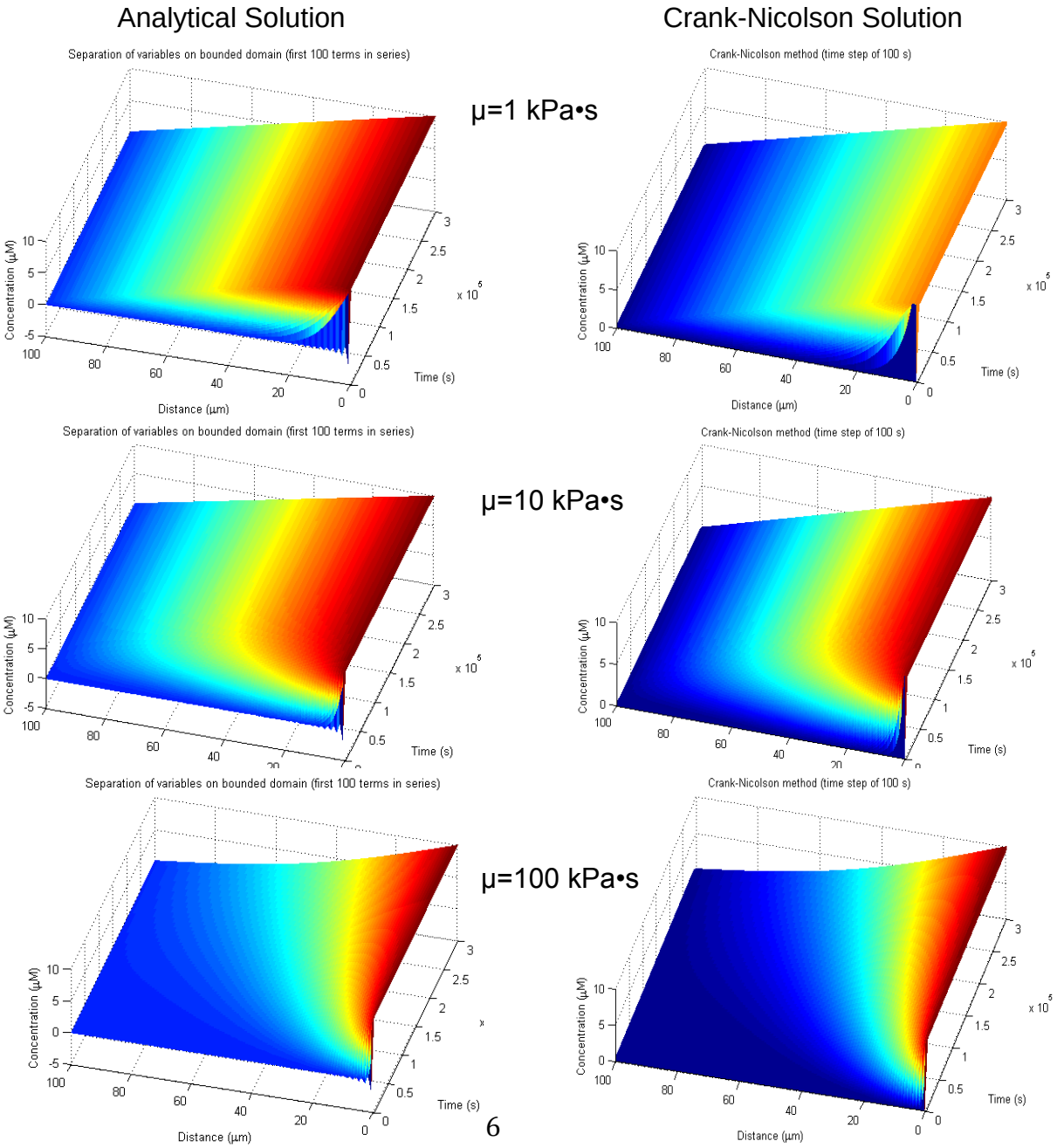

Figure 2: Comparison of the analytical solution using separation of variables and numerical solution using Crank-Nicolson at dynamic viscosities of 1, 10, and 100 kPa•s.

Using the Crank-Nicolson method, the system was then modeled with two layers, the 100 μm mucosa layer and the 800 μm vaginal wall layer, with viscosities of 10 kPa•s and 0.01 kPa•s respectively. The resulting plot is shown in Figure [X2]. In this model, diffusion begins slowly, but proceeds rapidly after the mucosa layer at 100 μm. Eventually, a linear steady state profile is reached, as in the single-layer model. However, the plot shows that diffusion through the vaginal wall should be considered. The two-layer model is an improved model for TDF diffusion from a vaginal ring.

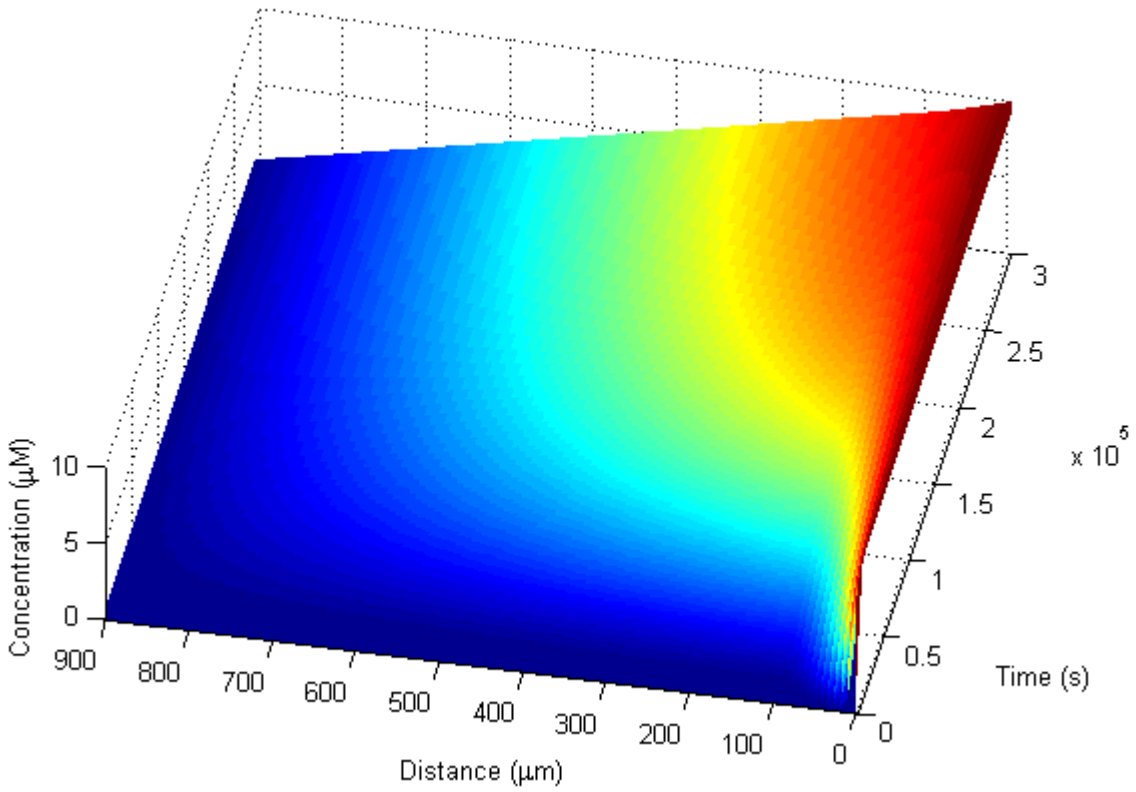

Figure 3: Two-layer model plotted using the Crank-Nicolson method.

Appendix:

Plotting the analytical solution

```
% Homogeneous PDE: Linear (1-D) Diffusion
% Analytical solutions on bounded and infinite domain
% ns: number of terms in the infinite series

% diffusion constant
ns=100;
D = 4.541*10^-10*(10^4)^2; % um^2/s
C0=10; %uM
% domain
dx = 1; % step size in x dimension (um)
dt = 100;  % step size in t dimension (s)
L=100; %um
endtime=300000; %(s)
xmesh = 0:dx:L; % domain in x; um
tmesh = 0:dt:endtime;  % domain in t
nx = length(xmesh); % number of points in x dimension
nt = length(tmesh); % number of points in t dimension
GS=C0-C0*xmesh/L;

% solution on bounded domain using separation of variables
sol_sep = zeros(nt, nx);

for n = 0:ns-1
    k = (2*(n+1))*pi/(2*L); % L = 2
    Bn= -2*C0/(pi*(n+1));
    sol_sep = sol_sep + Bn*exp(-D*(k^2)*tmesh)' * (sin(k*xmesh));

end

C_final=NaN(size(sol_sep));
for i=1:length(tmesh)
%     sol_sep(i,:)=sol_sep(i,:)+(4-4*cos((pi/(2*L))*xmesh));
    C_final(i,:)=GS+sol_sep(i,:);
end

figure(1)
surf(tmesh,xmesh,sol_sep', 'Edgecolor','none')
surf(tmesh,xmesh,C_final', 'Edgecolor','none')
title(['Separation of variables on bounded domain (first ',
num2str(ns), ' terms in series)'])
xlabel('t')
ylabel('x')
zlabel('u(x,t)')

title(['Separation of variables on bounded domain (first ',
num2str(ns), ' terms in series)'])
xlabel('Time (s)')
ylabel('Distance (mum)')
zlabel('Concentration (muM)')
```

Crank Nicolson Method-1 Layer

```
clear;close all; clc;
% Set the number of grid points and build a cell-center grid
% N=input(' Enter N, cell number - ')
N=900;
L=900; %um
Lm=100;%um
h=L/N; % step size
x=-.5*h:h:L+.5*h;
x=x'; % Turn x into a column vector.
% Load the diffusion coefficient array (make it a column vector)
D=ones(N+2,1); % (just 1 for now--we'll change it later)
% Load Dm with average values D(j-1/2) and Dp with D(j+1/2)
Dm=zeros(N+2,1);Dp=zeros(N+2,1); % Make the column vectors
Dm(2:N+1)=.5*(D(2:N+1)+D(1:N)); % average j and j-1
Dp(2:N+1)=.5*(D(2:N+1)+D(3:N+2)); % average j and j+1
C0=20; %
Dmu=4.541*10^-10*(10^4)^2; % um^2/s
Dt=1.135*10^-6*(10^4)^2;% um^2/s


D=Dmu;
% C=sin(pi*x/L); % Set the initial concentration distribution
C=zeros(N+2,1);
C(1)=C0;
Cmat=C;
Tmax=max(C);Tmin=min(C); % Find the maximum of T for setting plot
limits
% Choose the time step tau.
% The max tau for explicit stability is a reasonable choice
% fprintf(' Maximum explicit time step: %g \n',h^2/max(D))
% tau = input(' Enter the time step - ')
tau = 10; %timestep (s)
t=0;

check1=tau*Dmu/(h^2);
check2=tau*Dt/(h^2);
disp('\deltat*D_m/(\deltax^2)=')
disp(check1)
disp('\deltat*D_t/(\deltax^2)=')
disp(check2)
% Create the matrices A and B by loading them with zeros
A=zeros(N+2);
B=zeros(N+2);
% load A and B at interior points
const = 2*h^2 / tau*D;
% Set the number of time steps to take.
% tfinal=input(' Enter the total run time - ')
tfinal=6000;
nsteps=tfinal/tau;
for j=2:N+1
A(j,j-1)= -Dm(j);
A(j,j) = const + (Dm(j)+Dp(j));
A(j,j+1)= -Dp(j);
B(j,j-1)= Dm(j);
B(j,j) = const-(Dm(j)+Dp(j));
```

```
B(j,j+1)= Dp(j);
end
% load the boundary conditions into A and B
A(1,1)=0.5; A(1,2)=0.5; B(1,1)=0.; % T(0)=0
A(N+2,N+1)=0.5; A(N+2,N+2)=0.5; B(N+2,N+2)=0; % T(L)=0

% This is the time advance loop.
for mtime=1:nsteps
% define the time
t(mtime+1)=mtime*tau;
% find the right-hand side for the solve at interior points
r=B*C;
% apply the boundary conditions
r(1)=C0; % T(0)=0
r(N+2)=0; % T(L)=0
% do the linear solve to update T
C=A\r;
C(1)=C0;
C(length(x))=0;
% Make a plot of T every once in a while.
Cmat(:,mtime+1)=C;
if(rem(mtime,1) == 0)
plot(x,C)
axis([0 L Tmin Tmax])
pause(.001)
end

end
figure
surf(t,x,Cmat, 'EdgeColor', 'none')
xlabel('Time (s)')
ylabel('Distance (\mum)')
zlabel('Concentration (\muM)')
```

Crank Nicolson Method-2 Layers

```
clear;close all; clc;
% Set the number of grid points and build a cell-center grid
N=100; %number of x nodes
L=900; %um
Lm=100;%um
h=L/N; % step size
x=-.5*h:h:L+.5*h; %x vector
x=x'; % Turn x into a column vector.
% Load the diffusion coefficient array (a column vector)
D=ones(N+2,1); %this is NOT THE DIFFUSION COEFF
% Load Dm with average values D(j-1/2) and Dp with D(j+1/2)
Dm=zeros(N+2,1);Dp=zeros(N+2,1); % Make the column vectors
Dm(2:N+1)=.5*(D(2:N+1)+D(1:N)); % average j and j-1
Dp(2:N+1)=.5*(D(2:N+1)+D(3:N+2)); % average j and j+1
C0=10; %concentration at edge of ring (um) <NEED TO CHANGE THIS TO A
REASONABLE NUMBER
Dmu=4.541*10^-10*(10^4)^2; % um^2/s
Dt=1.135*10^-6*(10^4)^2;% um^2/s

%alternative diffusion coefficients based on my calculations
% Dmu=5.3393 e-10  ; % um^2/s low viscosity
```

```
% Dmu=1.5164e-10  ; % um^2/s high viscosity
% Dt=3.7909 e-07  ;% um^2/s

C=zeros(N+2,1);% Set the initial concentration distribution
C(1)=C0;
Cmat=C;
Tmax=max(C);Tmin=min(C); % Find the maximum of T for setting plot
limits
tau = 1000; %timestep (s)
tfinal=300000;
t=0; % set t0
jm=1;
% calculates jm, the x-node closest to the mucus/tissue barrier
while Lm>x(jm)
    jm=jm+1;
end

check1=tau*Dmu/(h^2);
check2=tau*Dt/(h^2);
disp('\deltat*D_m/(\deltax^2)=')
disp(check1)
disp('\deltat*D_t/(\deltax^2)=')
disp(check2)
%both check1 and check2 should be <0.5 to avoid spurious oscillations
in
%the solution.  change tau or N to make this happen.

% Create the matrices A and B by loading them with zeros
A=zeros(N+2);
B=zeros(N+2);
% load A and B at interior points
const1 = 2*h^2 / (tau*Dmu);
const2 = 2*h^2 / (tau*Dt);
% Set the number of time steps to take.
nsteps=tfinal/tau;

for j=2:N+1
    if j<jm
        A(j,j-1)= -Dm(j);
        A(j,j) = const1 + (Dm(j)+Dp(j));
        A(j,j+1)= -Dp(j);
        B(j,j-1)= Dm(j);
        B(j,j) = const1-(Dm(j)+Dp(j));
        B(j,j+1)= Dp(j);
        else
        A(j,j-1)= -Dm(j);
        A(j,j) = const2 + (Dm(j)+Dp(j));
        A(j,j+1)= -Dp(j);
        B(j,j-1)= Dm(j);
        B(j,j) = const2-(Dm(j)+Dp(j));
        B(j,j+1)= Dp(j);
    end
end
% load the boundary conditions into A and B
A(1,1)=0.5; A(1,2)=0.5; B(1,1)=0.; % C(0)=0, see later
A(N+2,N+1)=0.5; A(N+2,N+2)=0.5; B(N+2,N+2)=0; % C(L)=0
```

```
% time advance loop.
for mtime=1:nsteps
% define the time
t(mtime+1)=mtime*tau;
% find the right-hand side for the solve at interior points
r=B*C;
% apply the boundary conditions at each iteration
r(1)=C0; % T(0)=0
r(N+2)=0; % T(L)=0
% do the linear solve to update T
C=A\r;
C(1)=C0;
C(length(x))=0;
% Make a plot of T as code is running.
Cmat(:,mtime+1)=C;
if(rem(mtime,1) == 0)
plot(x,C)
axis([0 L Tmin Tmax])
pause(.001)
end
end

%Plots surface figure
figure
surf(t,x,Cmat, 'EdgeColor', 'none')
xlabel('Time (s)')
ylabel('Distance (\mum)')
zlabel('Concentration (\muM)')
```

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