Modeling Diffusion Process of Neurotransmitter Across Synapse

University of California, San Diego

BENG 221: Mathematical Methods in Bioengineering

Vivek George

Siqi Zhang

Guang Yang

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Introduction and Background

Neurotransmitters are chemicals that transmit signals from a neuron to a target cell through a synapse. They are released and diffuse across the synaptic cleft, where they bind to specific receptors in the membrane on the postsynaptic side of the synapse[1].

The process to release neurotransmitter can be described in the following steps: arrival of the action potential causing the opening of calcium channels for calcium ions to flow into the presynaptic cleft. The presence of calcium ions cause the synaptic vesicle to open and release neurotransmitters which diffuse into the cleft. Specific neurotransmitters binds to their own receptors in the post synaptic cleft, and the binding action causes ion channels open, thus leading to a change in membrane potential. Figure 1 shows the diffusion process of neurotransmitter in synapse.

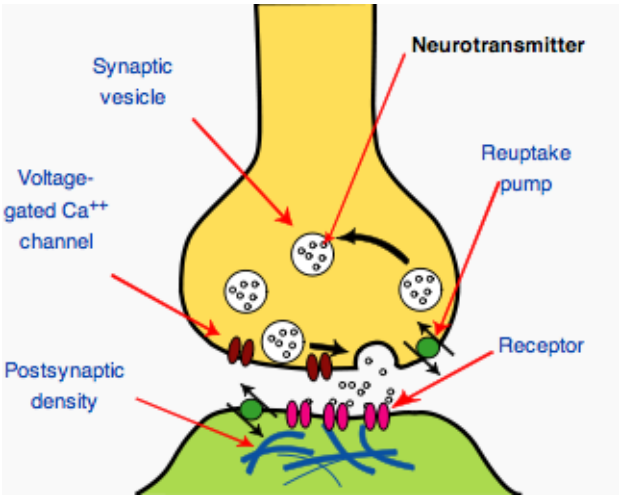

Figure 1: Diffusion process of neurotransmitter in synapse. http://en.wikipedia.org/wiki/Neurotransmitter

Neurotransmitters are synthesized from precursors such as amino acids and peptides. Common types of neurotransmitter are glutamate, nitric oxide, serotonin, acetylcholine (ACh) and GABA. Neurotransmitters can be characterized as excitatory or inhibitory. Excitatory neurotransmitter such as glutamate increases the probability that the target cell will fire an action potential[1]. Neurotransmitter such as GABA or dopamine, their receptors all have inhibitory effects. Other neurotransmitters such as Ach have both excitatory and inhibitory receptors.

Modeling diffusion process of neurotransmitters has a profound meaning since many neural disorder diseases are related to the release and diffusion of neurotransmitter. For example, patients suffering from Alzheimer's disease have damaged acetylcholine receptors, which results in memory loss and language degeneration. Patients suffering from epilepsy, their glutamate are released in large amounts, which trigger the release of calcium in post -synaptic cells. If we can successfully build a diffusion model of neurotransmitter across the synapse, we are able to model the diffusion process and

monitor the behavior of neurotransmitters.

Problem Statement and Assumptions

We model the synaptic cleft as a cylinder, and at time equals to zero, we inject the neurotransmitters at the center of the cylinder. Neurotransmitters will diffuse uniformly in the cylinder (D). The transmitter consumption rate is also constant (K). Furthermore, the receptor in post synapse absorbed all neurotransmitter, the flux of neurotransmitter only diffuse in one direction (from pre-synapse to post synapse) and all neurotransmitters which hit the surface of the cylinder are fully absorbed and do not bounce back. We will model the diffusion process over time along three dimensions.

To be problem-specific, we will model the diffusion of glutamate. The parameters we use are from reference 2.

Parameters for our model:

- Diffusion constant (D): 0.2 um^2/ms
- Consumption rate (K): $0.1nm^2/ms$
- Cleft height (Z) : 20nm
- Cylinder diameter: 400nm

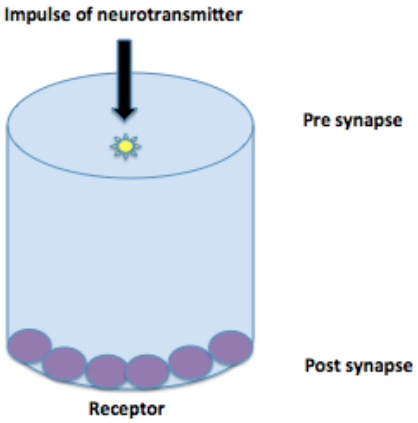

Figure 2: Schematic of diffusion of glutamate.

Mathematic model:

1. Analytical solution

We assume that $u(\rho, \theta, z, t)$ is the concentration of neuron transmitter through the synaptic cleft in the cylindrical coordinate.

Our diffusion equation for this model is:

$$\frac{\partial u}{\partial t} = D\left(\frac{1}{\rho}\frac{\partial}{\partial \rho}\left(\rho\frac{\partial u}{\partial \rho}\right) + \frac{1}{\rho^2}\frac{\partial^2 u}{\partial \theta^2} + \frac{\partial^2 u}{\partial z^2}\right) - ku \tag{1}$$

For initial Condition:

$$u(\rho, \theta, z, 0) = u_0\,\delta(\rho, \theta, z) \tag{2}$$

For boundary Condition:

$$\begin{cases} \dfrac{\partial u(\rho, \theta, z, t)}{\partial \rho}\Big|_{\rho=0} = 0 \\ u(R, \theta, z, t) = 0 \end{cases} \tag{3}$$

$$\begin{cases} \dfrac{\partial u(\rho, \theta, z, t)}{\partial z}\Big|_{z=0} = 0 \\ u(\rho, \theta, L, t) = 0 \end{cases} \tag{4}$$

$$u(\rho, \theta, z, t) = u(\rho, \theta + 2\pi, z, t) \tag{5}$$

Since the concentration function $u(\rho, \theta, z, t)$ is symmetry in the θ direction, the term θ doesn't affect the value of u. We simplified our equation as showing below:

$$\frac{\partial u}{\partial t} = D\left(\frac{1}{\rho}\frac{\partial}{\partial \rho}\left(\rho\frac{\partial u}{\partial \rho}\right) + \frac{\partial^2 u}{\partial z^2}\right) - ku \tag{6}$$

Initial Condition:

$$u(\rho, z, 0) = u_0\,\frac{\delta(\rho)\delta(z)}{\pi\rho} \tag{7}$$

Boundary Condition:

$$\begin{cases} \dfrac{\partial u(\rho, z, t)}{\partial \rho}\Big|_{\rho=0} = 0 \\ u(R, z, t) = 0 \end{cases} \tag{8}$$

$$\begin{cases} \dfrac{\partial u(\rho,z,t)}{\partial z}|_{z=0} = 0 \\ \mathrm{u}(\rho,\mathrm{L},\mathrm{t}) = 0 \end{cases} \tag{9}$$

The diffusion equation and B.C. are homogenous and the method of separation of variables is applied to solve the problem.

Let

$$\mathrm{u}(\rho,\mathrm{z},\mathrm{t}) = \Phi(\rho)\mathrm{L}(\mathrm{z})\mathrm{G}(\mathrm{t}) \tag{10}$$

The diffusion equation can be expressed as:

$$\frac{1}{D}\frac{1}{G(t)}\frac{\partial G(t)}{\partial t} + \frac{k}{D} = \frac{1}{\Phi(\rho)}\frac{1}{\rho}\frac{\partial}{\partial \rho}\left(\rho\frac{\partial \Phi(\rho)}{\partial \rho}\right) + \frac{1}{\mathrm{L}(\mathrm{z})}\frac{\partial^2 L(z)}{\partial z^2} \tag{11}$$

Assume:

$$\frac{1}{\mathrm{L}(\mathrm{z})}\frac{\partial^2 L(z)}{\partial z^2} = -{\lambda_n}^2 \tag{12}$$

$$\frac{1}{\Phi(\rho)}\frac{1}{\rho}\frac{\partial}{\partial \rho}\left(\rho\frac{\partial \Phi(\rho)}{\partial \rho}\right) = -{\lambda_i}^2 \tag{13}$$

For the solution of $L(z)$, according to (12),

$$\mathrm{L}(\mathrm{z}) = \mathrm{A}\cos(\lambda_n z) + B\sin(\lambda_n z) \tag{14}$$

Apply the boundary condition to (z) :

$$\begin{cases} \dfrac{\partial L(z=0)}{\partial z} = 0 \\ L(z=L) = 0 \end{cases} \tag{15}$$

Then we get

$$\begin{cases} B\lambda_n\cos(0) = 0 \\ \mathrm{A}\cos(\lambda_n L) + B\sin(\lambda_n L) = 0 \end{cases} \tag{16}$$

Therefore, B=0 and $\lambda_n = \frac{(2n+1)\pi}{2L}$ $(n = 0,1,2,3\ldots)$

Thus, the solution for $L(z)$ is:

$$\mathrm{L}(\mathrm{z}) = \mathrm{Acos}(\frac{(2n+1)\pi}{2L}\ \mathrm{z}) \tag{17}$$

Next, multiply both sides of equation (13) by $\rho^2\Phi(\rho)$:

$$\rho\frac{\partial}{\partial\rho}\left(\rho\frac{\partial\Phi(\rho)}{\partial\rho}\right)+{\lambda_i}^2\rho^2\Phi(\rho)=0$$

(18)

The solution of equation (13) is a Bessel Function, and it can be written as:

$$\Phi(\rho)=J_0(\lambda_i\rho)$$
$$\lambda_i\rho=roots\ of\ J_0\quad(i=1,2,3\ldots)$$

(19)

According to equation (12) and (13), $G(t)$ satisfies:

$$\frac{\partial G(t)}{\partial t}+\left({\lambda_n}^2+{\lambda_i}^2+\frac{k}{D}\right)DG(t)=0$$

(20)

Therefore, $G(t)$ can be described as:

$$G(t)=e^{-({\lambda_n}^2+{\lambda_i}^2+\frac{k}{D})Dt}$$

(21)

$$\mathrm{u}(\rho,\mathrm{z},\mathrm{t})=\sum_{n=0}^{\infty}\sum_{i=1}^{\infty}A_{ni}J_0(\lambda_i\rho)\cos(\frac{(2n+1)\pi}{2L}\ \mathrm{z})\,e^{-({\lambda_n}^2+{\lambda_i}^2+\frac{k}{D})Dt}$$

(22)

Apply initial condition (7) to solution (22)we get:

$$\mathrm{u}(\rho,\mathrm{z},0)=\sum_{n=0}^{\infty}\sum_{i=1}^{\infty}A_{ni}J_0(\lambda_i\rho)\cos\left(\frac{(2n+1)\pi}{2L}\ \mathrm{z}\right)$$
$$=u_0\frac{\delta(\rho)\delta(\mathrm{z})}{\pi\rho}$$

(23)

Then, A_{ni} can be solved by integral:

$$A_{ni}=\frac{\int_0^R\int_0^L u_0\frac{\delta(\rho)\delta(\mathrm{z})}{2\pi\rho}J_0(\lambda_i\rho)\cos(\frac{(2n+1)\pi}{2L}\ \mathrm{z})\rho\mathrm{d}\rho\mathrm{d}\mathrm{z}}{\frac{L}{2}\frac{R^2}{2}{J_1}^2(\lambda_iR)}$$

$$=\frac{2u_0}{\pi LR^2{J_1}^2(\lambda_iR)}$$

(24)

Therefore,

$$\mathrm{u}(\rho,\mathrm{z},\mathrm{t})=\sum_{n=0}^{\infty}\sum_{i=1}^{\infty}\frac{u_0}{\pi LR^2{J_1}^2(\lambda_iR)}\ J_0(\lambda_i\rho)\cos(\frac{(2n+1)\pi}{2L}\ \mathrm{z})\,e^{-({\lambda_n}^2+{\lambda_i}^2+\frac{k}{D})Dt}$$

(25)

By applying analytic solution [25] to Matlab, we can obtain the plots of concentration. Due to the limit of dimensions, we plot figure of variables ρ and t at different z. The range of z is [0, L] and we choose positions at z=0, z= $\frac{L}{4}$, z= $\frac{L}{2}$, and z= $\frac{3L}{4}$ to plot analytical solution and show how $u(\rho, z, t)$ changes with t and z.

The following figures show the change of neurotransmitter concentration along the synaptic cleft.

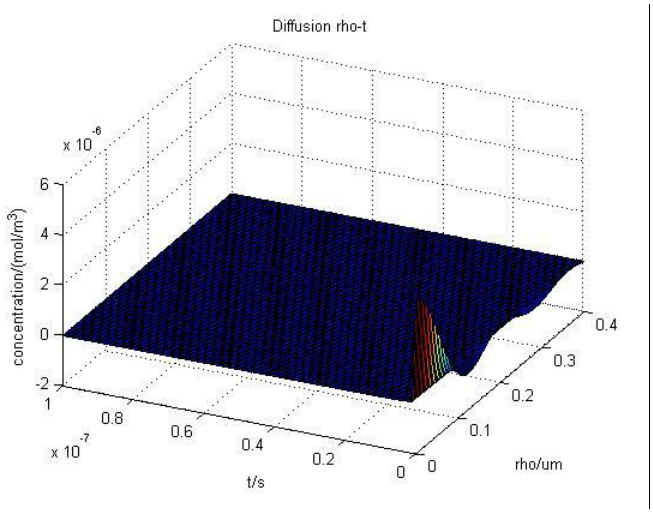

Figure 3: Concentration of neuron transmitter in plane $\rho - t$ at z=0

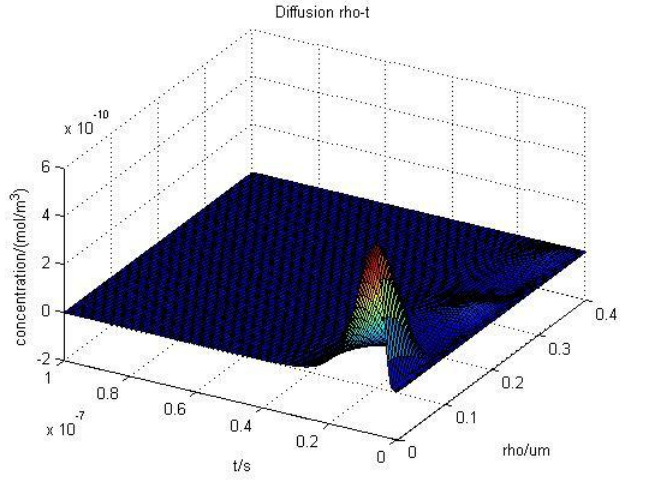

Figure 4: Concentration of neuron transmitter in plane $\rho - t$ at z= $\frac{L}{4}$

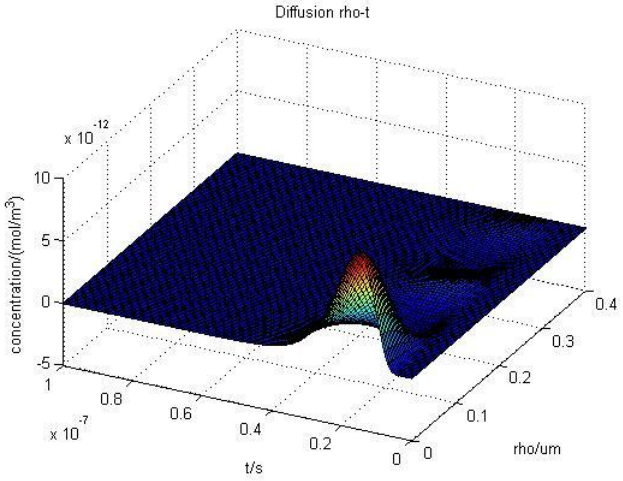

Figure 5: *Concentration of neuron transmitter in plane* $\rho - t$ *at* $z = \frac{L}{2}$

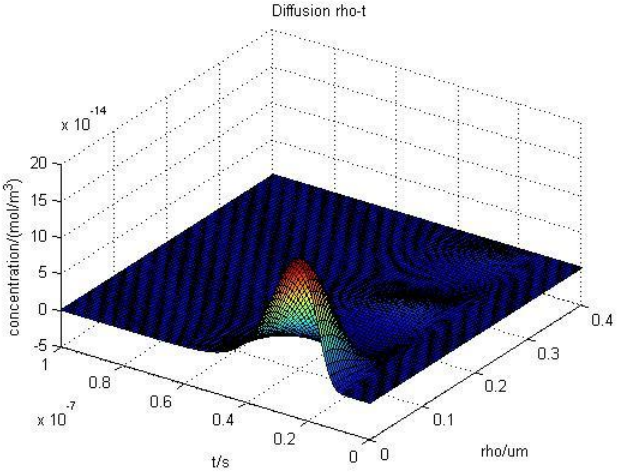

Figure 6: *Concentration of neuron transmitter in plane* $\rho - t$ *at* $z = \frac{3L}{4}$

From figure 3 to 6, there is a peak of concentration of neurotransmitter, representing the impulse release of transmitter goes through the synaptic cleft. From the dynamics of the graph we can see the diffusion process of neurotransmitter along z and ρ direction. The value of the concentration decreases due to the consumption term caused by enzymes. It should be mentioned that in the Matlab code, we only use first 5 roots of Bessel function which results in the large oscillation in the plots. The more roots we pick, the more accurate the plot will be. The plots show that the impulse of neuron transmitters go through the synaptic cleft with consumption, and spread out in the cross slices of the cylinder model of the cleft.

Numerical Solution

On our way to numerically solve our 4-D (3 space, 1 time) partial differential equation, we considered several approaches. To name a few we explored the possibility to use of MATLAB's PDE ToolBox, to develop a finite element based algorithm, and finally settled on implementing a finite differences algorithm.

Our initial approach was to use the PDE ToolBox, but we soon realized that the 2 spatial dimension analog to our problem would not be a sufficient since the volume of the space would cause the concentration at a point in the space to be lower than the concentration in a 2 dimensional plane. The next approach taken was to determine whether a finite element algorithm could be developed to solve our problem, but as the methodology to develop, such an algorithm became known to us, we realized its complexity, and abandoned that approach. Finally, we set to implement an explicit finite differences based algorithm, more specifically, the backward difference approach was used to numerically solve our PDE. The reason the backward difference approach was used was to minimize algorithm implementation complexity, and given the expected smoothness of our solution a more complex algorithm may not be necessary.

Figure 7 to Figure 10 shows the dynamic of diffusion process in the synaptic cleft. Before the inject of the impulse, we expected to see no diffusion on the plane since nothing happens (figure 7). As soon as the neurotransmitters have been injected, we see a spike of impulse in the plane (figure 8). The transmitters start diffuse in the synapse(figure 9) and as time goes on, we see the spike is spreading and its value decreases with time.

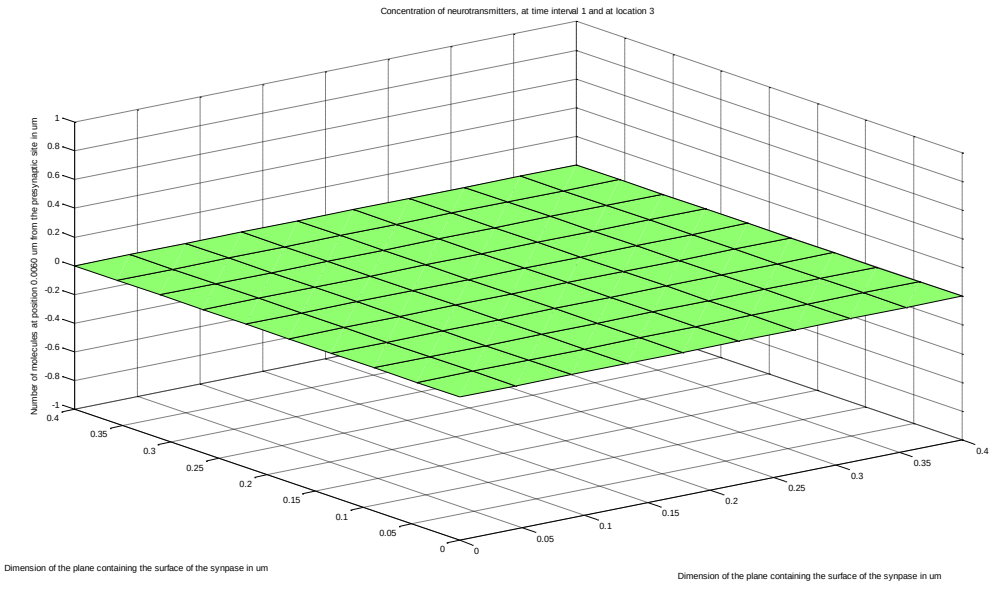

Figure 7: the concentration of the neurotransmitters at a time before impulse has

broken through the plane in the cleft.

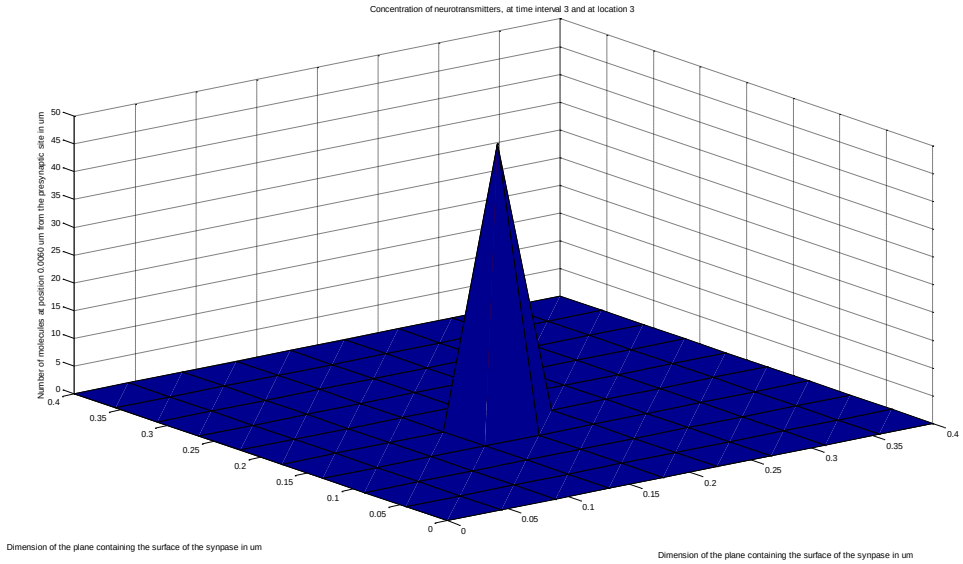

Figure 8: the concentration of the neurotransmitters at a time after impulse has broken through the plane in the cleft.

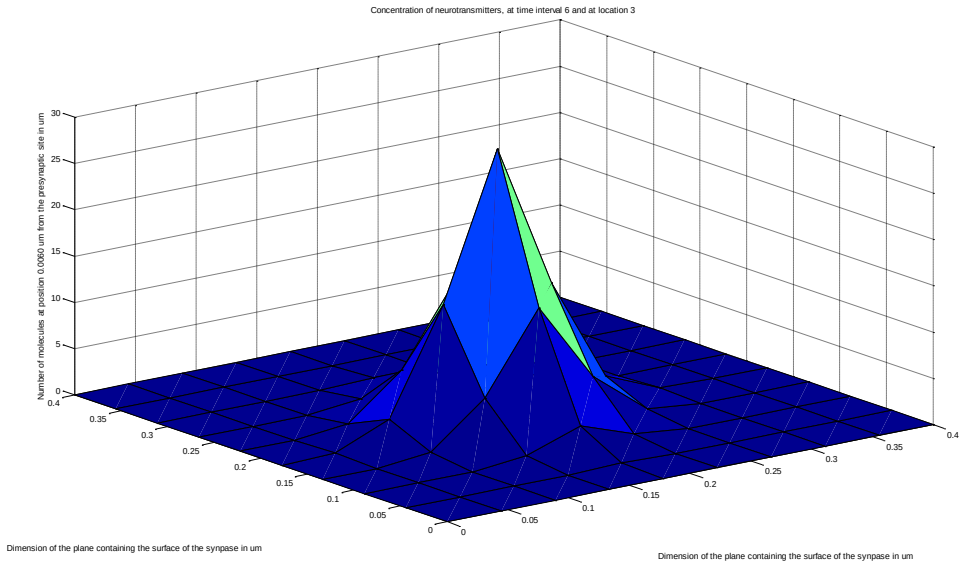

Figure 9: the concentration of the neurotransmitters at a later time after impulse has broken through the plane in the cleft.

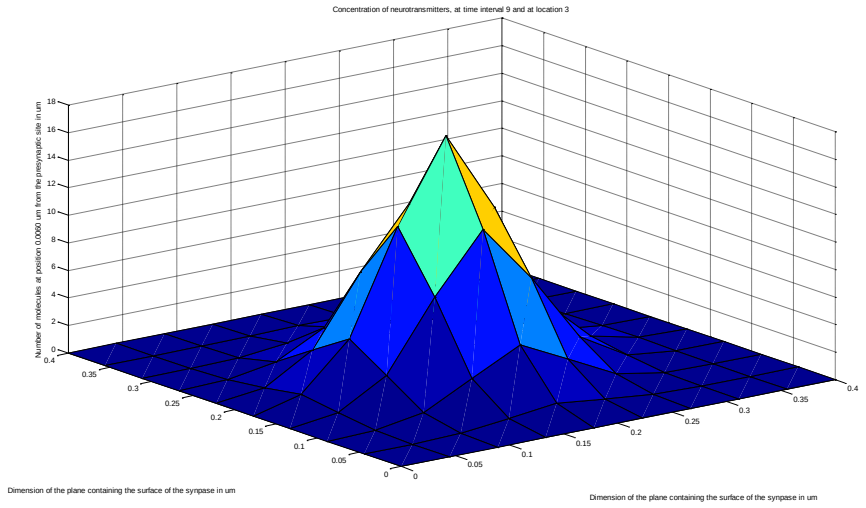

Figure 10: the concentration of the neurotransmitters after some time after impulse has broken through the plane in the cleft.

Conclusion and future work

We are able to see the diffusion of neurotransmitter through synapse by plotting both analytical and numerical solution. We are also be able to show that the concentration decreases with time by calculating the peak value of the impulse. However, since we are using different methods to plot the diffusion process, the graphs from analytical solution and numerical solutions are different. For future work, we would like to model the diffusion process for more general conditions. First, we want to vary boundary conditions to take into account additional chemical dynamics such as Michaels-Mention based receptor binding, and enzyme substrate interaction. To do so, we will need to incorporate into our model boundary conditions which are non-homogenous to account for chemical kinetics. Secondly, we would like to modulate the consumption term to simulate medical intervention of transmitter kinetics. In this model, the consumption term is linear and based on concentration, in future we would like to make it nonlinear and/or periodic. Third, we want to generalize the model with multiple vesicle dynamics rather than single vesicle and the release of neurotransmitter should be position dependent. Last, we want to extend the model that can be adapted to specific condition such as how does the diffusion process change with different calcium level.

Reference

1. http://en.wikipedia.org/wiki/Neurotransmitter

2. Freche, D et al. Synapse Geometry and Receptor Dynamics Modulate Synaptic Strength. 2011

3. Khaliq, A et al. A new 3D mass diffusion–reaction model in the neuromuscular junction. Journal of Computational Neuroscience, 2010

4. Liu D, Wang Yf, DeCoster MA. Spectral Element Simulation of Reaction-Diffusion System in the Neuromuscular Junction. Applied & Computational Mathematics, 2013

Appendix I:

Analytical solution

```
% parameters
D =400;    %Diffusion rate: 0.02um/s
k = 23e7;    %Consumption rate
L = 0.02;      %Cleft height: 0.02um
R = 0.4;    %Cylindrical diameter : 0.4um
u0 = 6e-13;
tmax=5e-7; %time range: 0--> 5*10(-5)ms


drho = R/100;    %rhostep
rho = 0:drho:R;
nrho = length(rho);

dt = tmax/100;    %timestep
t = 0:dt:tmax;
nt = length(t);

BesselRoots = ...    % first five roots of the first 5 Bessel functions of the 1st kind
[2.4048,    3.8317,    5.1356,    6.3802,    7.5883,    8.7715; ...
 5.5201,    7.0156,    8.4172,    9.7610, 11.0647, 12.3386; ...
 8.6537, 10.1735, 11.6198, 13.0152, 14.3725, 15.7002; ...
11.7915, 13.3237, 14.7960, 16.2235, 17.6160, 18.9801; ...
14.9309, 16.4706, 17.9598, 19.4094, 20.8269, 22.2178];

sol_ana = zeros(nt,nrho);
for n=1:500
      for i=1:5
            m = (2*n-1) * pi /(2* L);
            lam = BesselRoots(i,1) /R;
            A = 2 * u0 / (pi * L * R^2 * besselj(1, BesselRoots(i,1))^2);
            sol_ana = sol_ana + A *cos(m*z)*    besselj(0,lam*rho)'* exp(-D *(lam^2 +
m^2 + k/D) * t);
      end
end

% creat 3d plot(rho-t)
surf(rho,t,sol_ana');
title('Diffusion rho-t')
ylabel('t/s');
xlabel('rho/um');
zlabel('concentration/(mol/m^3)');
```

z=0

Appendix II
Numerical solution

```
clear all;
clc;

%%% Homogeneous PDE: Linear (3-D) Diffusion
%%% BENG 221 example, 11/22/2013

D     = 0.2;
height = 0.02;
width  = 0.400;
k     = 0.1;
ic    = 5000;
tstop  = 10;


% domain
xmesh = linspace(0,width,10);
ymesh = linspace(0,width,10);
zmesh = linspace(0,height,10);
tmesh = linspace(0,tstop,10);
dx = max(xmesh)/length(xmesh);
dy = max(ymesh)/length(ymesh);
dz = max(zmesh)/length(zmesh);
dt = max(tmesh)/length(tmesh);

% solution using finite differences (see Week 1 class notes)
nx = length(xmesh); % number of points in x dimension
ny = length(ymesh); % number of points in x dimension
nz = length(zmesh); % number of points in x dimension
nt = length(tmesh); % number of points in t dimension
stepsizex = 1/10; % stepsize for numerical integration
stepsizey = 1/10; % stepsize for numerical integration
stepsizez = 1/10; % stepsize for numerical integration
sol_fd = zeros(nx, ny, nz, nt);
sol_fdx = zeros(nx, ny, nz, nt);
sol_fdy = zeros(nx, ny, nz, nt);
sol_fdz = zeros(nx, ny, nz, nt);
```

```
sol_fd(ceil(nx/2), ceil(ny/2), 1, 1) = ic; % initial conditions; delta
impulse at center

for t = 1:nt-1
%    old_sol_fd = sol_fd;
    % update boundary conditions
    sol_fd(:, :, nz, t+1) = 0; % right boundary conditions; zero value
    sol_fd(:, 1, :, t+1)  = 0; % top boundary conditions; zero value.
    sol_fd(:, ny, :, t+1) = 0; % bottom boundary conditions; zero value
    sol_fd(1, :, :, t+1)  = 0; % forward boundary conditions; zero value
    sol_fd(nx, :, :, t+1) = 0; % back boundary conditions; zero value

    % update x coordinate for loops
    for z = 1:nz
        for y = 1:ny
            for x = 2:nx-1
                sol_fdx(x, y, z, t) = stepsizex * ...
                    (sol_fd(x-1,y, z, t) - 2 * sol_fd(x, y, z, t) +
sol_fd(x+1,y, z, t));
            end
        end
    end

    % update y coordinate for loops
    for z = 1:nz
        for x = 1:nx
            for y = 2:ny-1
                sol_fdy(x, y, z, t) = stepsizey * ...
                    (sol_fd(x, y-1, z, t) - 2 * sol_fd(x, y, z, t) + sol_fd(x,
y+1, z, t));
            end
        end
    end

    % update y coordinate for loops
    for x = 1:nx
        for y = 1:ny
            for z = 2:nz-1
                sol_fdz(x, y, z, t) = stepsizez * ...
                    (sol_fd(x, y, z-1, t) - 2 * sol_fd(x, y, z, t) + sol_fd(x,
y, z+1, t));
            end
        end
    end
```

```
    sol_fd(:,:,:,t+1) = sol_fd(:,:,:,t) + sol_fdx(:,:,:,t) +
sol_fdy(:,:,:,t) + sol_fdz(:,:,:,t) - stepsizez.*k.*sol_fd(:,:,:,t);
    sol_fd(:, :, 1, t+1)  = sol_fd(:, :, 2, t+1); % left boundary conditions;
zero flux
    figure(t)
    zz = 3;
    surf(xmesh,ymesh,sol_fd(:,:,zz,t))
    title(['Concentration of neurotransmitters, at time interval
',num2str(t*dt),' and at location ',num2str(zz)])
    xlabel('Dimension of the plane containing the surface of the synpase
in um')
    ylabel('Dimension of the plane containing the surface of the synpase
in um')
    zlabel('Number of molecules at position 0.0060 um from the presynaptic
site in um')
end
```