

Numerical Modeling of Drug Delivery in Solid Tumor Microvasculature

Andrew Lezia, Ariel Niedecken, Lauren Waller
University of California, San Diego
Department of Bioengineering
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I. Abstract

The heterogeneity of the microvascular network generated by tumor angiogenesis has been identified as one of the causes of unsuccessful treatment of a malignant tumor. [1] The microvascular organization of a tumor can affect the method of dosage on a patient-by-patient basis. Based on clinical findings, most cancer drug treatments fail to eliminate malignant tumor completely. [1] However, a stronger dose of the drug may in fact have more serious repercussions on the surrounding healthy tissue. To better understand the individual patient's reaction to a cancer drug such as Doxorubicin, solid tumor modeling and simulation is used to compute such parameters as ideal dosage, dose frequency, dose toxicity to tumor, and dose toxicity to surrounding healthy cells.

II. Introduction

High vascular variance is a major barrier to effective localized drug dosing to tumor sites. [1] The quantification, and therefore personalization, of cancer drug dosage perfusion into a tumor could have significant implications in patient care, including minimization of toxic drugs to healthy tissue, maximum effective dosage and dose frequency data for a particular patient, and dosage method.

The modeling of cancer drug delivery to solid tumor microvasculature is multi-scale in nature. On the macroscopic level, parameters such as tumor size, tumor shape, tumor density, and tumor vasculature, including changing radii of capillaries must be taken into account. On the microscopic level, blood flow, hematocrit levels, blood viscosity, fluid levels, lymphatic drainage, and material properties must be taken into account. In addition to these dynamic physiological morphologies and mechanisms, our inputs to the system, such as drug concentration, frequency, and input type change the concentration gradient output. The image below shows the order scales of these parameters within the system.

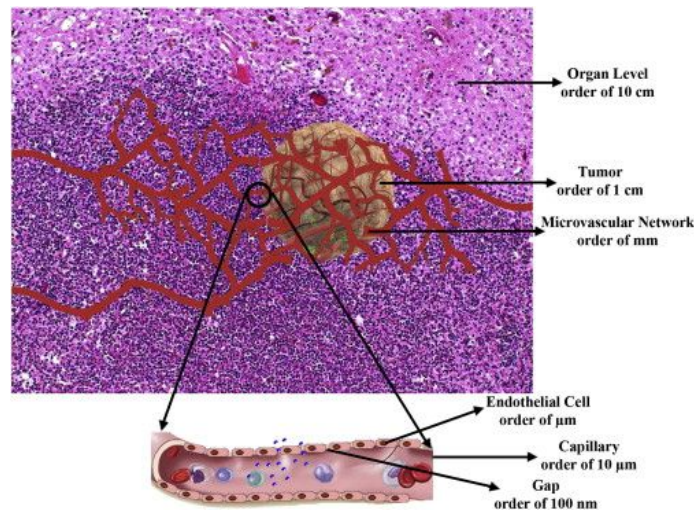


Fig. 1: Order Scales of Tumor Model (Sefidgar et al.)

In some cases, the location of the bolus, or dosage of cancer drug to the tumor, can significantly alter the effectivity of dosage. Consider the image below.

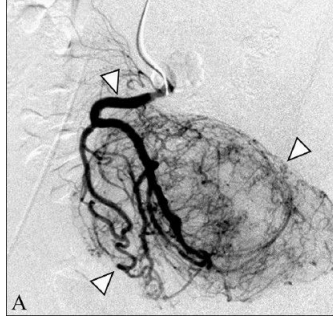


Fig. 2: Patient-Specific Tumor Vasculature Example

In this image, the arrows point to locations where the drug could be injected. Although it visually looks like injecting into the largest vasculature upstream of the tumor would deliver the greatest toxicity to the tumor, this vessel is also adjacent to healthy tissue, and may cause significant complications to healthy tissue. Therefore, a drug perfusion model with discrete input locations, vasculature geometry, and patient-specific parameters determined from routine blood work could be beneficial to patient-specific dosage efficacy of cancer drugs.

III. Background and Consideration of Current Models

There have been numerous attempts to devise a model for transport of a drug by taking into account diffusion, convection, and pressure gradients as well as adaptive vessel diameter and parameters of the blood flowing within the capillary itself. It is incredibly complex to assimilate all these variables that are changing continuously into one useful tool, but one approach that has achieved some success is the Sefidgar model. The model utilizes finite differences to update vessel diameter and interstitial pressure then calculate the diffusion and convection terms through the following equation [1]:

$$\frac{\partial C}{\partial t} = D_{eff} \nabla^2 C - \nabla \cdot (v_i C) + \left(\frac{L_p S}{V} (P_V - P_i - \sigma(\pi_b - \pi_i))(1 - \sigma_f) C_p + \frac{PS}{V} (C_p - C) \frac{Pe}{e^{Pe} - 1} \right) - \Phi_L \quad (1)$$

The model was primarily used to investigate differences in the delivery to healthy tissue versus tumor tissue, and considers the influence of a nearby blood vessel. For all situations, there are terms for diffusion and convection of the drug within the interstitial fluid. In the vicinity of a blood vessel, terms for diffusion and convection between the vessel and surrounding interstitial fluid are included. Lastly, in healthy tissue a term is added for lymphatic drainage, while this term is neglected in the case of tumor tissue, as only a blood vessel network develops within the tumor not a lymphatic network. These conditions are summarized in the following [1]:

$$\left\{ \begin{array}{l} \frac{\partial C}{\partial t} = D_{eff} \nabla^2 C - \nabla \cdot (v_i C) + \Phi_V - \Phi_L \quad \text{Normal w/ blood vessel} \\ \frac{\partial C}{\partial t} = D_{eff} \nabla^2 C - \nabla \cdot (v_i C) + \Phi_V \quad \text{Tumor w/ blood vessel} \\ \frac{\partial C}{\partial t} = D_{eff} \nabla^2 C - \nabla \cdot (v_i C) - \Phi_L \quad \text{Normal w/o vessel} \\ \frac{\partial C}{\partial t} = D_{eff} \nabla^2 C - \nabla \cdot (v_i C) \quad \text{Tumor w/o vessel} \end{array} \right. \quad (2)$$

IV. Mathematical Model: Assumptions and Simplifications

To look at one part of the overall process of drug delivery across the capillary wall, diffusion in the interstitial fluid alone may be considered. Since the distance of transport is so small, it can be assumed that diffusion dominates over convection. The problem can be set up in cylindrical coordinates, and the axes are defined in a way to align with a few assumptions. The simplified diagram of a capillary running through a tumor is presented below:



Fig. 3: Diagram of tumor and capillary orientation

The diffusion is assumed to be one-dimensional. The diffusion is symmetric with respect to θ and z , and the axes are defined such that $r = 0$ corresponds to the capillary wall. The plasma concentration of doxorubicin can be determined through experimentation, and it is assumed that this is equal to the concentration of the drug at the capillary wall, at $r = 0$.

Further, the delivery of the drug can be modeled as approximately a sinusoidal curve if the mode of delivery is an intravenous drip, where the sinusoidal function takes into account the frequency of the drops. This absolute value of the sinusoidal function is used, since there are no negative volumes drops of drug delivered.

The diffusion equation is utilized as presented below:

$$\frac{\partial C}{\partial t} = D_{eff} \nabla^2 C = D_{eff} \frac{\partial^2 C}{\partial r^2} \quad (3)$$

The initial condition is the concentration at the vessel wall at time $t = 0$ is the plasma concentration times the delta impulse function:

$$C(r = 0, 0) = C_o \delta(t)$$

Boundary conditions are defined at the capillary wall ($r = 0$) and at a distance far away from the capillary ($r = L$):

$$C(r = 0, t) = C_o \left| \sin\left(\frac{2\pi}{T}t\right) \right| \text{ where } T = \text{period of IV drip}$$

$$C(r = L, t) = 0$$

$$\frac{\partial C}{\partial r} \Big|_{r=L,t} = 0$$

At the distance L far from the capillary, the concentration of the drug and the rate of change of drug concentration are both zero.

III. Mathematical Model: Analytical Solution

For long distances of solute transport, convection dominates the equation (for example, in the pecllet number calculation given capillary size, velocity of blood flow, and diffusion coefficient of drug).

However, since the distance from capillary to tumor in our model is quite small, diffusion is the only significant component of the equation. Thus, convection is negligibly small and is thus ignored.

When only diffusion of drug in the tissue in the radial is considered, the Sefidgar equation describing our model reduces to the form of the diffusion/heat equation.

$$\frac{dC}{dt} = D_{eff} \frac{1}{r} \frac{d}{dr} \left(r \frac{dC}{dr} \right) - \phi_L \text{ for normal tissue}$$

$$\frac{dC}{dt} = D_{eff} \frac{1}{r} \frac{d}{dr} \left(r \frac{dC}{dr} \right) \text{ for cancerous tissue} \quad (4)$$

To solve the the diffusion equation in cylindrical coordinates analytically for the concentration profile in the radial direction and arrive at a closed-form solution, we further simplified our initial conditions and boundary conditions as follows:

- 1) $\frac{dC(t,r)}{dr} = 0$ at $r = 0$ (Boundary Condition 1)
- 2) $C(t, r) = 0$ at $r = r_f$ (Boundary Condition 2)
- 3) $C(t, r) = f(r) = Q$ for $t = 0$ (Initial Condition)

To solve this equation, the method of separation of variables is used. In this method, we assume that the solution to the partial differential equation (PDE) can be written as the product of a function of only t ($T(t)$) and a function of only r ($R(r)$). Thus, we have:

$$C(t, r) = T(t) * R(r) \quad (5)$$

Next, we plug this new expression for $C(t, r)$ into the initial PDE. Gathering the terms that only have t on one side of the equation and the terms that only have r on the other side of the equation we have:

$$\frac{T'(t)}{T(t)} = D_{eff} \frac{1}{r * R(r)} \frac{d}{dr} \left(r \frac{dR}{dr} \right) \quad (6)$$

This equation can only be true when both sides are equal to a constant. Setting both sides of the equation to the constant $-\lambda^2$, we obtain two ordinary differential equations that can be solved independently and whose solutions can be combined later to obtain the solution to the initial partial differential equation:

$$\frac{T'(t)}{T(t)} = -D_{eff} \lambda^2 \text{ and } \frac{1}{r * R(r)} \frac{d}{dr} \left(r \frac{dR}{dr} \right) = -\lambda^2 \longrightarrow r^2 \frac{d^2 R}{dr^2} + r \frac{dR}{dr} + r^2 \lambda^2 R = 0 \quad (7)$$

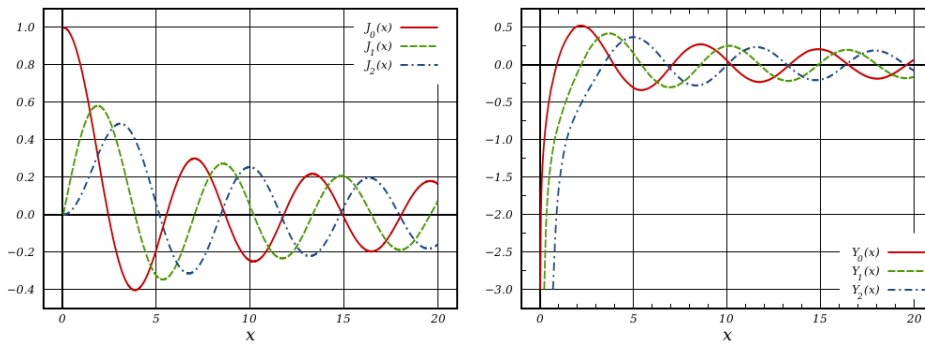
The solution to the ODE in t is simply a decaying exponential:

$$T(t) = K_1 \exp(-D_{eff} \lambda^2 * t) \quad (8)$$

The ODE in r is in the form of Bessel's differential equation. The general solution to the ODE in r is thus a sum of two Bessel functions:

$$R(r) = K_2 * J_0(\lambda r) + K_3 * Y_0(\lambda r) \quad (9)$$

$J_0(\lambda r)$ is a Bessel function of the first kind of order zero and $Y_0(\lambda r)$ is a Bessel function of the second kind of order zero. In general, Bessel functions can be precisely defined using their series expansions. The general shape of Bessel functions of the first kind and second kind are shown below:



Bessel functions of the first kind

Bessel functions of the second kind

Fig. 4: Bessel functions [6]

As the graphs above show, Bessel functions of the second kind diverge toward negative infinity as their argument approaches zero. Thus, since the solution to the diffusion equation must be bounded at $r = 0$, the constant K_3 must be equal to zero, and our equation in r becomes:

$$R(r) = K_2 * J_0(\lambda r) \quad (10)$$

Next, since, our right boundary condition is $C(t) = 0$ at $r = r_f$, it is required that:

$$R(r_f) = J_0(\lambda r_f) = 0$$

$$J_0(\lambda_n r_f) = 0$$

This above equation defines the eigenvalues (λ_n) and eigenfunctions ($J_0(\lambda_n r)$) for this problem. The eigenvalues (λ_n) can be found by looking up the roots of the Bessel function J_0 in a reference table. Now that we have solutions to both ODEs, we can combine them to find a particular solution to the original PDE.

$$C_n(r, t) = K_n * J_0(\lambda_n r) * \exp(-D_{eff} \lambda_n^2 * t) \quad (11)$$

By taking a superposition of particular solutions, we arrive at the general solution:

$$C(r, t) = \sum_{n=1}^{inf} K_n * J_0(\lambda_n r) * \exp(-D_{eff} \lambda_n^2 * t) \quad (12)$$

To solve for the constants K_n we use our initial condition. For simplicity we are assuming a uniform concentration profile initially, thus:

$$C(r, 0) = \sum_{n=1}^{inf} K_n * J_0(\lambda_n r) = Q \quad (13)$$

Now, to obtain values for K_n , we utilize the fact that the eigenfunctions $J_0(\lambda_n r)$ are all orthogonal. In general, a series of eigenfunctions can be used to represent any arbitrary function (in the same way an arbitrary function can be represented by a sum of weighted sinusoids). Using this eigenfunction expansion of the initial condition function (in this case a constant), it can be shown that the coefficient values K_n are given by:

$$K_n = \frac{2}{r_f^2 J_1^2(\lambda_n r_f)} \int_0^{r_f} r J_0(\lambda_n r) Q dr$$

The function $J_1(x)$ is a Bessel function of the first kind of order one and is related to $J_0(x)$ by

$$J_1(x) = -\frac{dJ_0(x)}{dx}. \text{ By solving the integral above, we arrive at an equation for the coefficients :}$$

$$K_n = \frac{2Q}{r_f J_1(\lambda_n r_f)}$$

Thus, the general solution to the diffusion problem in cylindrical coordinates is:

$$C(r, t) = \frac{2Q}{r_f} \sum_{n=1}^{inf} \frac{J_0(\lambda_n r)}{\lambda_n J_1(\lambda_n r_f)} * \exp(-\lambda_n^2 * t) \quad (14)$$

IV. Mathematical Model: Matlab Analysis

The pdepe function in MATLAB was utilized to plot the numerical solution.[2] The period of the IV drip was varied to show the results of one drop every hour, every thirty minutes, and every fifteen minutes. There is some cumulative effect of the concentration, where the drug concentration between peaks gradually increases slightly with successive dosage. Increasing the frequency of dosage results in a more consistent level of the drug present at any given time, so the frequency could be adjusted based on the therapeutic range for a specific patient. The drug concentration decreases quite rapidly in a short distance from the capillary, so the model could also be utilized to determine whether delivery of the drug through the vasculature is sufficient given a particular distance between the capillary and the tumor.

V. Results

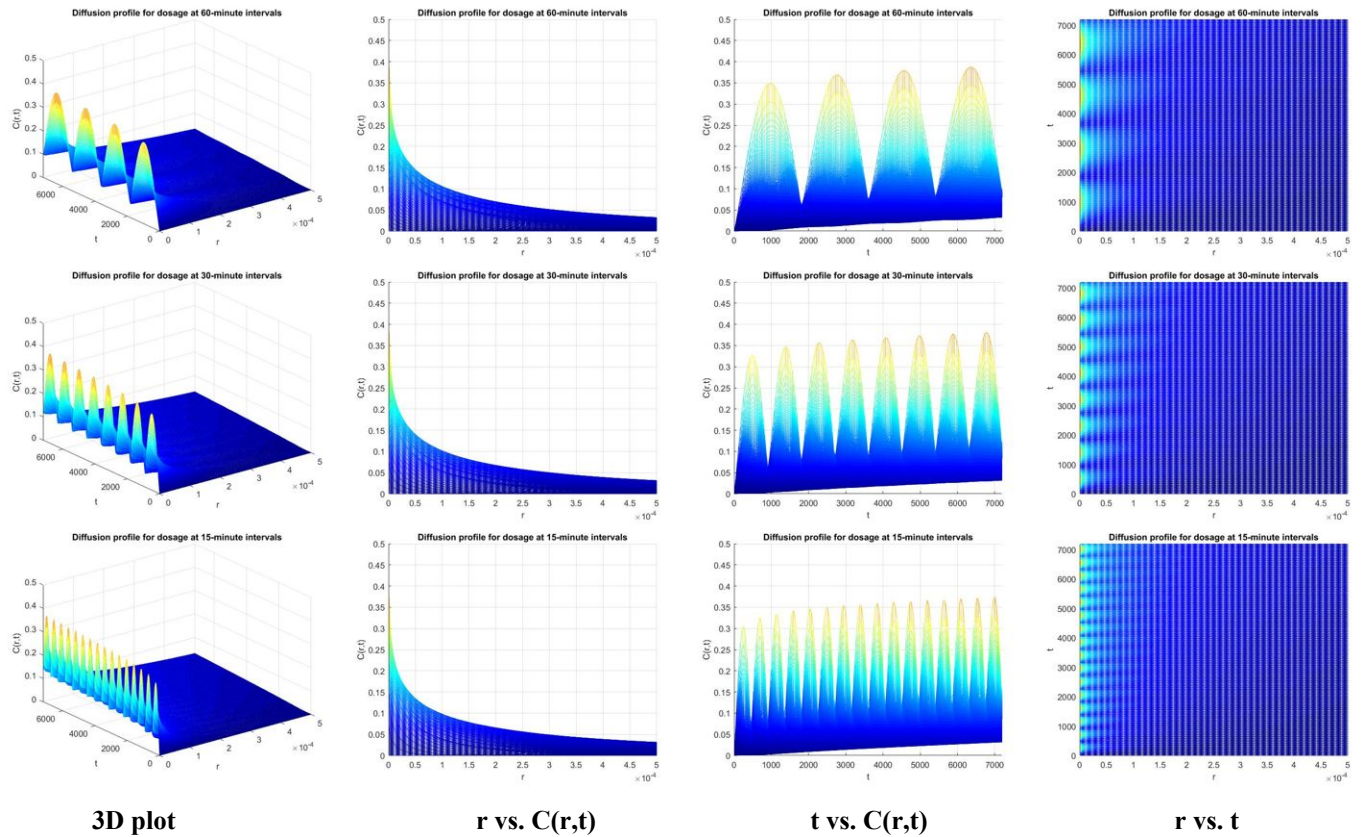


Fig. 5: Plots generated utilizing pdepe in MATLAB for dosage at 60 minute, 30 minute, and 15 minute intervals

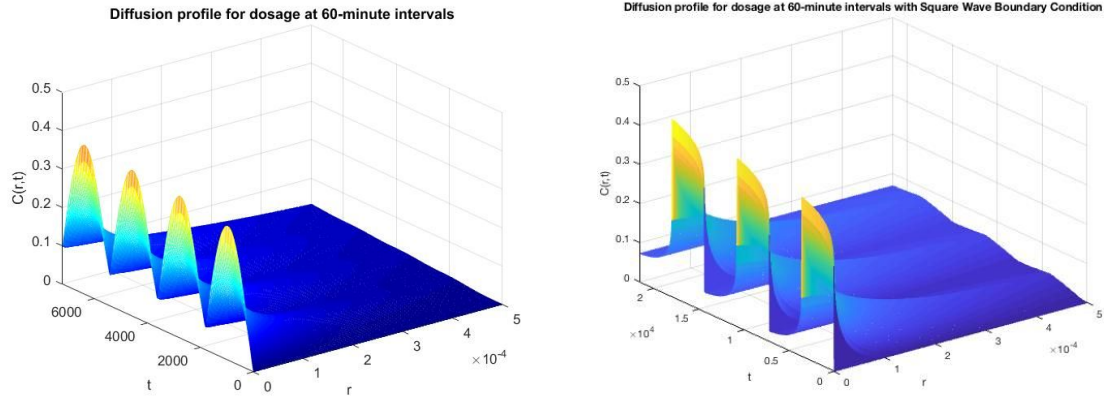


Fig. 6: Plots generated utilizing pdepe in MATLAB for IV drip modeled as a sinusoidal function and as a square function

VI. Conclusions

In conclusion, we studied a complex, mathematical model of drug delivery in tumor tissue and reduced it substantially to examine simple diffusion profiles in tumor tissue in response to different periodic, drug doses. We also showed how the diffusion partial differential equation can be solved analytically by separation of variables to yield a closed-form solution. For this problem, numerical methods are significantly more powerful because they provide substantially more flexibility in how the different components of the model can be varied, such as the boundary conditions.

The constant for plasma concentration and the diffusion coefficient for doxorubicin that were utilized in the model were taken from literature values for breast cancer treatment [3,4]. Therefore, the results of our model could predict the efficacy of doxorubicin in treating a tumor in the breast if the therapeutic concentration for a particular patient were known. The model can be extended to use for tumors in different locations in the body if only the diffusion coefficient and the plasma concentration of doxorubicin in a nearby capillary are known for that particular tissue type.

VII. Limitations and Future Directions

This is overall a fairly simplified model to observe only one of many transport phenomena involved in delivery of doxorubicin to a tumor. The results of our model yields useful results, but oversimplifies realistic patient vasculature since a single capillary is unrealistic for an advanced tumor. The first step to improving this model would be to use superposition with other capillaries in specific spatial and temporal parameters determined from patient angiograms or CT. This would yield a large mesh over the spatial coordinates of interest (probably $\sim 1\text{cm}$ into the healthy tissue surrounding the tumor). Following this step would be the re-addition of the convection terms into the solution, and the redefining of parameters in convenient terms that relate to common laboratory blood tests for cancer patients. The final and most complicated step

would be to change the model from static to dynamic. In this case, the concentration of solute at the source would no longer only be dependent on the input type (such as sine wave versus square wave). Instead, the instantaneous level of solute at the capillary wall would be dependent on the fluid dynamics of the blood through the capillary.

Another future direction for this project would be to research the necessary concentration of Doxorubicin in tumor tissue that is required to kill cancerous cells. Using this information, we could examine which dosing conditions resulted in the critical drug concentration being reached.

VIII. References

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- [3] Barpe, D.R., Rosa, D.D., Froehlich, P.E. (2010) Pharmacokinetic evaluation of doxorubicin plasma levels in normal and overweight patients with breast cancer and simulation of dose adjustment by different indexes of body mass. *European Journal of Pharmaceutical Sciences* 41(3-4): 458-463. <https://doi.org/10.1016/j.ejps.2010.07.015>
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- [6] “Bessel Function.” Wikipedia, Wikimedia Foundation, 10 Oct. 2017, en.wikipedia.org/wiki/Bessel_function.

IX. Appendix - Matlab Code

```
global L Co m D
L = 0.001;
Co = 630*100^3/10e3; %mg/m^3
m = 1;
D = 5.01e-11; %m^2s^-1

x = linspace(0.000001,L, 1000);
t = linspace(0,3600*12, 1000);

sol_pdepe1 = pdepe(m,@pdefun1,@ic,@bc1,x,t);
sol_pdepe2 = pdepe(m,@pdefun1,@ic,@bc2,x,t);
sol_pdepe3 = pdepe(m,@pdefun1,@ic,@bc3,x,t);

figure(1)
mesh(x,t,sol_pdepe1)
xlabel('r')
ylabel('t')
zlabel('C(r,t)')
axis([0 L/2 0 3600*2 0 0.5]);
```

```
title('Diffusion profile for dosage at 60-minute intervals');
```

```
figure(2)
mesh(x,t,sol_pdepe2)
xlabel('r')
ylabel('t')
zlabel('C(r,t)')
axis([0 L/2 0 3600*2 0 0.5]);
title('Diffusion profile for dosage at 30-minute intervals');
```

```
figure(3)
mesh(x,t,sol_pdepe3)
xlabel('r')
ylabel('t')
zlabel('C(r,t)')
axis([0 L/2 0 3600*2 0 0.5]);
title('Diffusion profile for dosage at 15-minute intervals');
```

```
function [c,f,s] = pdefun1(x,t,u,DuDx)
global D
```

```
c = 1/D;
f = DuDx;
s = 0;
end
```

```
function u0 = ic(x)
global Co
```

```
u0 = Co*(x==0);
end
```

```
function [pl,ql,pr,qr] = bc1(xl,ul,xr,ur,t)
global Co
pl = abs(Co*(sin(2*pi/3600*t)));
ql = 1;
pr = 0;
qr = 1;
end
```

```
function [pl,ql,pr,qr] = bc2(xl,ul,xr,ur,t)
global Co
pl = abs(Co*(sin(2*pi/1800*t)));
ql = 1;
pr = 0;
qr = 1;
end
```

```
function [pl,ql,pr,qr] = bc3(xl,ul,xr,ur,t)
global Co
```

```
p1 = abs(Co*(sin(2*pi/900*t)));  
q1 = 1;  
pr = 0;  
qr = 1;  
end
```