MODELING DIFFUSION IN THE SMALL INTESTINES

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INTRODUCTION

Background

The human intestine makes up the largest exposure to the environment with its surface area spanning around 200 m^2, equivalent to the size of a tennis court. It is not surprising from this figure that the human intestinal system has evolved to comprise multiple lines of defense mechanisms. Collectively termed the "gut barrier", these defensive components diligently recognize and react to any harmful molecules that are either potentially or immediately injurious to the body. The importance of the roles of the gut barrier is increasingly believed to be tightly related to human health and diseases as more studies find connections between disrupted intestinal homeostasis and negative outcomes.

Gut Barrier

As mentioned, the gut barrier is not simply a sheet of epithelial cells separating the environment from the body. The barrier however is made of three levels. Pre-epithelial level includes the fact that the intestine is enclosed inside the body. The bowel movement, along with epithelial cell fluids, also helps to flush any unabsorbed molecules downstream. At the epithelium cell level, there are two significant defensive mechanisms. First is the very rapidly regenerating epithelial cells themselves. If a cell damage causes a compromise to the overall effectiveness of the barrier, new cells will be rapidly regenerated and patch the affected area. Second is the regulation of the paracellular junction, also known as the tight junction. The junctions are located in the intercellular spacing between epithelial cells and function as an active filter for the systemic circulation. It is through tight junctions where most water-soluble compounds, which cannot penetrate the lipid membrane of the cell surface, enter the body. Lastly, complex immune networks serve as the post-epithelial barrier. Immunoglobin A and defensins constitute such level of defensive responses.

Permeation Test

The breach in the gut barrier and the consequent increased permeation of materials that are normally repelled is known as leaky gut syndrome. Some known causes of the syndrome are genetic mutation (Crohn's, celiac disease), excessive release of inflammatory cytokines, malnutrition, major surgery, trauma, burns, and non-steroidal anti-inflammatory drugs. Based on various causes of the syndrome, it is becoming more important for a physician to accurately diagnose the patient's condition.
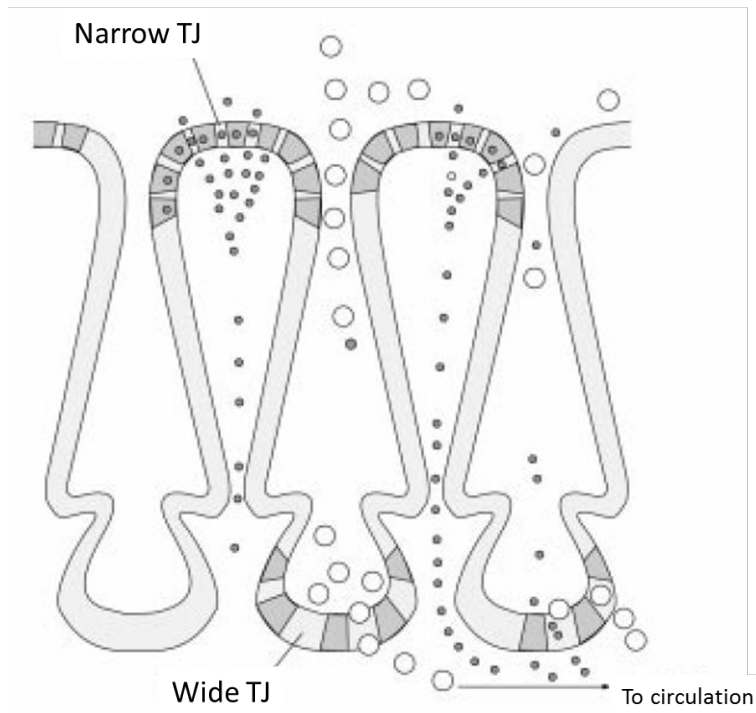
Figure 1. Probes used in the permeation test can penetrate intestinal membranes through weakened tight junctions and enter the systematic circulation. Probes with two different diameters (distinguished in the diagram as hollow and solid circles) can be used to increase the accuracy of the test.

As illustrated in Figure 1, intestinal permeability can be assessed by having a patient ingest specially designed probes (disaccharides, lactulose) that are not metabolized and have poor uptake in a healthy digestive tract. The probes will penetrate the epithelial layer and enter the blood stream only if there is an increased permeation in the tight junction, then, because they are not metabolized, will be filtered in the kidneys and excreted in the urine proportion to the amount absorbed. This testing method is particularly useful in assessing the degree of activity of Crohn's disease, where the level of permeability reflects the severity and activity of the disease, because of its noninvasiveness, reproducibility, and high accuracy. Detail illustration of the permeation of probes and its consequential collection in the urine is described in Figure 2.
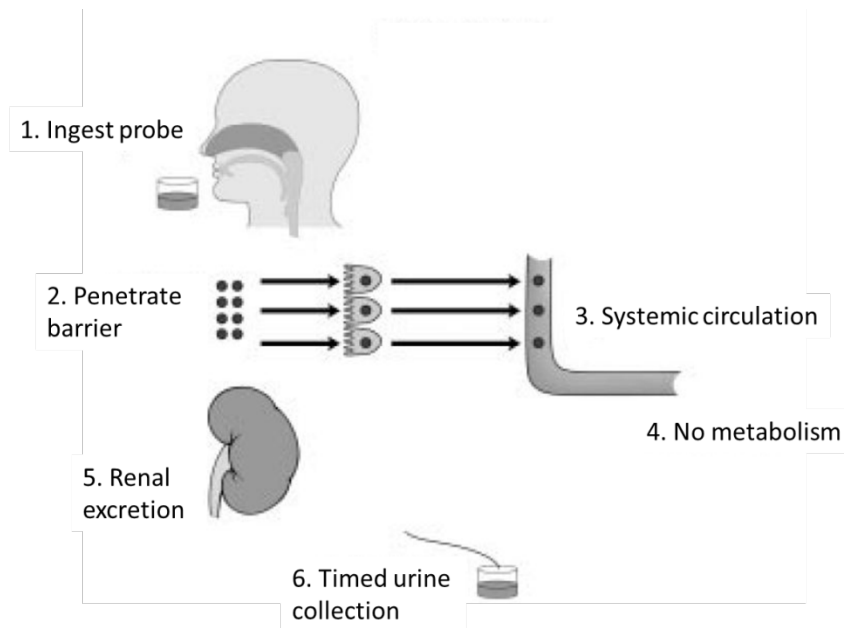
Figure 2. The schematic illustrates the sequences involved with the collection of ingested probes used in the permeation test.

METHODS

In this report, we model the diffusion behavior of the test probes used in the permeation test discussed above. For this model, the assumptions we made are:

- The model assumes a two-part system (luminal volume and intestinal membrane)
- Each medium has a uniform diffusion coefficient.
- The probes cannot diffuse through any other digestive organ (e.g. stomach).
- At any given time, the probes are uniformly mixed inside the small intestine.
- It takes 6 hours for water to make it through the small intestine.

For the simplest approach we can focus on the small section of the membrane and allow us to assume a one-dimensional slab (see Figure 3). In such case, diffusion equation and its initial and boundary conditions are expressed as below:

Diffusion Equation	Initial Condition	Boundary Conditions

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

$$C(x < 12, 0) = 0.05$$

$$\frac{\partial C}{\partial t}(0, t) = 0$$

$D \approx 10^{10} (x < 12)$
$D = \text{variable} (x > 12)$

$$C(x > 12, 0) = 0$$

$$C(15, t) = 0$$

In this set-up the diffusion equation is simply the Fick's second law. The high diffusion coefficient is adopted to ensure that the probes are uniformly mixed inside the intestine. Two initial conditions illustrates that when t=0 the probe concentration inside the small intestine is 0.05 whereas the concentration within the membrane is zero. We assumed no-flux state for the left boundary condition since probes concentration in the center of the intestine can be considered isolated. The right boundary condition means that the bloodstream effectively carries away all probes that have penetrated the membrane.

Though the slab model is a simple and efficient approach, deviation is expected due to the fact that human intestines are tubular. To better simulate the actual diffusion phenomenon we adopt the cylindrical coordinate system, and the set-up can be written as:

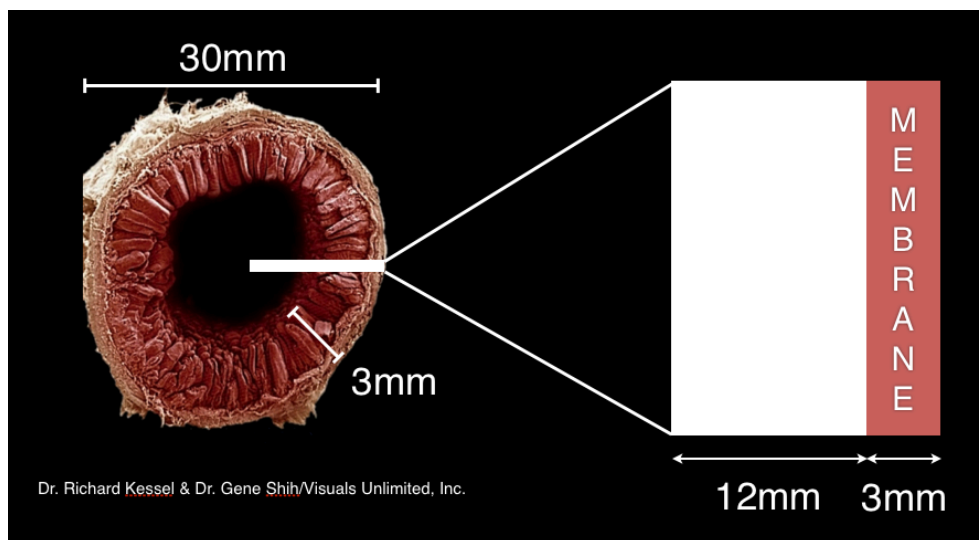| Diffusion Equation	Initial Condition	Boundary Conditions
$\frac{\partial C}{\partial t} = D \frac{1}{r} \frac{\partial}{\partial r} r \frac{\partial C}{\partial r}$	$C(r < 12, 0) = 0.05$	$\frac{\partial C}{\partial t}(0, t) = 0$
$D \approx 10^{10} (r < 12)$ $D = \text{variable}(r > 12)$	$C(r > 12, 0) = 0$	$C(15, t) = 0$

Figure 3. The schematic shows the dimensions of the model including the 1-D approximation.

RESULTS/DISCUSSION

Analytical Solution

The diffusion model set up is difficult to solve analytically because we are considering two compartments, inside the small intestines and the membrane. Therefore, for the analytical solution we made further assumptions. We only considered the membrane and modeled the initial concentration as an impulse at the inside wall.

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

BCs: $C(0,\, t) = 0$ IC: $C(x,\, 0) = 0.05 \cdot \delta(x - L)$

$\qquad \frac{dC}{dx}(L,\, t) = 0$

Separation of Variables:

$$C(x,\, t) = \Phi(x) \cdot G(t)$$

$$\frac{\frac{d^2\Phi(x)}{dx^2}}{\Phi(x)} = \frac{1}{D}\frac{\frac{dG(t)}{dt}}{G(t)} = -\lambda$$

$$\frac{dG}{dt} = -\lambda D G \rightarrow G(x) = G(0)e^{-\lambda D t} \neq 0 \;\; \forall t$$

$$\frac{d^2\Phi}{dx^2} + \lambda\Phi = 0, \quad \text{BCs:} \;\; \Phi(0) = 0, \; \frac{d\Phi}{dx}(L) = 0$$

$\lambda = 0:\; \Phi(x) = Ax + B \rightarrow A = B = 0, \;\text{ trivial solution}$

$\lambda < 0:\; \Phi(x) = Ae^{\sqrt{-\lambda}x} + Be^{-\sqrt{-\lambda}x} \rightarrow A = B = 0, \;\text{ trivial solution}$

$\lambda > 0:\; \Phi(x) = A\cos\left(\sqrt{\lambda}x\right) + B\sin\left(\sqrt{\lambda}x\right)$

$\qquad \Phi(0) = 0:\; 0 = A\cos(0) + B\sin(0) \rightarrow A = 0$

$\qquad \frac{d\Phi}{dx}(L) = 0:\; 0 = -A\sqrt{\lambda}\sin\left(\sqrt{\lambda}L\right) + B\sqrt{\lambda}\cos\left(\sqrt{\lambda}L\right)$

$\qquad\qquad 0 = B\sqrt{\lambda}\cos\left(\sqrt{\lambda}L\right) \rightarrow \cos\left(\sqrt{\lambda}L\right) = 0 \rightarrow \lambda = \frac{(2n+1)\pi}{2L}, \; n = 0,1,2,3\ldots$

$$C(x, t) = \sum_{n=0}^{\infty} B_n \sin\left(\frac{(2n+1)\pi}{2L}x\right) e^{-D\left(\frac{(2n+1)\pi}{2L}\right)^2 t}$$

$$B_n = \frac{2}{L}\int_0^L g(x)\cdot\sin\left(\frac{(2n+1)\pi}{2L}x\right) dx, \quad n = 0,1,2,3...$$

$$B_n = \frac{2}{L}\int_0^L 0.05\cdot\delta(x-L)\cdot\sin\left(\frac{(2n+1)\pi}{2L}x\right) dx = \frac{0.1}{L}$$

$$C(x, t) = \sum_{n=0}^{\infty} \frac{0.1}{L}\cdot\sin\left(\frac{(2n+1)\pi}{2L}x\right) e^{-D\left(\frac{(2n+1)\pi}{2L}\right)^2 t}$$

Since the analytical solution could not provide the necessary information inside the small intestine, we turned to the numerical solution for a more complete picture.
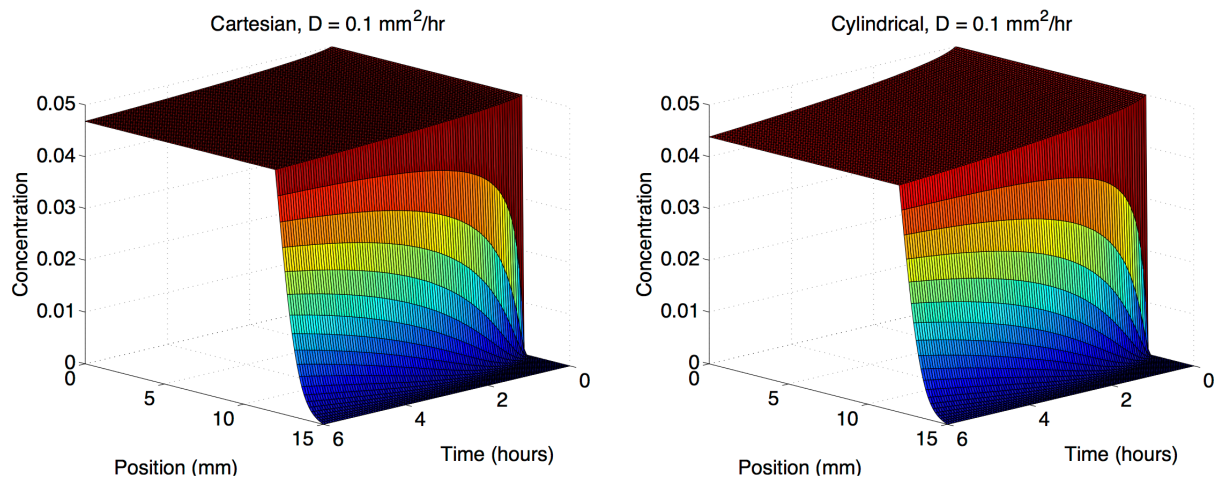
Numerical Solution

Figure 4. Comparing Cartesian and Cylindrical coordinates at D = 0.1 mm^2/hr.

The intestinal wall can have different levels of permeability depending on the individual. The membrane of a healthy individual should not allow the passage of any of the ingested molecules. Figure 4 illustrates what we would expect for such a case. The diffusion coefficient in the membrane is very low (D = 0.1 mm^2/hr). After six hours, the concentration has dropped from 5% to about 4.7% (4.3% for the cylindrical model). Also, the diffusion gradient has not fully developed inside the membrane.
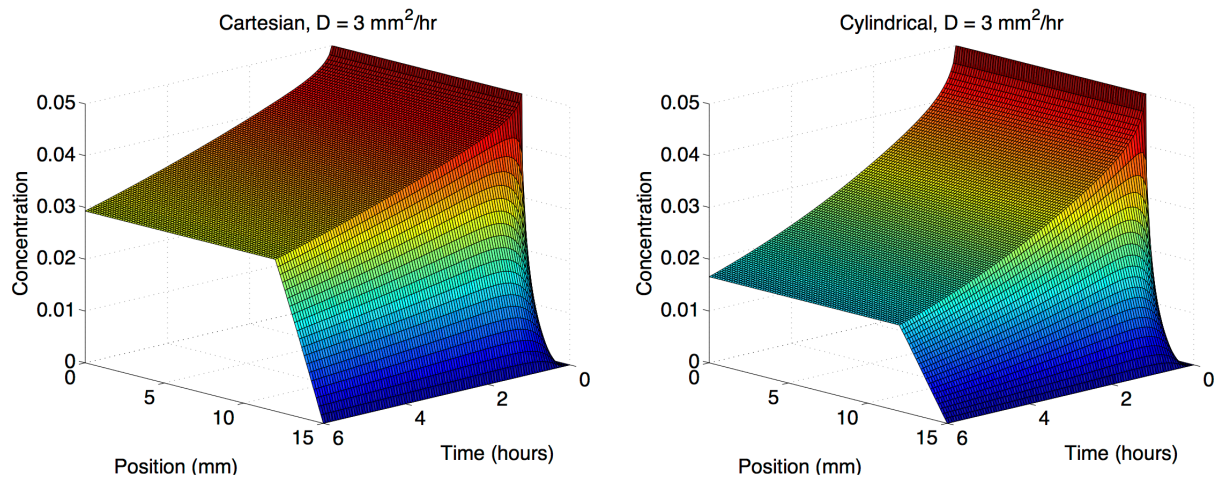
Figure 5. Comparing Cartesian and Cylindrical coordinates at D = 3 mm²/hr.

Figure 5 shows a moderate case, where the diffusion coefficient inside the wall is at a higher level (D = 3 mm²/hr). After six hours, the concentration has dropped from 5% to about 3% (1.8% for the cylindrical model). At this point, a significant amount of particles have made it into the bloodstream. Also, the diffusion gradient has fully developed inside the membrane. A considerable difference can be seen between the Cartesian and cylindrical model for this case. As expected, the cylindrical model shows more of a concentration drop because there is a greater surface area to diffuse through. Figure 6 displays a severe case, where most of the particles have diffused out of the small intestines (D = 10 mm²/hr).

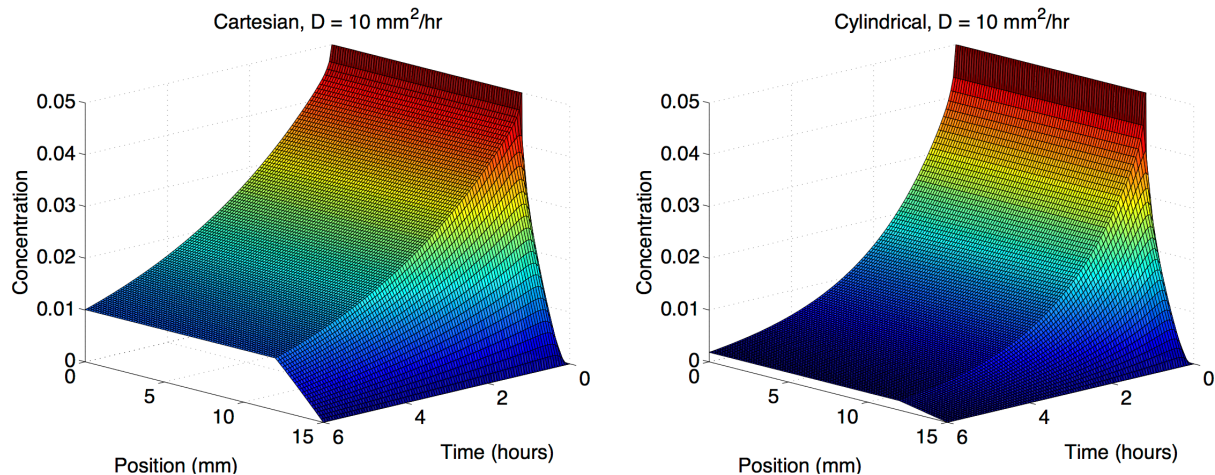**Figure 6. Comparing Cartesian and Cylindrical coordinates at D = 10 mm²/hr.**
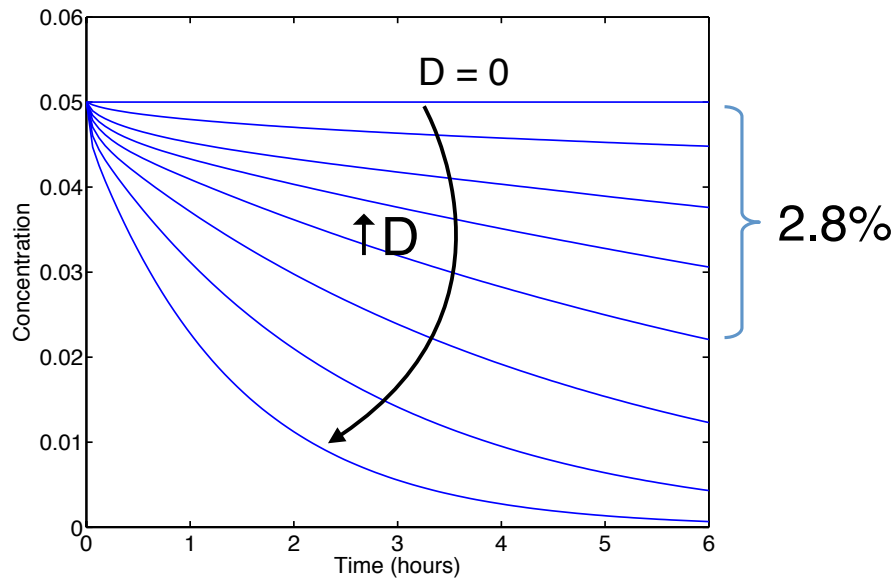
Figure 7. Effect of membrane diffusion coefficient (D) on concentration inside the small intestines.

We can look at the problem from a different perspective by only considering what is happening inside the small intestines. Figure 7 shows the ideal case for a healthy individual ($D = 0$ mm^2/hr) and the family of curves for increasing membrane permeability (increasing D). An interesting application of the model would be to work on the problem backwards. For example, if a doctor conducts a permeation test and discovers a concentration of 2.8% in the urine, a specific curve can be identified with that result (see Figure 7). From the model, we can then estimate the diffusion coefficient of the small intestines. Since we know that the diffusion coefficient is related to the particle size and pore size, another model can estimate the size of the pores in the membrane. The model can provide useful information when trying to develop a treatment plan specifically for the individual.

CONCLUSIONS

With a rise in the interest in the relation between intestinal homeostasis and various disorders, the proposed model, in addition to the current noninvasive permeation test, might reveal detailed dynamics of the leakiness in the breached intestinal tissues. Leaky gut syndrome is of particular interest because functionally decreased gut barrier evidently leads to various other diseases or even death. The importance of monitoring the integrity of intestinal tight junctions is widely being acknowledged. In this report, we have successfully demonstrated that simple mathematical analysis in combination with computing power can provide additional information to current permeation tests. The proposed tool effectively describes the dynamics of diffusion profile inside the intestinal membrane and potentially become extremely useful for physicians who might want to isolate the affected areas.

FUTURE WORK

Numerous assumptions were made throughout the model and deviation from biological phenomenon is expected. While some assumptions are inevitable given the complex and dynamic nature of a biological system, we can increase the accuracy of the model by taking into account the fact that the ingested probe/water mixture is not held stationery, but rather travels through different parts of the intestine over the 6-hour period. This would introduce variable diffusion coefficients along the length of the intestine. Another important aspect should be considered for the better model: the diffusion coefficient within the membrane is not uniform, but will vary over its thickness. A model assuming two types of probes with different diameter could be useful in the clinical setting where the accuracy of the test is crucial. As the apical portion of the cells are more prone to permeations, larger size probes can also be introduced, and their relative amount compared in the urine collection. The ratio between large and small probes would help in the diagnosing a patient with the level of severity because the large probes are nearly unabsorbed and function as a baseline to the small probes. Finally, given above designs along with further investigation, a quantitative relationship between measured diffusion coefficient and the size of each tight junction could be calculated. Knowing the exact size of the tight junction will not only reveal the condition of the patient but also help determine the types of treatment that patient should receive.

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MATLAB CODE

```matlab
function pdexfunc

global diff_coef

diff_coef = 10; % [mm^2/hr]

x = linspace(0,12+3,100); % [mm]
t = linspace(0,6,100); % [hr]

% PDEPE

m = 0; %0: cartesian, 1:cylindrical

sol = pdepe(m,@pdex,@pdexic,@pdexbc,x,t);
u(:,:,ii)=sol(:,:,1);

h = figure(1);
surf(t,x,u(:,:,ii)')
view(136,18);
xlabel('Time (hours)');
ylabel('Position (mm)');
zlabel('Concentration');
title('Cartesian, D = 10 mm^2/hr');
zlim([0 0.05]);

%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
function [c, f, s] = pdex(x, t, u, DuDx)
global diff_coef

if x < 12
    D = 10^10; % This forces the concentration to be 0.05 from 0 to 12 mm
else
    D = diff_coef; % mm^2 / hour
end

c = 1;
f = D * DuDx;
s = 0;

%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
function u0 = pdexic(x)
if x < 12
    u0 = .05;
else
    u0 = 0;
end

%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
function [pl, ql, pr, qr] = pdexbc(xl,ul,xr,ur,t)
pl = 0;
ql = 1;
pr = ur;
qr = 0;
```