Hydrogel Drug Delivery: Diffusion Models

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BENG 221 – Fall 2012

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Introduction

Hydrogels have proved to be an optimal biomaterial in drug delivery applications requiring controlled-release, in which a single dose of drug administered maintains a desired concentration within the blood circulation for reasonable periods of time for therapeutic efficacy. A three dimensional structure composed of chemically and physically cross-linked polymer chains, hydrogels are often characterized with good water imbibing abilities that allow the polymer structure to swell extensively by absorbing biological fluids ten to twenty times their molecular weight [1]. The cross-linkage renders the gel insoluble in water through ionic interactions and hydrogen bonding. Also, the hydrogel mimics biological tissues relatively well, inducing minimal immune-responses from hosts and thus demonstrating an excellent biocompatibility. Porous in structure, drugs can be concentrated or trapped within the polymer and released through diffusion mechanisms based on zero-order kinetics. The inherent properties of the hydrogel, drug-polymer interactions, amount of entrapped drug, and drug solubility determine the diffusion kinetics, duration, and rate of solute release from the hydrogel [2].

Figure 1. Various forms of hydrogel base on the materials that are mixed with water [3].

Various types of hydrogels can be engineered with addition of specific functional moieties and material-based manipulations such that their drug release, swelling behaviors, and mechanical characteristics can be altered in response to changes in temperature, pH, and glucose level in the external environment. Drugs enclosed or immersed within a hydrogel can represent various controlled-delivery systems, such as diffusion-, swelling-, chemically- and environmentally controlled systems [4]. This project will focus on the solute release characteristics of diffusion- and swelling-based systems.

The diffusion-controlled system consists of reservoir and matrix systems. A reservoir delivery system comprises a drug core entrapped in a spherical, cylindrical, and slab-like-shaped reservoir, which is in turn encapsulated within a hydrogel membrane. In order to ensure drug delivery at a constant rate, the drug can be concentrated in the center of the device such that the

concentration gradient across the membrane is maintained zero. The matrix system features a drug dispersed uniformly throughout the entire hydrogel lying within another bigger polymer structure, rather than isolated and encapsulated within a separate reservoir in the center. These hydrogel matrix tablets are constructed through compression of the drug and polymer powder mixture. Drug permeates the macromolecular mesh or water filled pores into the exterior of the hydrogel and blood stream. In case of swelling-controlled systems, the drug is initially dispersed throughout the non-crystalline, glassy polymer containing the hydrogel. Upon contact with water or some biofluid, the polymer starts to swell and its glass transition temperature is lowered such that its brittle property is shifted towards assuming a more flexible, elastic property with relaxation of molecular chains, which then allows for drug diffusion out of the rubbery boundary of the polymer. In many cases, a combination of both diffusion and swelling-mediated drug releases occurs [5].

Modeling Assumptions

Drug diffusion in a swelling hydrogel

Let the drug concentration within the polymer equal $c = c(x, y, z, t)$, at any time in three dimensional domains. The drug can diffuse out of the domains at the boundaries which may swell or grow as fluids are absorbed. The general advection-diffusion equation for a growing domain [6] is

$$\frac{\partial c}{\partial t} = D\nabla^2 c - \nabla(c\mathbf{u}). \quad (1)$$

We consider drug diffusing out of the domain in only one dimension, so the velocity of drug is $\mathbf{u} = u\mathbf{i}$, and the diffusion equation will be

$$\frac{\partial c}{\partial t} = D\frac{\partial^2 c}{\partial x^2} - c\frac{\partial u}{\partial x} - \frac{\partial c}{\partial x}u$$

where $\frac{\partial c}{\partial t} = D\frac{\partial^2 c}{\partial x^2}$: homogeneous diffusion equation

$-c\frac{\partial u}{\partial x}$: the hydrogel is swollen, so the local volume change

$-\frac{\partial c}{\partial x}u$: the local concentration dilutes.

The initial and boundary conditions

In the beginning, the drug concentration is assumed to be constant everywhere inside the hydrogel with dimension, 0 < x < X(0). For t > 0, hydrogel is swollen with the outside fluid. Its boundary will grow at one side x = X(t) = Lf(t), where L is the original length of hydrogel, and f(t) is a growing function over time (f(t) > 1). In this boundary, the concentration is assumed to be zero all the time. We can express the problem with its initial and boundary conditions as:

$$\frac{\partial c}{\partial t} = D\frac{\partial^2 c}{\partial x^2} - \frac{\partial c}{\partial x}u - c\frac{\partial u}{\partial x} \qquad ,0 < x < X(t),\ t > 0 \tag{2}$$

with

$$\begin{aligned} &c(x,0) = 1 && ,0 < x < X(0) \\ &X(0) = L \\ &\frac{\partial c}{\partial x}(0,t) = 0 && ,t > 0 \\ &c(X(t),t) = 0 \end{aligned} \tag{3}$$

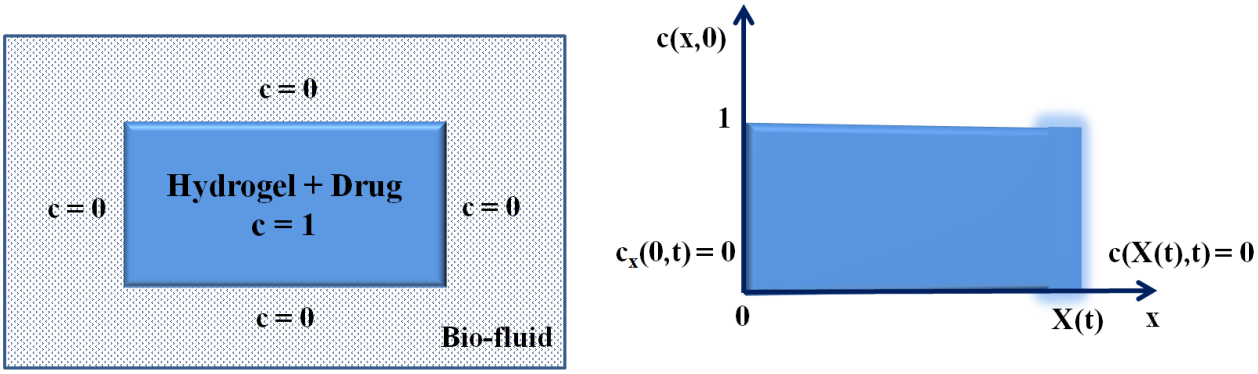

Figure 2. The mixed solution between hydrogel and drug is surrounded by bio-fluid. Left figure shows hydrogel system at t=0. Right figure shows the system when t > 0, on the right edge of hydrogel growing as a function of time.

Growing boundary

We consider the growth of boundary as uniform growth velocity $u(x,t)$ in $0 \le x \le X(t)$. At t = 0, the left edge of the boundary (x = 0) is not moving, so the velocity $u(0,0) = 0$ is zero; on the right edge, the velocity is $u(X(0),0) = \dot{X}(0) \neq 0$ where *X(0)* = L, the length at the beginning.

At time t > 0, the velocity of the left edge is still the same $u(0,t)=0$; on the right edge, the boundary grows over time. Since *X(t)* is the growing length of hydrogel on the right edge, the growing velocity of the edge can be written as $u(X(t),t)=\frac{dX(t)}{dt}=\dot{X}(t)$. From this relation between the growing edge velocity and length, the gradient of velocity can be rewritten in terms of moving length as shown below.

$$u(X(t),t)=u(0,t)=\int_0^{X(t)}\frac{\partial u}{\partial x}dx=\frac{dX(t)}{dt}$$

If velocity gradient is independent of x,

$$\frac{\partial u}{\partial x}\int_0^{X(t)}dx=\dot{X}(t)\quad\rightarrow\quad X(t)\frac{\partial u}{\partial x}=\dot{X}(t),$$

therefore the velocity as a function of *X(t)* is

$$\frac{\partial u}{\partial x}=\frac{\dot{X}(t)}{X(t)}\quad\rightarrow\quad u(x,t)=\frac{\dot{X}(t)}{X(t)}x. \tag{4}$$

Now, the growing edge velocity can be written in terms of growing edge length as shown in Equation (4). We can correlate the growth of the system with the function X(t) (see [7]). In this work, we study two types of growth function.

1. The growth function increases over time. In this case, the domain expands to infinite volume as time increase such that
   - Linear growth

$$X(t)=L(1+rt) \tag{5}$$

   - Exponential growth

$$X(t)=Le^{rt} \tag{6}$$

2. The growth function increases up to a finite volume and remains the same size as time increase i.e.
   - Logistic growth

$$X(t)=\frac{Le^{rt}}{1+(1/m)(e^{rt}-1)} \tag{7}$$

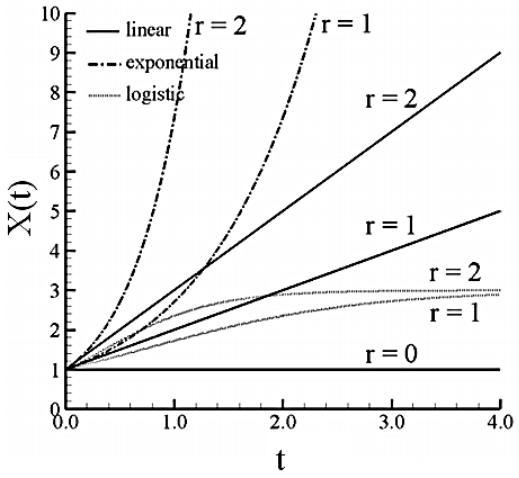

Figure 3. Growth function: linear, exponential, and logistic growth [5].

Advection-diffusion equation and analytical solution

The advection-diffusion equation in Equation (2) can be rewritten by substituting the expression defined in Equation (4) as

$$\frac{\partial c}{\partial t} = D\frac{\partial^2 c}{\partial x^2} - \left(\frac{\dot{X}}{X}x\right)\frac{\partial c}{\partial x} - \frac{\dot{X}}{X}c \qquad \text{in} \quad 0 < x < X(t),\ \mathrm{t} > 0 \tag{8}$$

with the initial and boundary conditions:

$$\begin{aligned} &c(x,0) = 1 && ,0 < x < X(0) \\ &X(0) = L \\ &\frac{\partial c}{\partial x}(0,t) = 0 && ,\mathrm{t} > 0 \\ &c\left(X(t),t\right) = 0 \end{aligned} \tag{9}$$

Landau transformation

Two difficulties with analytically solving Equation (8) are the presence of an advection term, $\left(\frac{\dot{X}}{X}x\right)\frac{\partial c}{\partial x}$, and the moving boundary of hydrogel, *X(t)*, whose behavior is described by Equations (5)-(7). With these difficulties, Landau transformation [8] is used to simplify the problem. This transformation is defined by

$$\zeta = \frac{x}{X(t)}, \text{ and } \tau = t. \tag{10}$$

If any phase extends from x = 0 to x = X(t), then ζ in the above form is used to fix the extent of that phase to the new domain $0 \le \zeta \le 1$.

Therefore the new diffusion equation becomes easier to solve analytically (see Appendix A)

$$\frac{\partial c}{\partial \tau} = \frac{D}{X^2}\frac{\partial^2 c}{\partial \zeta^2} - \frac{\dot{X}}{X}\frac{\partial c}{\partial \zeta} \qquad \text{in } 0 < \zeta < 1, \quad \tau > 0 \tag{11}$$

with the new initial and boundary conditions:

$$\begin{aligned} & c(\zeta, 0) = 1 && ,0 < \zeta < 1 \\ & \frac{\partial c}{\partial x}(0, \tau) = 0 && ,\tau > 0 \\ & c(1, \tau) = 0 \end{aligned} \tag{12}$$

Analytic solution of advection-diffusion equation

The concentration of drug released from the swelling hydrogel can be defined as a function of Landau variables by using the technique of variable separation (see Appendix A):

$$c(\zeta, \tau) = \frac{4}{\pi}\sum_{n=0}^{\infty}\frac{(-1)^n}{(2n+1)}\frac{L}{X(\tau)}\cos\left(\left(\frac{2n+1}{2}\right)\pi\zeta\right)e^{-D\left(\frac{(2n+1)\pi}{2}\right)^2\int_{t=0}^{\tau}X^{-2}dt} \tag{13}$$

This solution is a drug concentration in terms of Landau variables ξ and τ. It can be transformed back to the original variables by using the relations in Equation (10), so the solution of this problem is:

$$c(x, t) = \frac{4}{\pi}\sum_{n=0}^{\infty}\frac{(-1)^n}{(2n+1)}\frac{L}{X(t)}\cos\left(\frac{(2n+1)\pi x}{2X(t)}\right)e^{-D\left(\frac{(2n+1)\pi}{2}\right)^2\int_{t=0}^{t}X(t')^{-2}dt} \tag{14}$$

The above solution can be used to explain how drug concentration changes with respect to time and spatial variation in one dimension, as the drug is released from the hydrogel expanding with a moving boundary. This expansion can be described by the function X(t), based on three different growth models: linear, exponential , and logistic growth (Equations (5)-(7)).

Numerical Analysis

Parameter settings:

L = 1cm
D = 1 µmol cm^{-2} s^{-1}
Co = 1 µmol
Number of terms in series: 20

Analytical Solution

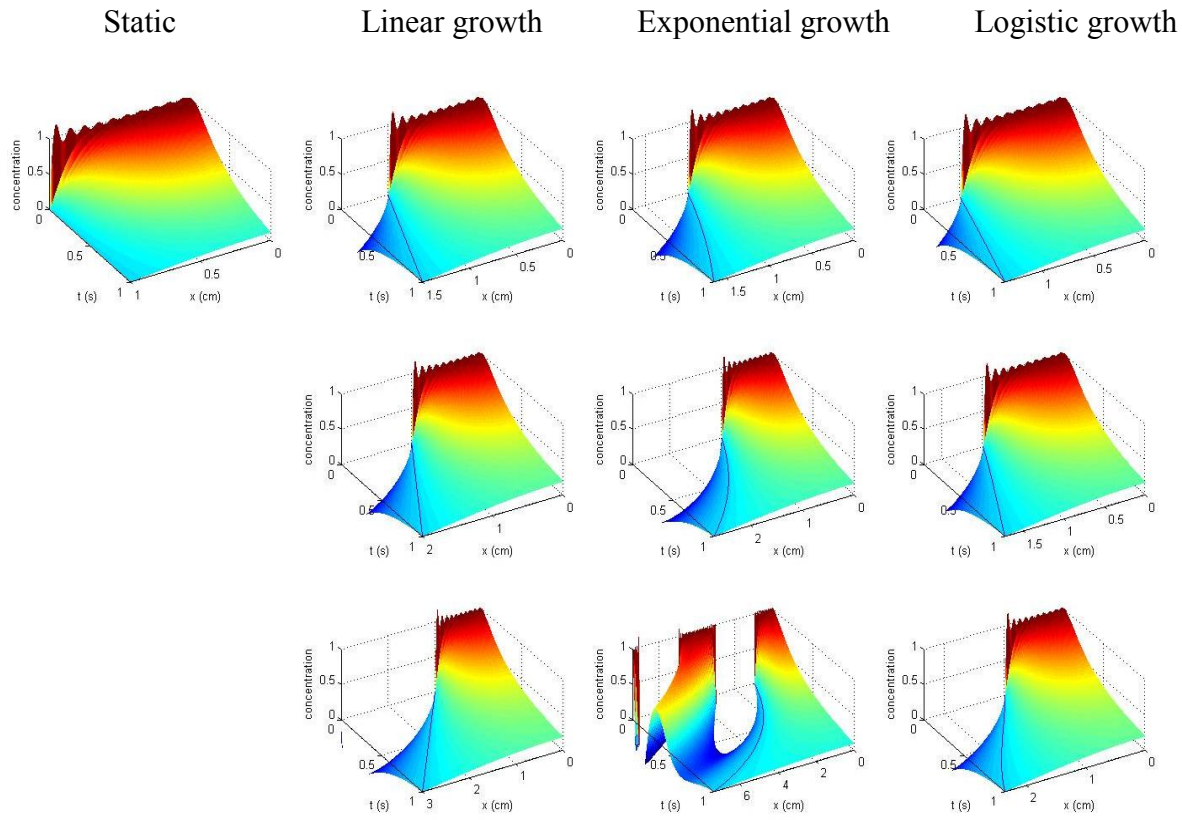

Figure 4. Surface plot of drug concentration based on analytical solution. The boundary X(t) is shown in blue line. Note that the gradient outside of 0 to X(t) is not part of the solution.

The processes of drug diffusion and hydrogel expansion are shown in these plots. Drug concentration within the hydrogel decreases with time, and the hydrogel boundary grows farther away from the original length. Among three types of the growth model simulated, the exponential model shows an increase in growing velocity as time increases, but the logistic growth tends to slow down and approaches its limit gradually. The fluctuation in the initial concentration profile is due to the number of terms in the solution series being finite.

Finite Difference Method

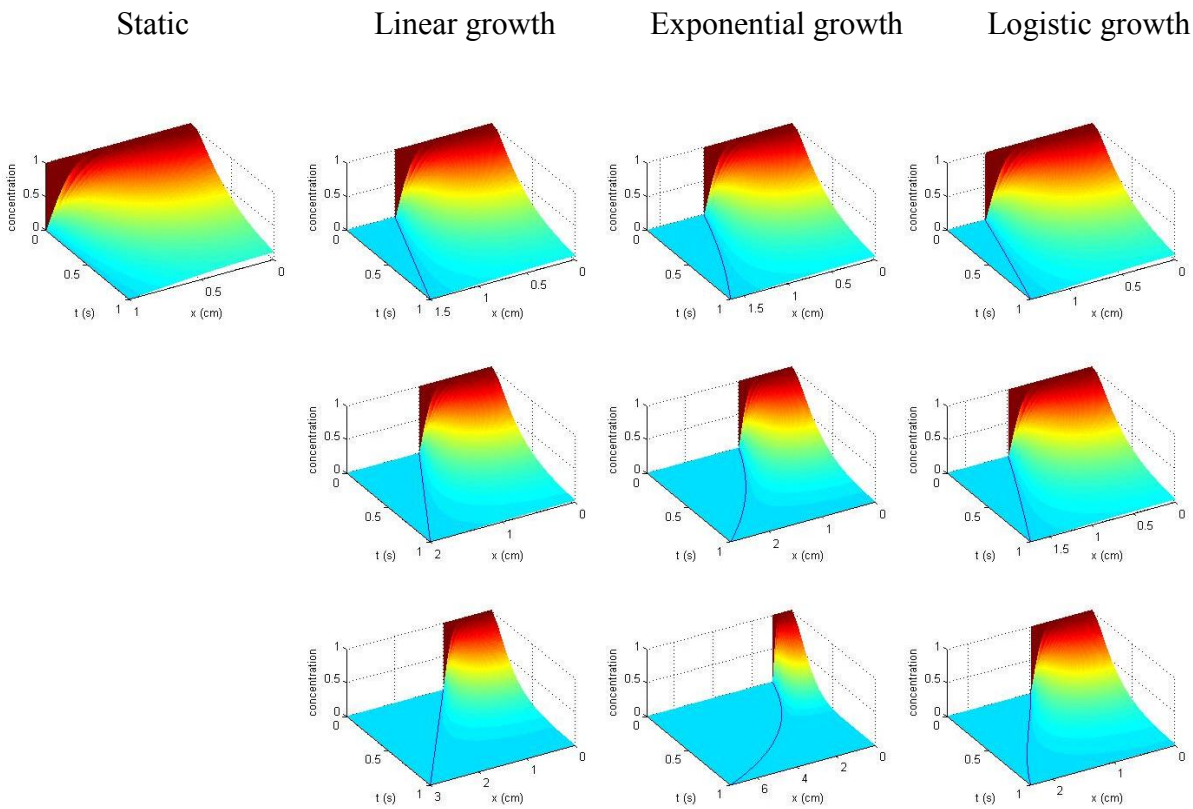

Figure 5. Surface plot of drug concentration using finite difference method.

MATLAB pdepe

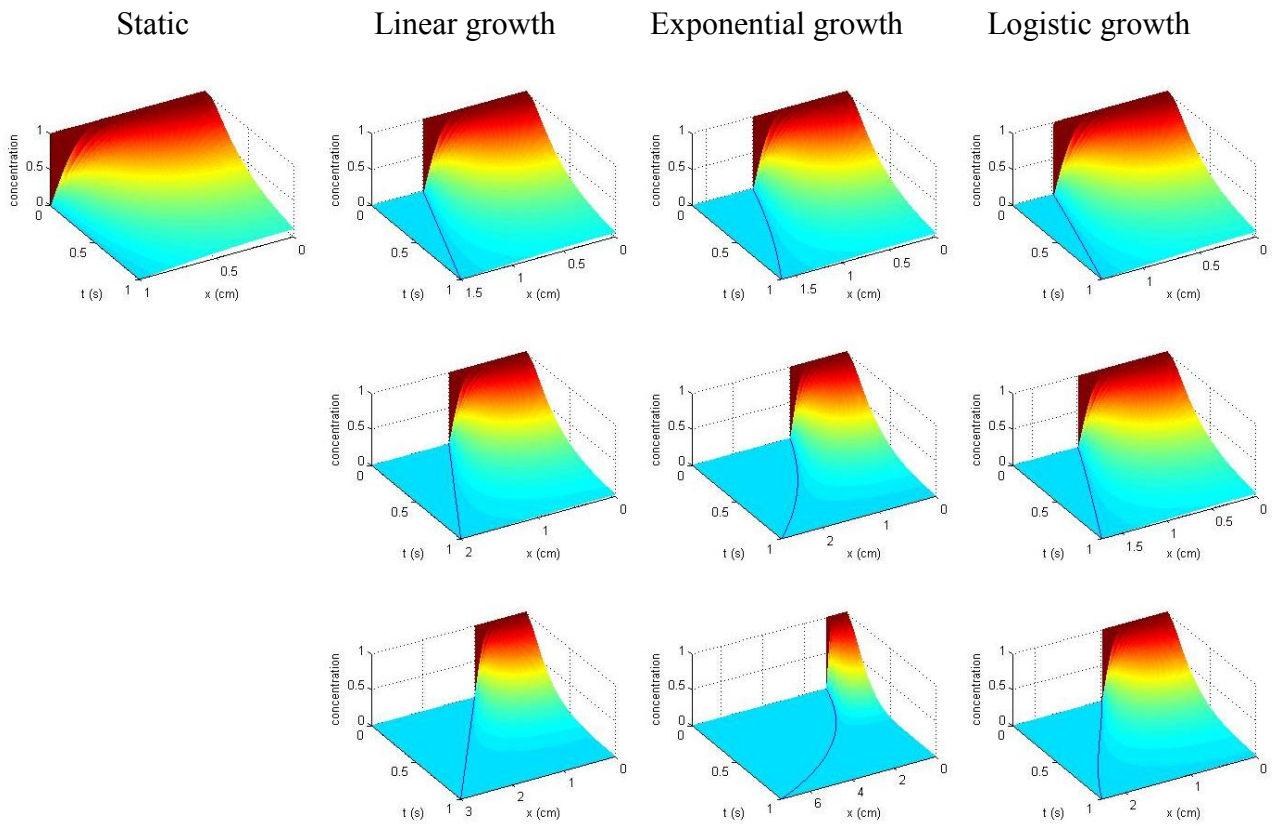

Figure 6 Surface plot of drug concentration using MATLAB pdepe.

Comparison of Concentration Profiles in Different Types of Growth

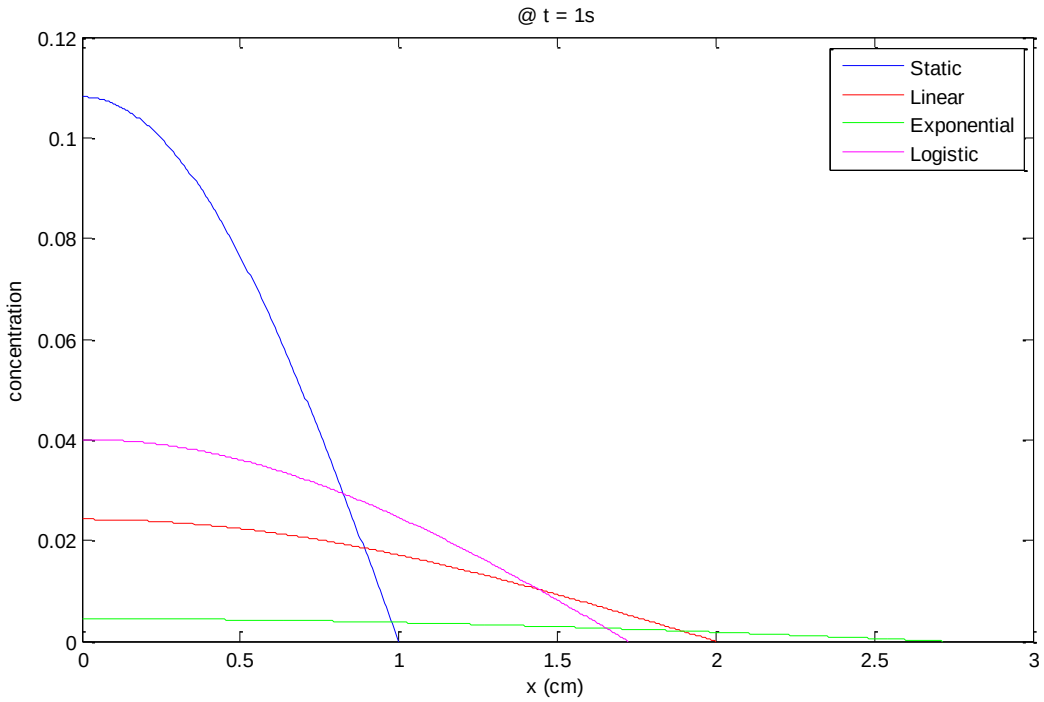

Figure 7. Concentration profile simulated with different growth models at t = 1 second. The static boundary condition results in highest concentration initially since drug can only diffuse within a static range. The dynamic boundary simulated with the exponential growth model results in lowest concentration consistently along the spatial domain, as the extent of hydrogel expansion is largest (with the largest stretch in the moving boundary, close to "x=3cm") for the exponentially growing case.

Conclusion and Future work

Limitation and future work

The hydrogel swelling should be technically modeled with respect to all three dimensions to approximate its behavior in reality most accurately, even though the growth models presented in this report are sufficient enough to demonstrate how much the hydrogel swells one dimensionally. In order to simulate the hydrogel expansion in 3-D, the MCell software was used to show drug diffusion stochastically.

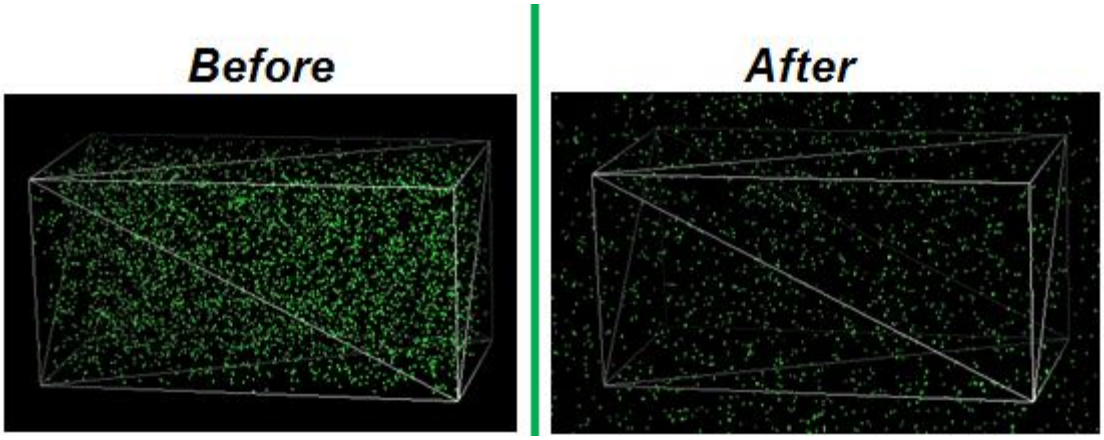

Figure 8 MCell simulation for drug diffusion analysis in 3-D

Figure 8 shows the results of MCell simulation for drug diffusion in all three dimensions, where white box represents hydrogel and green particles represent drug. Initially, all drugs are entrapped within the hydrogel and none is present on its outside. With the lapse of time, drugs gradually diffuse out of the box and become absorbed into the external biofluid or bloodstream represented by the black space. However, the size of box could not be expanded to take dynamic boundary conditions into account due to inherent limitations in the software. Therefore, the result obtained this way may not fully grasp the behavior of three-dimensional drug release in reality.

Conclusion

In this report, we showed one-dimensional diffusion behavior of drug released from the hydrogel with static and dynamic boundaries, respectively. Even though the static boundary case is somewhat straightforward, dynamic boundary conditions are not easy to be dealt with. In order to solve this problem, we used the Landau transformation which enables the fixation of moving boundaries using variables ζ and τ, instead of x and t. With this transformation, we were able to show the full analytical solution for both static and dynamic boundary cases. But provided that the variables x and t are our actual variables of interest, the inverse transformation was applied to the result. To compare our analytical results with those of numerical simulations, the MATLAB software was used. Also, the linear interpolation method was employed to obtain numerical solution, which makes it possible to approximate the value between two real values. Based on this linear interpolation scheme, two numerical solutions can be obtained: finite difference and

pdepde. These results are highly similar to those of our analytical solution, with some minor inevitable discrepancies that can be adequately explained. Finally, the MCell simulation results were shown that approximate three dimensional diffusion of drug from the hydrogel with the static boundary conditions only.

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Appendix A: Analytical solution

Landau Transformation

The advection-diffusion equation is transformed with the use of new Landau variables in Equation (10). By using chain rule, we rewrite Equation (8) in terms of variables ζ and τ.

$$\frac{\partial c}{\partial t}=\frac{\partial c}{\partial \zeta}\frac{\partial \zeta}{\partial t}+\frac{\partial c}{\partial \tau}\frac{\partial \tau}{\partial t}=-\frac{x}{X^2}\frac{\partial c}{\partial \zeta}+\frac{\partial c}{\partial \tau}=-\zeta\frac{\dot{X}}{X^2}\frac{\partial c}{\partial \zeta}+\frac{\partial c}{\partial \tau}$$

$$\frac{\partial^2 c}{\partial x^2}=\frac{\partial}{\partial x}\left(\frac{\partial c}{\partial x}\right)=\frac{\partial}{\partial \zeta}\frac{\partial \zeta}{\partial x}\left(\frac{\partial c}{\partial \zeta}\frac{\partial \zeta}{\partial x}\right)=\frac{1}{X}\frac{\partial}{\partial \zeta}\left(\frac{\partial c}{\partial \zeta}\frac{1}{X}\right)=\frac{1}{X^2}\frac{\partial^2 c}{\partial \zeta^2}$$

$$\frac{\partial c}{\partial x}=\frac{\partial c}{\partial \zeta}\frac{\partial \zeta}{\partial x}=\frac{1}{X}\frac{\partial c}{\partial \zeta}$$

The new domain is

$$x:0\to X(t),\quad \zeta:0\to 1\ \text{, and}\quad t:0\to t,\quad \tau:0\to\tau$$

Substituting the expressions above into Equation (8), the identical advection terms on both sides can cancel each other out, as in:

$$-\zeta\frac{\dot{X}}{X^2}\frac{\partial c}{\partial \zeta}+\frac{\partial c}{\partial \tau}=\frac{D}{X^2}\frac{\partial^2 c}{\partial \zeta^2}-\zeta\frac{\dot{X}}{X}\frac{\partial c}{\partial \zeta}-\frac{\dot{X}}{X}\frac{\partial c}{\partial \zeta}$$

Therefore the new diffusion equation becomes easier to solve analytically

$$\frac{\partial c}{\partial \tau}=\frac{D}{X^2}\frac{\partial^2 c}{\partial \zeta^2}-\frac{\dot{X}}{X}\frac{\partial c}{\partial \zeta}\qquad \text{in } 0<\zeta<1,\quad \tau>0 \tag{A1}$$

Analytical solution for c(ζ,τ) by separation of variables

In the previous section we simplified Equation (8) down to (11) by using Landau transformation. In this section, we solve Equation (11) analytically to find the concentration of drug as it is released from the hydrogel, by using the separation of variables technique where A(ζ) represents space dependence as a function of new positional variable as shown in Equation (10), and B(τ) represents time dependence.

Separation of variable:

$$c(\zeta,\tau) = A(\zeta)B(\tau) \tag{A2}$$

Substituting it into Equation (11):

$$A(\zeta)\frac{\partial B(\tau)}{\partial \tau} = \frac{D}{\left(X(\tau)\right)^2}B(\tau)\frac{\partial^2 A(\zeta)}{\partial \zeta^2} - \frac{1}{X(\tau)}\frac{dX(\tau)}{d\tau}A(\zeta)B(\tau).$$

Using the abbreviated form, the above equation can be reduced to:

$$A\dot{B} = \frac{D}{X^2}BA'' - \frac{\dot{X}}{X}AB$$

Dividing both sides by AB:

$$\frac{\dot{B}}{B} = \frac{D}{X^2}\frac{A''}{A} - \frac{\dot{X}}{X}$$

Rearranging to get all time dependent functions on the left and space dependent functions on the right-hand side, the expressions on both sides equal a negative constant:

$$\frac{X^2}{D}\frac{\dot{B}}{B} + \frac{X\dot{X}}{D} = \frac{A''}{A} = -\lambda^2$$

The partial differential equation in (11) can then be reduced into two ordinary differential equations:

$$\dot{B} + \left(\frac{\dot{X}}{X} + \frac{\lambda^2 D}{X^2}\right)B = 0 \text{ , and } \quad A'' + \lambda^2 A = 0$$

The solution for A(ζ)

In terms of space dependence:

$$A'' + \lambda^2 A = 0$$

with boundary conditions: A(0) = 0, and A(1) = 0.

The solution can be written in terms of cosine and sine functions:

$$A(\zeta) = a_1 \cos\lambda\zeta + a_2 \sin\lambda\zeta$$

From the boundary conditions, we can calculate a_1 and a_2:

$$A'(\zeta) = -a_1\lambda\sin\lambda\zeta + a_2\lambda\cos\lambda\zeta \quad \rightarrow \quad A'(\zeta = 0) = a_2 = 0$$

$$A(\zeta) = a_1 \cos\lambda\zeta + a_2 \sin\lambda\zeta \quad \rightarrow \quad A(\zeta = 1) = a_1 \cos\lambda = 0$$

In order to avoid obtaining a trivial solution, the coefficient a_2 cannot be made to equal zero but rather cosλ is set equal to zero such that

$$\lambda = \left(n + \frac{1}{2}\right)\pi = \left(\frac{2n+1}{2}\right)\pi, \quad n = 0,1,2,\ldots .$$

Therefore, the solution for A is:

$$A_n(\zeta) = a_n \cos\frac{(2n+1)\pi\zeta}{2}, \quad \text{n} = 0,1,2,\ldots . \tag{A3}$$

The solution for B(τ)

In terms of time dependence:

$$\dot{B} + \left(\frac{\dot{X}}{X} + \frac{\lambda^2 D}{X^2}\right) B = 0$$

Since this is the first order ODE, we can find the solution B(τ) by simple integration. In order to do so, we have to rearrange the equation by separating B from time dependence terms:

$$\frac{1}{B}\dot{B} = -\left(\frac{\dot{X}}{X} + \frac{\lambda^2 D}{X^2}\right)$$

Integration with respect to B and τ yields:

$$\int_{B(0)}^{B(\tau)} \frac{1}{B} dB = -\int_{t=0}^{\tau} \left(\frac{\dot{X}}{X} + \frac{\lambda^2 D}{X^2}\right) dt$$

Rearranging the terms and solving the integral:

$$\int_{B(0)}^{B(\tau)} \frac{1}{B} dB = -\int_{t=0}^{\tau} \left(\frac{\dot{X}}{X} + \frac{\lambda^2 D}{X^2}\right) dt$$

$$\ln B(\tau) = -\int_{t=0}^{\tau} \frac{1}{X}\frac{dX}{dt} dt - \int_{t=0}^{\tau} \frac{\lambda^2 D}{X^2} dt + \ln C$$

$$\ln B(\tau) = -\ln X(\tau) + \ln X(0) - \lambda^2 D \int_{t=0}^{\tau} X^{-2} dt + \ln C$$

$$\ln\left(\frac{B(\tau)X(\tau)}{CL}\right) = -\lambda^2 D\int_{t=0}^{\tau} X^{-2}dt$$

The solution becomes:

$$B(\tau) = \frac{CL}{X(\tau)}e^{-\lambda^2 D\int_{t=0}^{\tau} X^{-2}dt} \tag{A4}$$

The general solution for Equation (11) can be calculated by multiplying A in (A3) and B in (A4) together, expressed as a superposition of the spatial and temporal dependent functions as

$$c(\zeta,\tau) = \sum_{n=0}^{\infty}\frac{C_n L}{X(\tau)}\cos\left(\left(\frac{2n+1}{2}\right)\pi\zeta\right)e^{-D\left(\frac{(2n+1)\pi}{2}\right)^2\int_{t=0}^{\tau} X^{-2}dt} \tag{A5}$$

We can calculate C_n based on the initial condition, which states that drug concentration is constant everywhere inside the hydrogel at time t = 0, c(ξ,0) = 0:

$$c(\zeta,0) = 1 = \sum_{n=0}^{\infty}\frac{C_n L}{X(0)}\cos\left(\left(\frac{2n+1}{2}\right)\pi\zeta\right) = \sum_{n=0}^{\infty} C_n\cos\left(\left(\frac{2n+1}{2}\right)\pi\zeta\right)$$

From orthogonality relationship of cosine, C_n is calculated as an integral below where L = 1:

$$C_n = \frac{2}{L}\int_0^L \cos\left(\left(\frac{2n+1}{2}\right)\pi\zeta\right)d\zeta$$

$$C_n = 2\frac{2}{(2n+1)\pi}\sin\left(\left(\frac{2n+1}{2}\right)\pi\zeta\right)_0^1$$

$$C_n == \frac{4(-1)^n}{(2n+1)\pi}$$

Therefore, the solution in Equation (A5) with substitution of the C_n term becomes:

$$c(\zeta,\tau) = \frac{4}{\pi}\sum_{n=0}^{\infty}\frac{(-1)^n}{(2n+1)}\frac{L}{X(\tau)}\cos\left(\left(\frac{2n+1}{2}\right)\pi\zeta\right)e^{-D\left(\frac{(2n+1)\pi}{2}\right)^2\int_{t=0}^{\tau} X^{-2}dt} \tag{A6}$$

This solution is a drug concentration in terms of Landau variables ξ and τ. It can be inverse-transformed to be written in terms of the original variables x and t, by using the relations defined in Equation (10). So the full analytical solution of this problem becomes:

$$c(x,t)=\frac{4}{\pi}\sum_{n=0}^{\infty}\frac{(-1)^n}{(2n+1)}\frac{L}{X(t)}\cos\left(\frac{(2n+1)\pi x}{2X(t)}\right)e^{-D\left(\frac{(2n+1)\pi}{2}\right)^2\int_{t=0}^{t}X(t')^{-2}dt} \quad \text{(A7)}$$

Appendix B: Matlab Code

```
function hydrogel(sim_type)
growth_type = [0 1 2 3];
growth_rate = [0.5 1 2];
simulation_time = [1];
for i = 1:length(growth_type)
    for j = 1:length(growth_rate)
        subplot(3,4,i+length(growth_type)*(j-1));
        if(sim_type==3)
            hydrogel_p(growth_type(i),growth_rate(j),simulation_time);
        elseif(sim_type==2)

hydrogel_fd_dynamic(growth_type(i),growth_rate(j),simulation_time);
        else

hydrogel_analytical(growth_type(i),growth_rate(j),simulation_time);
        end
    end
end

%---profile extraction
sim_type = 3;
growth_type = [0 1 2 3];
growth_rate = [1];
simulation_time = [1];

for i = 1:length(growth_type)
    for j = 1:length(growth_rate)
        subplot(3,4,i+length(growth_type)*(j-1));
        if(sim_type==3)
            [x3(i,j).x,t3(i,j).t,c3(i,j).c] =
hydrogel_p(growth_type(i),growth_rate(j),simulation_time);
        elseif(sim_type==2)
            [x2(i,j).x,t2(i,j).t,c2(i,j).c] =
hydrogel_fd_dynamic(growth_type(i),growth_rate(j),simulation_time);
        else
            [x1(i,j).x,t1(i,j).t,c1(i,j).c] =
hydrogel_analytical(growth_type(i),growth_rate(j),simulation_time);
        end
    end
end

% subplot(1,4,1);
i=1;j=1;
profile = c3(i,j).c((t3(i,j).t==1),:);
```

```
plot(x3(i,j).x,profile,'b');xlabel('x (cm)');ylabel('concentration');title('@
t = 1s');xlim([0,3]);ylim([0,0.12]);hold on;
% subplot(1,4,2);
i=2;j=1;
profile = c3(i,j).c((t3(i,j).t==1),:);
plot(x3(i,j).x,profile,'r');xlabel('x (cm)');ylabel('concentration');title('@
t = 1s');xlim([0,3]);ylim([0,0.12]);
% subplot(1,4,3);
i=3;j=1;
profile = c3(i,j).c((t3(i,j).t==1),:);
plot(x3(i,j).x,profile,'g');xlabel('x (cm)');ylabel('concentration');title('@
t = 1s');xlim([0,3]);ylim([0,0.12]);
% subplot(1,4,4);
i=4;j=1;
profile = c3(i,j).c((t3(i,j).t==1),:);
plot(x3(i,j).x,profile,'m');xlabel('x (cm)');ylabel('concentration');title('@
t = 1s');xlim([0,3]);ylim([0,0.12]);
legend('Static','Linear','Exponential','Logistic');

function [x,t,anal_sol] =
hydrogel_analytical(growth_type,growth_rate,simulation_time)
L = 1;
D = 1;
r = growth_rate;
m = 3;

if (growth_type == 3)
    Xt = @(t) L*exp(r*t) ./ (1+(1/m)*(exp(r*t)-1)); % Logistic growth
    dX = @(t) L*r*exp(r*t)*(1-1/m) ./ (1+(1/m)*(exp(r*t)-1))^2;
    integral_term = @(t) ((1-exp(-2*r*t))*(m-1)^2+4*(m-1)*(1-exp(-
r*t))+2*r*t)/2/r/m^2/L^2;
elseif (growth_type == 2)
    Xt = @(t) L*exp(r*t); % Exponential growth
    dX = @(t) L*r*exp(r*t);
    integral_term = @(t) (1-exp(-2*r*t))/2/r/L^2;
elseif (growth_type == 1)
    Xt = @(t) L*(1+r*t); % Linear growth
    dX = @(t) L*r;
    integral_term = @(t) t/L^2./(1+r*t);
else
    Xt = @(t) L; % Static
    dX = @(t) 0;
    integral_term = @(t) t/L^2;
end

dynamic_xmax = Xt(simulation_time);
dt = 0.01 * simulation_time;
dx = 0.005 * dynamic_xmax;
t = 0:dt:simulation_time;
x = 0:dx:dynamic_xmax;
[X,T] = meshgrid(x,t);

k = @(n) (2*n+1)*pi/2;
c = @(x,t,n) (4/pi) * (L*(-1)^n)/(2*n+1)./Xt(t) .* cos(k(n)*x ./ Xt(t)) .*
exp(-D*integral_term(t)*(k(n))^2);
anal_sol = zeros(size(X));
```

```
for i = 1:20
    n = i-1;
    anal_sol = anal_sol + c(X,T,n);
end

surf(x,t,anal_sol,'LineStyle','none');hold on;
line(Xt(t),t,'Color','b');
xlabel('x (cm)');xlim([0 dynamic_xmax]);
ylabel('t (s)');ylim([0 simulation_time]);
zlabel('concentration');zlim([0 1]);
view(150,50);
caxis([-0.5 1]);

function [dynamic_x,tmesh,fd_dynamic] =
hydrogel_fd_dynamic(growth_type,growth_rate,simulation_time)

L = 1;
D = 1;
r = growth_rate;
m = 3;

simulation_x = L;
dt = 0.00025 * simulation_time;
dx = 0.025 * simulation_x;
tmesh = 0:dt:simulation_time;
xmesh = 0:dx:simulation_x;
nx = length(xmesh);
nt = length(tmesh);
sol_fd = zeros(nt,nx);
sol_fd(1,:) = ones(1,nx);
sol_fd(:,nx) = 0;
update_const = D*dt/dx^2;
for t = 1:nt-1
    for x = 1
        sol_fd(t+1,1) = sol_fd(t,2);
    end
    for x = 2:nx-1
        sol_fd(t+1,x) = sol_fd(t,x) + ...
            update_const*(sol_fd(t,x+1)+sol_fd(t,x-1)-2*sol_fd(t,x)) -...
            (r*dt/(1+r*t))*(sol_fd(t,x)+(x/2/dx)*(sol_fd(t,x+1)-sol_fd(t,x-
1)));
    end
end

if (growth_type == 3)
    Xt = @(t) L*exp(r*t) ./ (1+(1/m)*(exp(r*t)-1)); % Logistic growth
    dX = @(t) L*r*exp(r*t)*(1-1/m) ./ (1+(1/m)*(exp(r*t)-1))^2;
elseif (growth_type == 2)
    Xt = @(t) L*exp(r*t); % Exponential growth
    dX = @(t) L*r*exp(r*t);
elseif (growth_type == 1)
    Xt = @(t) L*(1+r*t); % Linear growth
    dX = @(t) L*r;
else
    Xt = @(t) L; % Static
    dX = @(t) 0;
```

```
end
dynamic_xmax = Xt(simulation_time);
dynamic_x = 0:dx:dynamic_xmax;
fd_dynamic = zeros(length(tmesh),length(dynamic_x));
for j = 1:length(tmesh);
    interp_t = tmesh(j);
    x_max = Xt(interp_t);
    interp_x = linspace(0,simulation_x,floor(x_max/dx)+1);
    interp_sol = interp1(xmesh,sol_fd(j,:),interp_x);
    fd_dynamic(j,1:length(interp_sol)) = interp_sol;
    clear interp_sol;
end

surf(dynamic_x,tmesh,fd_dynamic,'LineStyle','none');hold on;
line(Xt(tmesh),tmesh,'Color','b');
xlabel('x (cm)');xlim([0 dynamic_xmax]);
ylabel('t (s)');ylim([0 simulation_time]);
zlabel('concentration');zlim([0 1]);
view(150,50);
caxis([-0.5 1]);

function [dynamic_x,t,pde_dynamic] =
hydrogel_p(gt,growth_rate,simulation_time)
global L D r m growth_type;
L = 1;
D = 1;
r = growth_rate;
m = 3;
growth_type = gt;
simulation_x = L;
dt = 0.01 * simulation_time;
dx = 0.005 * simulation_x;
t = 0:dt:simulation_time;
x = 0:dx:simulation_x;

if (growth_type == 3)
    Xt = @(t) L*exp(r*t) ./ (1+(1/m)*(exp(r*t)-1)); % Logistic growth
    dX = @(t) L*r*exp(r*t)*(1-1/m) ./ (1+(1/m)*(exp(r*t)-1))^2;
elseif (growth_type == 2)
    Xt = @(t) L*exp(r*t); % Exponential growth
    dX = @(t) L*r*exp(r*t);
elseif (growth_type == 1)
    Xt = @(t) L*(1+r*t); % Linear growth
    dX = @(t) L*r;
else
    Xt = @(t) L; % Static
    dX = @(t) 0;
end

pde_sol = pdepe(0,@hydrogel_pde,@hydrogel_ic,@hydrogel_bc,x,t);
dynamic_xmax = Xt(simulation_time);
dynamic_x = 0:dx:dynamic_xmax;
pde_dynamic = zeros(size(pde_sol,1),length(dynamic_x));

for j = 1:length(t);
    interp_t = t(j);
```

```
    x_max = Xt(interp_t);
    interp_x = linspace(0,simulation_x,floor(x_max/dx)+1);
    interp_sol = interp1(x,pde_sol(j,:),interp_x);
    pde_dynamic(j,1:length(interp_sol)) = interp_sol;
    clear interp_sol;
end
surf(dynamic_x,t,pde_dynamic,'LineStyle','none');hold on;
line(Xt(t),t,'Color','b');
xlabel('x (cm)');xlim([0 dynamic_xmax]);
ylabel('t (s)');ylim([0 simulation_time]);
zlabel('concentration');zlim([0 1]);
view(150,50);
caxis([-0.5 1]);

%--------------------------------
function [c,f,s] = hydrogel_pde(x,t,u,DuDx)
global L D r m growth_type;
if (growth_type == 3)
    Xt = @(t) L*exp(r*t) ./ (1+(1/m)*(exp(r*t)-1)); % Logistic growth
    dX = @(t) L*r*exp(r*t)*(1-1/m) ./ (1+(1/m)*(exp(r*t)-1))^2;
elseif (growth_type == 2)
    Xt = @(t) L*exp(r*t); % Exponential growth
    dX = @(t) L*r*exp(r*t);
elseif (growth_type == 1)
    Xt = @(t) L*(1+r*t); % Linear growth
    dX = @(t) L*r;
else
    Xt = @(t) L; % Static
    dX = @(t) 0;
end
c = L^2/D;
f = DuDx;
s = -(dX(t).*Xt(t)/D)*u;
function u0 = hydrogel_ic(x)
% Initial conditions function
u0 = 1;
function [pl, ql, pr, qr] = hydrogel_bc(xl, ul, xr, ur, t)
% Boundary conditions function
pl = 0; % no value left boundary condition
ql = 1;  % zero flux left boundary condition
pr = ur; % zero value right boundary condition
qr = 0;  % no flux right boundary condition
```