Modeling of Oxygen Diffusion Across the Blood-Brain Barrier for Potential Application in Drug Delivery

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Problem Statement

The blood-brain barrier is a series of tight junctions between endothelial cells and a thick basement membrane that serves to separate circulating blood in the brain and the brain extracellular fluid.[1] This barrier prevents the diffusion of bacteria and hydrophilic molecules, and allows the movement of hydrophobic molecules, such as oxygen. The tight junction between cells is composed of transmembrane proteins such as occludin and claudins.[2] The cells in the brain capillaries are at a higher density than the cells in other capillaries and this also helps restrict the passage across the blood-brain barrier. The basement membrane lies directly underneath the endothelium and is composed of two lamina - the basal lamina and the reticular lamina.[3]

Safe passage of drugs across the blood-brain barrier is a major limitation of current therapeutics for the brain. Therefore, it would be useful to model the diffusion of a potential drug across the blood-brain barrier to determine the distance it travels across the barrier for a given systemic concentration. The information obtained from this model can be used to determine what systemic concentration of a drug is necessary to reach a target distance across the blood-brain barrier.

For our model, as seen in Figure 1, we chose to model the diffusion of oxygen into the brain, a molecule that is known to diffuse regularly across the blood-brain barrier. To translate our model for oxygen to a model for a potential drug, we would simply substitute the diffusivity value of the drug, obtained from literature, and the expected concentration of drug in the body once it is administered.
Boundary conditions are important for our model. For our purposes, we will take the location at which the blood meets the blood-brain barrier as our zero point for distance (x=0) and set our target distance (x=L) to 400nm, which is the average length of the blood-brain barrier. At the interface between the blood and the barrier, we designated an initial concentration of oxygen (C0), choosing the value 0.02945 L / L blood. As discussed earlier, this constant concentration value can be changed to see the effect on species diffusion through the blood-brain barrier. We also set our oxygen concentration at x=L to 0, assuming that all of the oxygen is immediately consumed once it reaches the end of the blood-brain barrier.

In order to solve this one-dimensional linear partial differential equation, both analytically and numerically, several simplifications were put into effect:

1) There will be no oxygen initially present in the brain or in the blood-brain barrier. This is an important assumption as it allows us to set an initial condition to our equation for concentration at time t = 0. Of course, in a healthy human, physiological oxygen concentrations would be greater than zero, but this is a necessary assumption to simplify the math.
2) There will be an oxygen gradient as oxygen diffuses through the blood-brain barrier, but at the interface of the barrier and the brain tissue, all oxygen will be consumed. This does not take into consideration the fact that normally, oxygen needs to diffuse into the

interior brain tissues as well so that those regions can get their necessary supply of oxygen. However, it is an imperative assumption in order to establish a boundary condition for concentration of oxygen at the edge of the blood-brain barrier. This sets concentration at x = L to 0 liters of oxygen per liter of blood.

3) There will be a constant concentration of oxygen in the bloodstream, set at the physiological concentration of oxygen in a normal, healthy adult human. Although blood oxygen concentration is constantly changing, this will allow us to set up a second boundary condition for concentration of oxygen at the interface of the blood vessel and the blood-brain barrier. It sets the concentration at x = 0 to 0.02945 liters of oxygen per liter of blood.
4) The diffusivity of oxygen that will be assigned will be based on the diffusivity of oxygen in water. This is because, although our oxygen molecules will be traveling through blood, cellular junctions, and brain tissue, water is a predominant component of each of these levels and thus we can approximate the diffusivity of oxygen through the blood-brain barrier to be similar to the diffusivity of oxygen through water, which is 3.24*10^-5 cm^2/s.
5) One-dimensional linear diffusion of oxygen is a necessary and valid assumption to make since we are focusing in on a small-scale region of the blood-brain barrier. Since we are looking at such a small area, we can assume the oxygen travels in a straight line from one side of the barrier to the other. In reality, the blood vessels follow a convoluted path and, given that blood is constantly flowing, the oxygen molecules are not likely to travel in a perfectly linear path.
6) This model must apply not only to oxygen, but to other drugs as well in order to consider the diffusion of a drug through the blood-brain barrier. Oxygen has been used because it is a small molecule known to easily pass through this barrier, however, drugs are much larger and as a result would have much lower diffusivities in aqueous solutions. We will use this oxygen diffusion model and input it into MATLAB with significantly lower diffusivity constants to simulate the diffusion of drugs.

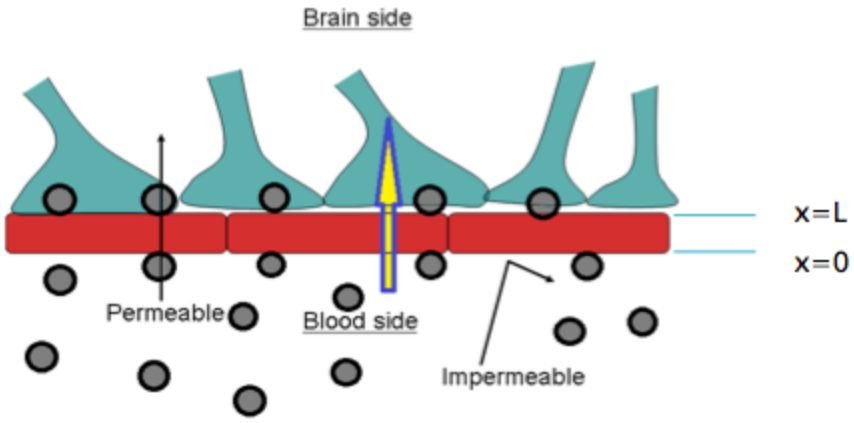

Figure 1. Depicts the model for this one-dimensional linear differential equation with the dark grey circles representing Oxygen molecules and the red membrane representing the blood brain barrier. As shown, oxygen molecules readily diffuse from the blood across the barrier and into the brain. This analytical and numerical analysis aims to model this phenomenon.

Analytical Solution

Initial Conditions:

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

Boundary Conditions:

$$C(L,t) = 0$$
$$C(0,t) = C_0$$

Our concentration profile is equal to the steady-state solution plus the transient solution:

$$C(x,t) = C_T + C_{SS}$$

Partial Differentiation Equation:

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

In a steady-state condition, the concentration does not change with time:

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

Therefore, our PDE becomes:

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

Integration of the above equation yields:

$$C = ax + b$$

Plug in boundary conditions to find a & b:

$$b = C_0$$

$$a = -\frac{C_0}{L}$$

Therefore, the steady-state solution, $C_{ss}(x)$ equals:

$$C_{ss}(x) = -\frac{C_0}{L}x + C_0$$

Since our BCs are nonhomogeneous, we must transform the BCs:

$$C_T(L,t) = C(L,t) - C_{SS}(0) = 0 - 0 = 0$$

$$C_T(0,t) = C(0,t) - C_{SS}(L) = C_0 - C_0 = 0$$

We also must transform the IC:

$$C_T(x,0) = C(x,0) - C_{SS}(x) = 0 - (-\frac{C_0}{L}x + C_0) = \frac{C_0}{L}x - C_0$$

In order to continue with the PDE, we must solve via separation of variables:

$$C_T(x,t) = \varphi(x)G(t)$$

Using this in the original PDE, and rearranging the variables yield:

$$\varphi(x)\frac{\partial G(t)}{\partial t} = D\frac{\partial^2 \varphi(x)}{\partial x^2}G(t)$$

$$\frac{\frac{\partial^2 \varphi(x)}{\partial x^2}}{\varphi(x)} = \frac{\partial G(t)}{\partial t}\frac{1}{G(t)D} = -\lambda$$

Time-dependent function:

$$\frac{dG(t)}{dt} = -\lambda D G(t)$$

$$G(t) = G_0 e^{-\lambda D t}$$

Spatially-dependent function:

$$\frac{d^2\Phi(x)}{dx^2} = -\lambda\Phi(x)$$

$$\frac{d^2\Phi(x)}{dx^2} + \lambda\Phi(x) = 0$$

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

Plug in the BCs:

$$\Phi(0) = 0 = Acos(0) + Bsin(0)$$
$$A = 0$$

$$\Phi(L) = 0 = Acos\left(\sqrt{\lambda}L\right) + Bsin(\sqrt{\lambda}L)$$
$$Bsin(\sqrt{\lambda}L) = 0$$
$$B = 0$$

Since both A and B equal zero here, the solution is trivial. Therefore, one of the following must be true:

$$'B' \,\&\, '\text{cosine}' = 0,$$

in which case:

$$\sqrt{\lambda} = \frac{(2n+1)\pi}{2L}$$

-or-

$$'A' \,\&\, '\text{sine}' = 0$$

in which case:

$$\sqrt{\lambda} = \frac{n\pi}{L}$$

Thus we now combine these with both the time-dependent function, G(t), and the spatially-dependent function, $\Phi(x)$:

$$\mathrm{C(x,t)} = Acos\left(\left[\frac{(2n+1)\pi}{2L}\right]x\right)e^{-D\left[\frac{(2n+1)\pi}{2L}\right]^2 t} \quad n = 0,1,2,3\ldots$$

$$\mathrm{C(x,t)} = Bsin\left(\left[\frac{(n\pi}{L}\right]x\right)e^{-D\left[\frac{(n\pi}{L}\right]^2 t} \quad n = 1,2,3\ldots$$

$$\mathrm{C(x,t)} = \sum_{n=0}^{\infty} Acos\left(\left[\frac{(2n+1)\pi}{2L}\right]x\right)e^{-D\left[\frac{(2n+1)\pi}{2L}\right]^2 t} + \sum_{n=1}^{\infty} Bsin\left(\left[\frac{n\pi}{L}\right]x\right)e^{-D\left[\frac{n\pi}{L}\right]^2 t}$$

Plugging in boundary condition of C(0,t) = 0, we can drop the “cosine” term as that can only be equal to zero if A = 0. Thus we are left with:

$$\mathrm{C(x,t)} = \sum_{n=1}^{\infty} Bsin\left(\left[\frac{n\pi}{L}\right]x\right)e^{-D\left[\frac{n\pi}{L}\right]^2 t}$$

Add the particular solution to get a general solution of:

$$\mathrm{C(x,t)} = \sum_{n=1}^{\infty} Bsin\left(\left[\frac{n\pi}{L}\right]x\right)e^{-D\left[\frac{n\pi}{L}\right]^2 t} + C_0\left(1-\frac{1}{L}x\right)$$

To solve for the value of the constant *B*, plug in initial condition at C(x,0) = 0

$$\mathrm{C(x,t)} = 0 = \sum_{n=1}^{\infty} Bsin\left(\left[\frac{n\pi}{L}\right]x\right)e^{-D\left[\frac{n\pi}{L}\right]^2 (0)} + C_0\left(1-\frac{1}{L}x\right)$$

$$\mathrm{C(x,t)} = 0 = \sum_{n=1}^{\infty} B_n sin\left(\left[\frac{n\pi}{L}\right]x\right) + C_0\left(1-\frac{1}{L}x\right)$$

Rearrange the terms to get the following equation:

$$C_0\left(\frac{1}{L}x-1\right) = \sum_{n=1}^{\infty} B_n sin\left(\left[\frac{n\pi}{L}\right]x\right)$$

Multiply both sides by $sin\left(\left[\frac{n\pi}{L}\right]x\right)$:

$$C_0\left(\frac{1}{L}x-1\right) * sin\left(\left[\frac{n\pi}{L}\right]x\right) = \sum_{n=1}^{\infty} B_n sin\left(\left[\frac{n\pi}{L}\right]x\right) * sin\left(\left[\frac{n\pi}{L}\right]x\right)$$

Integrate:

$$\int_0^L C_0\left(\frac{1}{L}x-1\right) * sin\left(\left[\frac{n\pi}{L}\right]x\right)dx = \int_0^L \sum_{n=1}^{\infty} B_n sin\left(\left[\frac{n\pi}{L}\right]x\right) * sin\left(\left[\frac{n\pi}{L}\right]x\right)dx$$

Simplify this to become:

$$\int_0^L C_0\left(\frac{1}{L}x-1\right) * sin\left(\left[\frac{n\pi}{L}\right]x\right)dx = B_m\frac{L}{2} \quad if\ m=n \quad -or- \quad = 0\ if\ m \neq n$$

Therefore, our B_m equals:

$$\frac{2}{L}\int_0^L C_0\left(\frac{1}{L}x-1\right) * sin\left(\left[\frac{m\pi}{L}\right]x\right)dx = B_m$$

Simplify this to solve for B_m:

$$B_m = \frac{-2C_0}{m\pi}$$

Plugging this back into our equation yields the complete concentration profile:

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

Limitations

Although our model promises to give a strong prediction of diffusion of a species across the blood-brain barrier, it is limited by the assumptions we made to simplify the model. One of these assumptions, that the concentration of oxygen at the blood-brain barrier-brain interface is zero, is especially simplifying and could have a significant impact on the model if it is not made. To account for this, our model can be further complicated by introducing a new term: a differential equation for the consumption of oxygen in the brain with respect to distance. Introducing this term, we could accurately assess the proper concentration at our target distance in the brain, and thus have a more accurate model for oxygen, and ultimately drug, diffusion.

A further limitation we have with our oxygen model is the assumption that the initial concentration of oxygen in the brain is zero. This assumption was made to simplify the analytical solution when solving the system of partial differential equations. To produce a more accurate oxygen diffusion model, we would have to further complicated our analytical solution by introducing an the value for initial concentration of oxygen in the brain, which would be obtained from literature. However, although this seems like an enormous assumption to make when it comes to oxygen modeling, this case proves to be true when this model is used for drug delivery applications. When a drug is introduced to the blood stream, it is a perfectly good assumption that there is no drug initially present inside the brain. Therefore, this model can be applied as it is for drug delivery analysis.

Numerical Validation

The solutions were plotted analytically, by solving the mathematical equation by hand, and also numerically by using the pde function in MATLAB. Solutions were plotted for 100 terms, with varying diffusivity constants between simulations. All graphs follow the general trend, shown in Figure 2, in which for all distance equal to zero the concentration is C_0, held steady by our first boundary condition. Our second boundary condition ensures for all distance equal to L the concentration goes to zero, assuming the brain acts as a perfect sink.

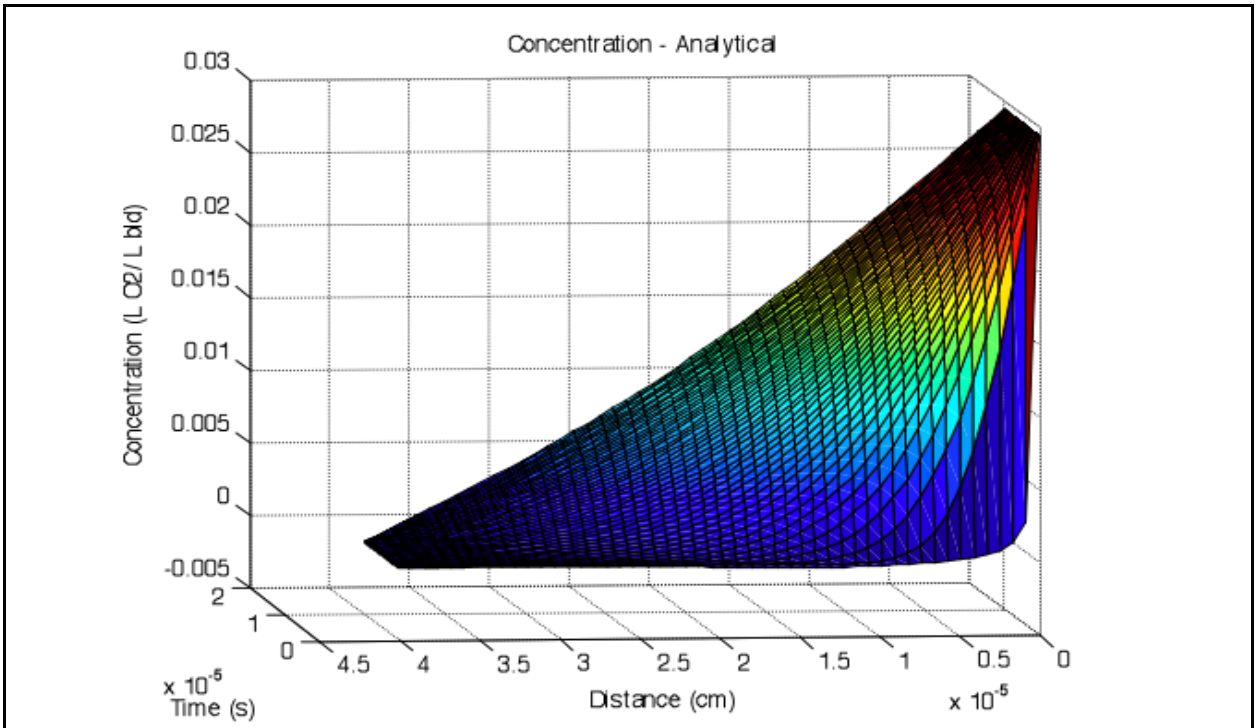

Figure 2. Displays analytical approximation model of oxygen diffusing through the blood brain barrier and into the brain with a diffusivity constant of 3.24 * 10^(-5) cm^2/s.

Figure 2 drops below zero at u(0,0) as a result of the sine function in the analytical solution. Next, we compared our analytical solution to the numerical solution found using the pde solver in MATLAB, shown in Figure 3.

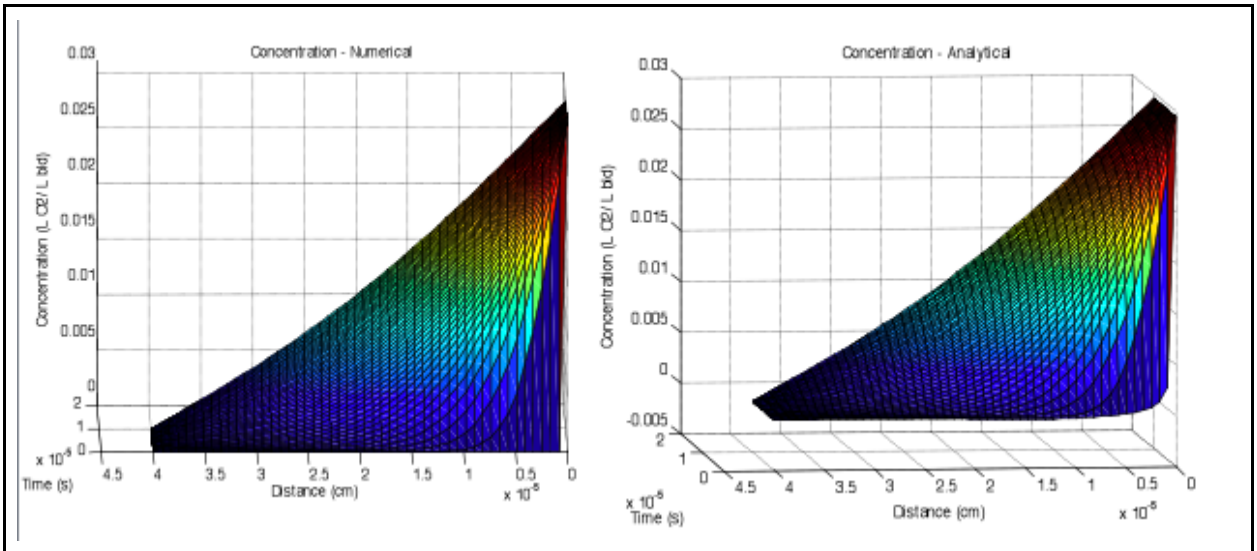

Figure 3. Compares the numerical solution found by using pde function in MATLAB, left, to the analytical solution found by hand, right. Both graphs utilize a diffusivity constant of 3.24 * 10^(-5) cm^2/s.

When comparing our analytical solution to the numerical solution, we were pleased to see that the MATLAB pde function generated very similar concentration plots for our system. Finally, we

simulated different drug diffusivity constants over the same time scale to view the effect of changing diffusivity on tissue concentration, Figure 4.

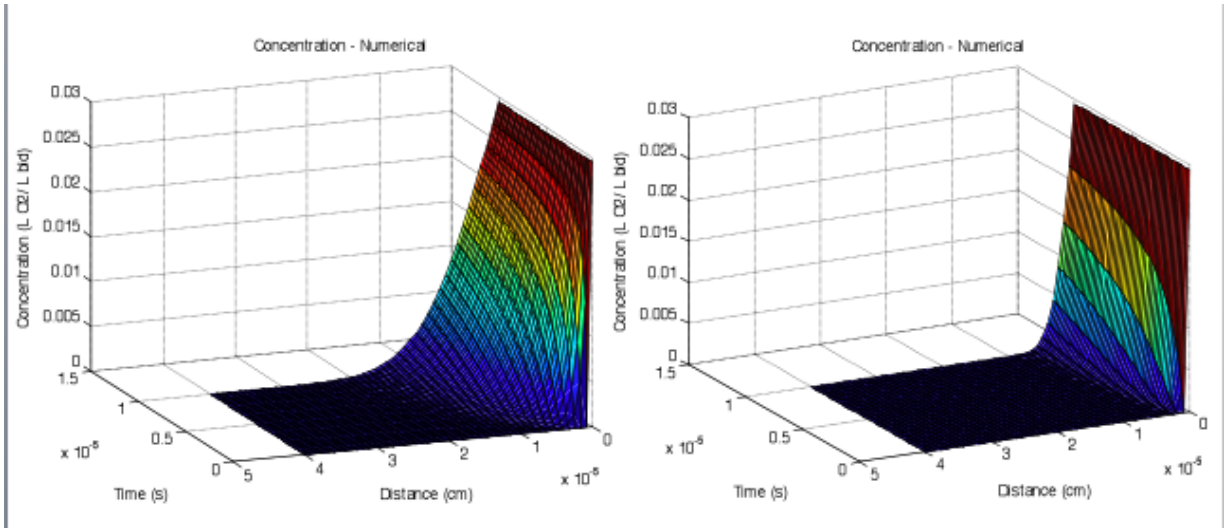

Figure 4. Displays the changes in concentration for different diffusivities using numerical simulation. Left plot has a diffusivity constant of 3.24 * 10^(-6) C, and the right plot has a diffusivity constant of 3.24 * 10^(-7) cm^2/s.

The altered diffusivity values represent different diffusivity values for potential drugs passing through the blood-brain barrier. As the diffusivity constant decreases, the concentration of oxygen, or drug, which diffused through the blood-brain barrier in the same time period also decreases.

Conclusions

In this study we have established a model for one-dimensional diffusion of oxygen through the blood-brain barrier. As we can see from our graphs, our numerical solution very closely resembles our analytical solution. This is most likely due to our simple model and the fact that we did not have to make too many assumptions to solve it analytically. We will most likely see more divergence in our solutions if we increased the the complexity of the model. Our numerical model would be more correct. Our simplistic model is obviously not going to be too effective in a real world scenario, but it will serve well for initial predictions and as a proof of concept.

Further, our model can be used to model the diffusion of a drug across the blood-brain barrier as well. For example if we were looking at a drug(L-DOPA) with a diffusivity of 3.24 * 10^(-6) cm^2/s and we needed a therapeutic dosage 28 uM within 10^(-6)s (assuming our drug was injected as a bolus directly outside the blood-brain barrier) then our model suggest that we would need a concentration of .1 mM drug/L in the blood. As expected, with lowering diffusivity values the diffusing species does not diffuse as far. We can use this to estimate the effectiveness of drugs crossing the blood-brain barrier.

References

[1] Helga E. de Vries, Johan Kuiper, Albertus G. de Boer, Theo J. C. Van Berkel and Douwe D. Breimer (1997). "The Blood-Brain Barrier in Neuroinflammatory Diseases".

[2]"About". *Blood Brain Barrier*. Johns Hopkins University. Retrieved 7 May 2013.\\ History of the Blood-Brain Barrier by T.J. Davis. Department of Pharmacology, University of Arizona, Tucson, United States

[3]Ballabh, P; Braun, A; Nedergaard, M (June 2004). "The blood–brain barrier: an overview: structure, regulation, and clinical implications.".*Neurobiology of disease* **16** (1): 1–13.

Appendix

Matlab code for Analytical Solution

```
%Blood Brain Barrier
clear all;
close all;
clc;

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

C0 = .02945; %.02945 L O2/ L bld .02945
D = 0.0000324; % cm^2/s diffusivity of oxygen in water
L = 400e-7; % cm legnth of diffusion area
final_time = .00001; % s

x = linspace(0,L,50);
t = linspace(0,final_time,50);
c = zeros(length(x),length(t));


for index_x=1:1:length(x)
 for index_t=1:1:length(t)
 total = 0;

 for n=1:1:100 %
     Bm = -2*C0/n/pi;
 total = total + Bm * exp(-D*t(index_t)*(n*pi/L)^2)...
     * sin(((n*pi/L)*x(index_x)));

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

 end
end


figure(1);
surf(t,x,c);
xlabel('Time (s)');
ylabel('Distance (cm)');
zlabel('Concentration (L O2/ L bld)');
title('Concentration - Analytical');

figure
plot(t,c)
title('Solution - Analytical')
xlabel('Time (s)')
ylabel('Concentration (L O2/ L bld)')
```

Matlab code for Numerical Solution

```
function Project_pde
%Blood Brain Barrier

global D
global C0
global L

C0 = .02945; %.02945 L O2/ L bld
D = 0.0000324; % 0.0000324 cm^2/s diffusivity of oxygen in water
L = 400e-7; % cm legnth of diffusion area
final_time = .00001; % s

x = linspace(0,L,50);
t = linspace(0,final_time,50);

%solve pde
sol_pdepe = pdepe(0,@pdefun,@ic,@bc,x,t);

figure(1)
plot(t,sol_pdepe')
title('Solution - Numerical')
xlabel('Time (s)')
ylabel('Concentration (L O2/ L bld)')

figure(2)
surf(t,x,sol_pdepe')
title('Concentration - Numerical')
xlabel('Time (s)');
ylabel('Distance (cm)');
zlabel('Concentration (L O2/ L bld)');

% function definitions for pdepe:
% --------------------------------------------------------------
function [c, f, s] = pdefun(x, t, u, DuDx)
% PDE coefficients functions
global D
c = 1;
f = D * DuDx; % diffusion
s = 0; % homogeneous, no driving term
% --------------------------------------------------------------
function u0 = ic(x)
% Initial conditions function

u0 = 0; %initial concentration is 0

% --------------------------------------------------------------
function [pl, ql, pr, qr] = bc(xl, ul, xr, ur, t)
% Boundary conditions function
global C0
pl = ul-C0; % ul-C0 zero value left boundary condition
ql = 0; % 1 % no flux left boundary condition
pr = ur; %ur % zero value right boundary condition
qr = 0; %0 % no flux right boundary condition
```