

University of California, San Diego

Bioengineering

BENG 221

Mathematical Methods in Bioengineering

Project

Nicotine Patch Modeling

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Introduction

The U.S. Department of Health calls tobacco, "the single greatest cause of disease and premature death in America today," with over 430,000 deaths each year. Nearly 25% of adult Americans—46 million people—are addicted to tobacco products. Worldwide, between 80,000 and 100,000 kids start smoking every day according to the World Health Organization. Smoking is responsible for killing one in ten adults globally, or six million deaths annually. More than 70% of smokers want to stop, but fewer than 10% succeed. Clinical studies have shown that use of a transdermal patch roughly doubles the success rate to 19% cessation. The first published study of the pharmacokinetics of a transdermal nicotine patch in humans was Rose et al. (1984). The following year the same group released a study demonstrating the use of a patch reduced nicotine cravings. Since then there have been hundreds of published studies on the usefulness of transdermal patches.

We would like to study the various parameters involved in order to determine more ideal dosage concentrations and times. One of the most commonly reported adverse side effects is a burning or stinging sensation at the site of application. In some cases this could be considered an allergic response to the adhesive used, but there is also the possibility that it is a response to the high concentration of nicotine being administered to a small area over several hours. It is in fact recommended that subsequent patch applications be placed in a different location each time. Based on this, we would like to investigate the diffusion of nicotine over time, and examine the possible reduction in the amount of time a patch is worn. One of the most successful brands is NicoDerm, and we have used the available data on their products to provide our baseline information.

Problem Solving Initial Considerations

From the NicoDerm website: "NicoDerm comes in 3 different variations ranging from 7 mg to 21 mg. The main difference between each level is not the amount of nicotine placed between the backing and the adhesive, but the size of the patch. This is due to the nature of the adhesive. For the adhesive to maintain its hold properly, the consistency of it must remain the same, thereby allowing only a specific amount of nicotine." We have used this information to make the assumption that the diffusion of nicotine across the skin is linear, and that the thickness of the patch has no effect on diffusion. Furthermore, the skin is taken as a homogeneous structure. From basic physiology, we know this not to be the case as the skin is a complex structure. Moving from a homogeneous structure to a heterogeneous one where different diffusivities and lengths are employed does not however entail a different mathematical analysis, but simply a more cumbersome one.

The intended duration is 16 to 24 hours, with the assumption being that the patch has transferred all of its contents to the patient after 24 hours. Until that point, it is assumed that the rate of transfer into the skin is constant. In other words, there is a constant influx of nicotine being diffused into the skin over time and the concentration is always at a set value. This assumption is crucial as it defines the first boundary condition.

The NicoDerm website advises that nicotine continues to be absorbed through the skin for several hours after the patch is removed. The implication here is that there is no equilibrium of concentration that is reached within the skin layer, but rather that nicotine is constantly being withdrawn by the bloodstream. From this we base our assumption that the concentration at the inner boundary of the skin layer is 0. The bloodstream boundary is thus modeled as a perfect sink where the concentration for the drug in question is always zero: all of the drug that reaches the outer boundary will therefore be immediately absorbed, with no accumulation. This is a very important assumption as it involves the other boundary condition.

We will be modeling this system in a 1-D fashion once there is really no outstanding reason for doing otherwise. The area itself where diffusion occurs is significantly smaller than that of the surface of the arm, leg or belly, which are the commonest areas used for patch application. Therefore, a 1-D analysis is deemed appropriate and reasonable.

Finally, we will use the diffusion equation on an interval of $[0, L]$, where L is the length of skin from the end of the patch up to the bloodstream.

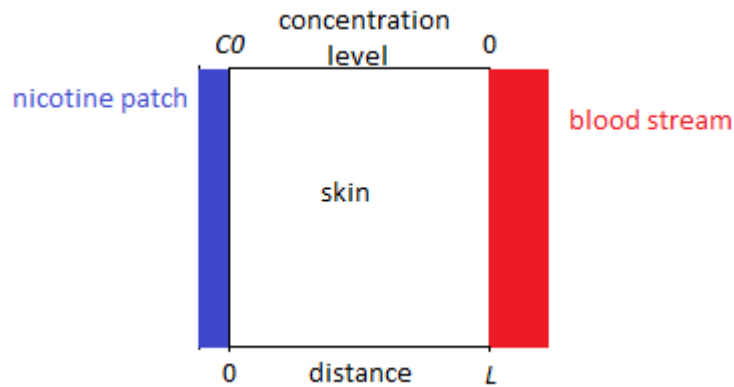


Figure 1 – Model of diffusion of nicotine from the patch to the blood stream.

Analytical Solution

The partial differential equation, or our governing equation, is the diffusion equation:

$$\frac{\partial c(x, t)}{\partial t} = D \frac{\partial^2 c(x, t)}{\partial x^2} \quad (1)$$

Based on our simplifications and assumptions, our initial and boundary conditions are as follows:

$$c(x, 0) = 0 \quad (2)$$

$$c(0, t) = C_0 \quad (3)$$

$$c(L, t) = 0 \quad (4)$$

Where the first equation is our initial condition (IC) and the remaining two the boundary conditions (BC).

In order to facilitate the solution of this PDE, we will separate the solution in two portions, namely, a steady-state solution and a transient one:

$$c(x, t) = c_T(x, t) + c_{SS}(x) \quad (5)$$

For the steady-state portion, as $t \rightarrow \infty$, its derivative with respect to time equals to zero (it is independent of time). And so:

$$\frac{\partial c(x, t)}{\partial t} = 0 \quad (6)$$

This reduces the governing equation for the steady-state case to:

$$D \frac{\partial^2 c(x, t)}{\partial x^2} = 0 \quad (7)$$

We may then eliminate D and integrate twice, yielding:

$$c_{SS}(x) = ax + b \quad (8)$$

The BCs on equations (3) and (4) can be applied:

$$c_{SS}(0) = C_0, \text{ yielding } b = C_0 \quad (9)$$

$$c_{SS}(L) = 0, \text{ yielding } a = -\frac{C_0}{L} \quad (10)$$

Thus, the steady-state solution is:

$$c_{SS} = -\frac{C_0}{L}x + C_0 \quad (11)$$

This intuitively makes sense since the solution presents itself as the equation of a line with a slope that depends on length L and concentration C_0 . At $x=0$, the concentration will be C_0 , while at $x=L$, the concentration drops to zero, as it should.

We may now turn our attention to the transient solution, which is inherently harder and more involved to solve. The first step is to set up the new boundary conditions based on the values already given:

$$c_T(0, t) = c(0, t) - c_{SS}(0), \text{ gives } c_T(0, t) = C_0 - C_0 = 0 \quad (12)$$

$$c_T(L, t) = c(L, t) - c_{SS}(L), \text{ gives } c_T(L, t) = 0 - (-C_0 + C_0) = 0 \quad (13)$$

It then becomes a homogeneous boundary condition for the transient solution.

As for the initial conditions:

$$c_T(x, 0) = c(x, 0) - c_{SS}(x), \text{ which results in}$$

$$c_T(x, 0) = 0 - \left(\frac{-C_0}{L}x + C_0\right) = C_0\left(\frac{x}{L} - 1\right) \quad (14)$$

We may now proceed to solve the transient $u(x, t)$ with homogeneous boundary and initial conditions as given by equations (12)-(14).

Returning to the diffusion equation given by equation (1) and applying equation (5):

$$\frac{\partial c(x, t)}{\partial t} = \frac{\partial c_T(x, t)}{\partial t} + \frac{\partial c_{SS}(x)}{\partial t} \quad (15)$$

But since the steady-state solution does not depend on time:

$$\frac{\partial c(x, t)}{\partial t} = \frac{\partial c_T(x, t)}{\partial t} \quad (16)$$

Second derivatives with respect to time become:

$$\frac{\partial^2 c(x, t)}{\partial x^2} = \frac{\partial^2 c_T(x, t)}{\partial x^2} + \frac{\partial^2 c_{SS}(x)}{\partial x^2} \quad (17)$$

However, second derivative of the steady-state portion equals to zero, reducing to:

$$\frac{\partial^2 c(x, t)}{\partial x^2} = \frac{\partial^2 c_T(x, t)}{\partial x^2} \quad (18)$$

Thus, the new governing equation becomes:

$$\frac{\partial c_T(x, t)}{\partial t} = D \frac{\partial^2 c_T(x, t)}{\partial x^2} \quad (19)$$

To solve this PDE, we will assume there is a solution such that:

$$c_T(x, t) = X(x) \cdot T(t) \quad (20)$$

Differentials become:

$$\frac{\partial c_T(x, t)}{\partial t} = X(x) \frac{dT(t)}{dt} \quad \text{and} \quad \frac{\partial^2 c_T(x, t)}{\partial x^2} = T(t) \frac{d^2 X(x)}{dx^2} \quad (21)$$

Hence, using equations (21) into (19) gives:

$$X(x) \frac{dT(t)}{dt} = D \cdot T(t) \frac{d^2 X(x)}{dx^2} \quad (22)$$

Rearranging it, we can set ratios equal to a constant $-\lambda$:

$$\frac{1}{D} \frac{1}{T(t)} \frac{dT(t)}{dt} = \frac{1}{X(x)} \frac{d^2 X(x)}{dx^2} = -\lambda \quad (23)$$

Separating variables ensues:

$$\frac{dT(t)}{dt} = -\lambda D T(t) \quad (24)$$

$$\frac{d^2X(x)}{dx^2} = -\lambda X(x) \quad (25)$$

Solving the ordinary differential equation of (24) results in:

$$T(t) = k_3 e^{-\lambda Dt} \quad (26)$$

As for equation (25), it is essentially a second order differential equation and an eigenvalue problem at that. We need to analyze all cases for λ :

$$\lambda < 0 : X(x) = k_1 e^{\sqrt{-\lambda}x} + k_2 e^{-\sqrt{-\lambda}x} \quad (27)$$

$$\lambda = 0 : X(x) = k_1 x + k_2, \text{ with } k_1 = k_2 = 0 \quad (28)$$

$$\lambda > 0 : X(x) = k_1 \cos(\sqrt{\lambda}x) + k_2 \sin(\sqrt{\lambda}x) \quad (29)$$

Analyzing equations (27) and (28), the only solution possible is the trivial solution, where $k_1=k_2=0$.

Therefore, we are left with equation (29) to solve. Multiplying the solutions for both λ cases ($T(t)$ and $X(x)$) results in:

$$c_T(x, t) = k_3 e^{-\lambda Dt} [k_1 \cos(\sqrt{\lambda}x) + k_2 \sin(\sqrt{\lambda}x)] \quad (30)$$

Applying the BC from equation (12) into equation (30) results in:

$$c_T(0, t) = 0 : k_3 e^{-\lambda Dt} k_1 = 0 \quad (31)$$

For it to be zero, the constant must be zero since the exponential part will never be:

$$k_3 e^{-\lambda Dt} \neq 0 : k_1 = 0 \quad (32)$$

Applying the BC from equation (13) into equation (30) results in:

$$c_T(L, t) = 0 : k_3 e^{-\lambda Dt} [k_2 \sin(\sqrt{\lambda}L)] = 0 \quad (33)$$

Again, the exponential part will never reach zero and so it is up to the sine function to equal zero. Sine functions are zero at angles of $(0 + n\pi)$ rad/s:

$$\sqrt{\lambda}L = n\pi, \text{ where } n = 1, 2, 3, \dots \therefore \sqrt{\lambda} = \frac{n\pi}{L}, \text{ where } n = 1, 2, 3, \dots \quad (34)$$

Finally, we can plug equations (34) into (33):

$$c_T(x, t) = k e^{-(\frac{n\pi}{L})^2 Dt} \sin(\frac{n\pi}{L}x), n = 1, 2, 3, \dots \quad (35)$$

We now possess an infinite number of solutions that satisfy the BC, but none of these satisfy the IC given by equation (14):

$$c_T(x, 0) = C_0(\frac{x}{L} - 1) : k \sin(\frac{n\pi}{L}x) \neq C_0(\frac{x}{L} - 1) \quad (36)$$

Since with one value of n we are not able to solve the equation, we may turn to superposition as a resource. The linear time-invariant characteristics of our system

guarantee that any linear combination of two solutions to the equation is also a solution to the equation. Therefore, the superposition results in:

$$c_T(x, t) = \sum_{n=1}^{\infty} K_n e^{-(\frac{n\pi}{L})^2 Dt} \sin(\frac{n\pi}{L} x) \quad (37)$$

The IC of the equation must still be satisfied:

$$c_T(x, 0) = f(x) \quad (38)$$

Where we then obtain:

$$f(x) = \sum_{n=1}^{\infty} K_n \sin(\frac{n\pi}{L} x) \quad (39)$$

In our case, x ranges from $[0, L]$ and so equation (39) can be solved as follows:

$$\int_0^L f(x) \sin(\frac{m\pi}{L} x) dx = \int_0^L \sum_{n=1}^{\infty} K_n \sin(\frac{n\pi}{L} x) \sin(\frac{m\pi}{L} x) dx \quad (40)$$

Since $\sin(n\pi x)$ and $\sin(m\pi x)$ are orthogonal for all $m \neq n$, we have:

$$\int_0^L f(x) \sin(\frac{m\pi}{L} x) dx = \int_0^L K_m \sin^2(\frac{m\pi}{L} x) dx$$

Computing it:

$$\int_0^L f(x) \sin(\frac{m\pi}{L} x) dx = K_m \left[\frac{x}{2} - \frac{\sin(\frac{2m\pi}{L} x)}{\frac{4m\pi}{L}} \right] \Big|_0^L = K_m \frac{L}{2} \quad (41)$$

Rearranging (41) and noting that this is only valid when $m=n$, we obtain:

$$K_n = \frac{2}{L} \int_0^L f(x) \sin(\frac{n\pi}{L} x) dx \quad (42)$$

As for $f(x)$, we know it to be:

$$f(x) = c_T(x, 0) = C_0 \left(\frac{x}{L} - 1 \right) \quad (43)$$

Plugging equation (43) into equation (42), K_n can be written as:

$$K_n = \frac{2}{L} \int_0^L C_0 \left(\frac{x}{L} - 1 \right) \sin(\frac{n\pi}{L} x) dx \quad (44)$$

Solving the integral in equation (44) results in:

$$K_n = -\frac{2C_0}{n\pi} \quad (45)$$

Hence, using equation (45) in equation (37) we obtain:

$$c_T(x, t) = -\frac{2C_0}{n\pi} \sum_{n=1}^{\infty} e^{-(\frac{n\pi}{L})^2 Dt} \sin(\frac{n\pi}{L}x) \quad (46)$$

We can now, at last, rewrite equation (5) as:

$$c(x, t) = C_0(1 - \frac{x}{L}) - \frac{2C_0}{n\pi} \sum_{n=1}^{\infty} e^{-(\frac{n\pi}{L})^2 Dt} \sin(\frac{n\pi}{L}x) \quad (47)$$

Equation (47) is our ultimate equation and constitutes our analytical solution.

We are also interested in looking into the flux of drug, which by Fick's law is given by equations (48) and (49):

$$\frac{\partial c(x, t)}{\partial x} = -\frac{C_0}{L} - \frac{2C_0}{L} \sum_{n=1}^{\infty} e^{-D(\frac{n\pi}{L})^2 t} \cos(\frac{n\pi}{L}x) \quad (48)$$

$$J(x, t) = -D \frac{\partial c(x, t)}{\partial x} \quad (49)$$

As it can be seen from the solution, the independent variable x does not influence at all the steady-state value for the flux, which is $D \cdot C_0 / L$.

Lastly, Q, or the amount of drug that is being taken by the patient is given by:

$$Q(t) = Area \int_0^t J(x, t) dx \quad (50)$$

Graphing

The solutions were plotted for 200 terms, varying mainly diffusivity between the simulations. The typical shape of the concentration curve looks like that of Figure 2. The concentration starts at C_0 at one of the boundaries (patch) and progressively decreases until the other boundary (blood stream) acting as a perfect sink.

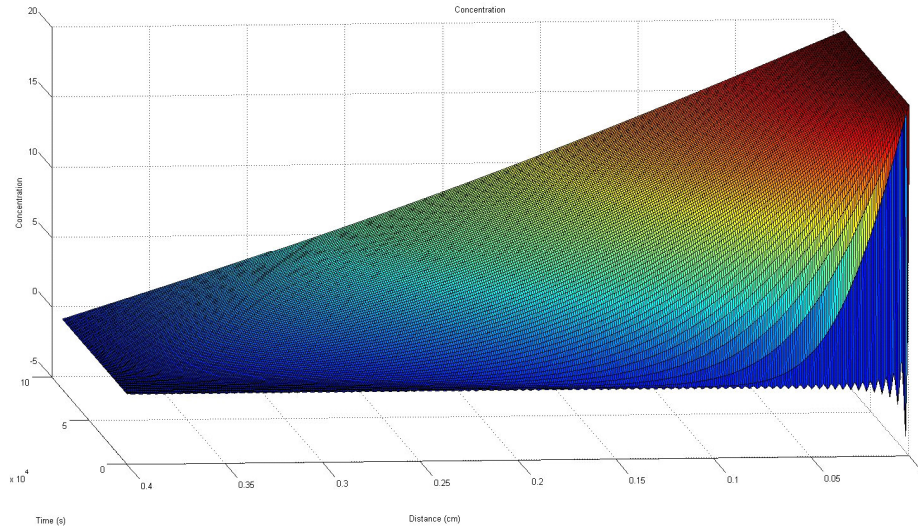


Figure 2 - Analytical solution surf plot for $c(x,t)$.

Plotting the concentration in function of x after a time t where $t \gg L^2/D$ yields Figure 3, illustrating the approach towards steady-state.

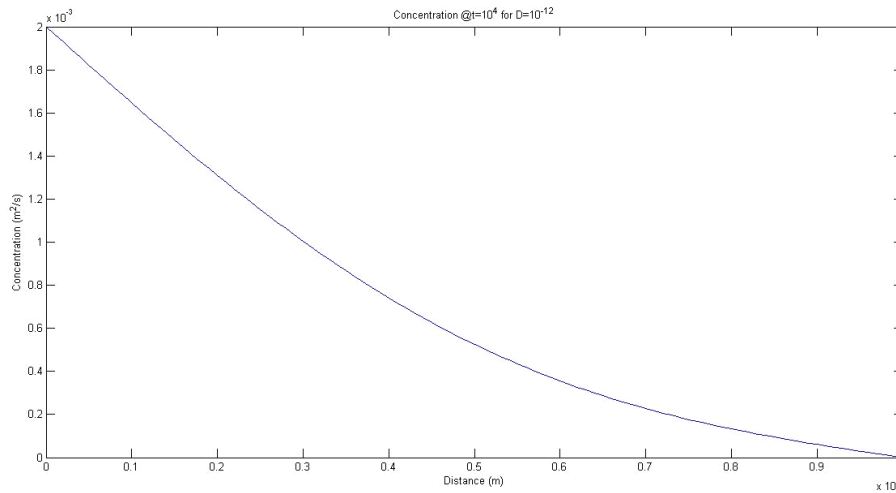


Figure 3 - Concentration at time t approaching steady-state.

If we are to plot a surf of flux with diffusivity of $5 \cdot 10^{-7}$, we get Figure 4. The flux at the beginning is very high and then quickly decreases towards a steady state. This phenomenon is expected since at the beginning, the concentration gradient driving this flux is the greatest as there is no initial concentration of nicotine in the skin.

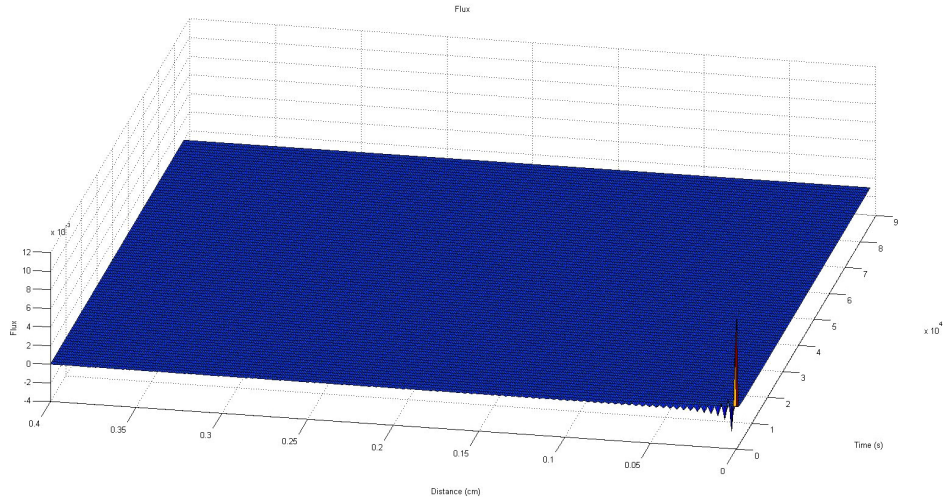


Figure 4 - Surf plot of Flux.

Finally, graphing Q over time gives the following graph.

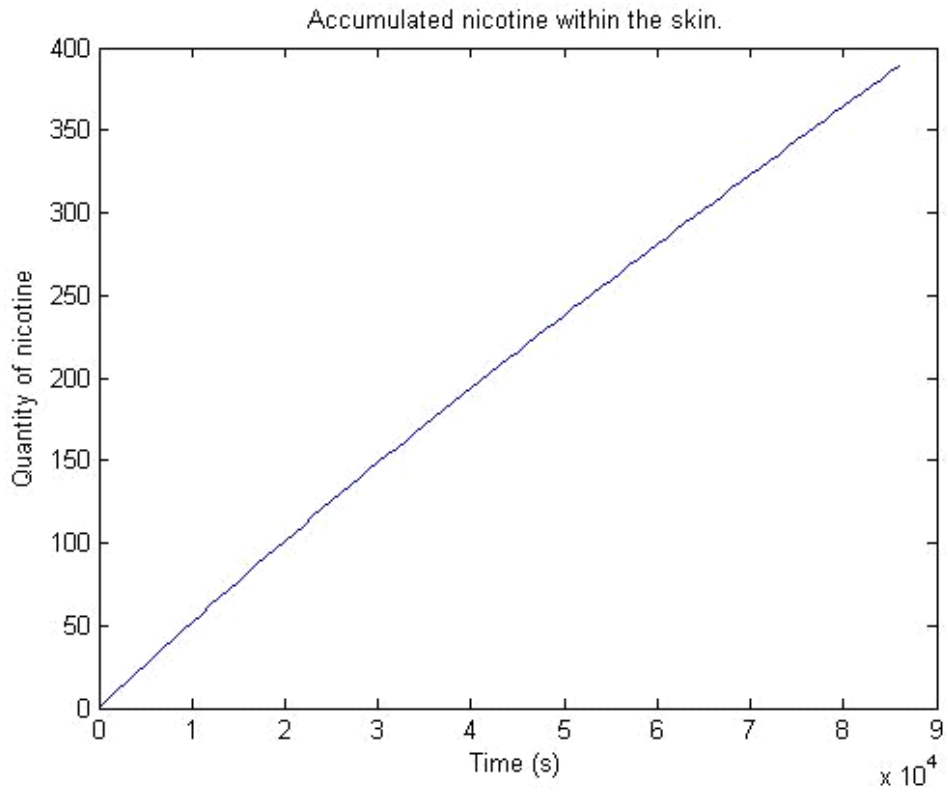


Figure 5 - Plot of $Q(t)$ - amount of nicotine intake by patient.

Conclusion

This report focused on a very basic approach at understanding transdermal diffusion of a particular drug, in this case Nicotine, over time and solve for its concentration. Various assumptions were made in order to make the model simpler.

Making a large assumption on the diffusivity of nicotine through skin, we see that the rate achieves a steady state of flux within 20 minutes of patch administration. This rate would continue until the concentration of the patch itself noticeably decreased, which unfortunately was outside the scope of our simulation. Also ultimately outside the scope of our simulation was the correct model of a sudden change resulting from patch removal. The natural direction of this study would be to employ more sophisticated geometries and models. In other words, the skin would be heterogeneous, with different layers having specific diffusivities and lengths, as well as account for patch heterogeneity.

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MatLab coding

```
clear all;
close all;
clc;

distance_step = 1e-3;
time_step = 1e3;

C0 = 20;
D = 5e-7; % cm^2/s
L = 0.4; % cm
final_time = 86400; % s

x = [0:distance_step:L];
t = [0:time_step:final_time];
c = zeros(length(x),length(t));
flux = zeros(length(x),length(t));

for index_x=1:1:length(x)
    for index_t=1:1:length(t)
        total = 0;
        total_flux = 0;
        for n=1:1:200
            total = total + (-2*C0/(n*pi)) * exp(-D*t(index_t)*(n*pi/L)^2) *
sin(n*pi*x(index_x)/L);
            total_flux = total_flux + (-2*C0/L) * exp(-
D*t(index_t)*(n*pi/L)^2) * cos(n*pi*x(index_x)/L);
```

```

        end
        c(index_x,index_t) = C0*(1-x(index_x)/L) + total;
        flux(index_x,index_t) = (-C0/L) + total_flux;
    end
end
flux = -D*flux;

figure(1);
surf(t,x,c);
xlabel('Time (s)');
ylabel('Distance (cm)');
zlabel('Concentration');
title('Concentration');

figure(2);
surf(t,x,flux);
xlabel('Time (s)');
ylabel('Distance (cm)');
zlabel('Flux');
title('Flux');

Q = zeros(1,length(t));
area_eq = zeros(1,length(t));
area_acc = zeros(1,length(t));

for index_t=1:1:length(t)
    Q = 0;
    Q_acc = 0;
    for n=1:1:200
        Q = Q + (2*C0*L/(n^2*pi^2)) * exp(-D*t(index_t)*(n*pi/L)^2) *
cos(n*pi);
    end
    if index_t > 1
        area_eq(1,index_t) = area_eq(index_t-1) + C0*(L/2) + abs(Q);
    end
end

figure(3);
plot(t,area_eq);
xlabel('Time (s)');
ylabel('Quantity of nicotine');
title('Accumulated nicotine within the skin.')

```

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<http://www.nicodermcq.com/>