BEENG 221: Mathematical Methods in Bioengineering

Diffusion of Acetylcholine in the Synapse

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Problem Statement

Alzheimer's patients experience a decrease in the functionality of their memory and ability to learn and problem solve. Generally, the cause of symptoms relates to the rate of diffusion of acetylcholine (ACh) in the synaptic cleft. This can be modeled by random walk diffusion and the 1-D diffusion equation to estimate the how the change the diffusivity affects the probability distribution of ACh in the synaptic cleft.

Background

Healthy Brain

Neurons are cells in the nervous system. These cells communicate with each other by sending signals across the synaptic cleft, the space between the neurons, in the form of neurotransmitters. ACh is a common neurotransmitter that when released from a neuron, binds to a receptor protein on another neuron, causing the propagation of action potential down that neuron [1].

Figure 1. ACh release in neuron.

Alzheimer's Brain

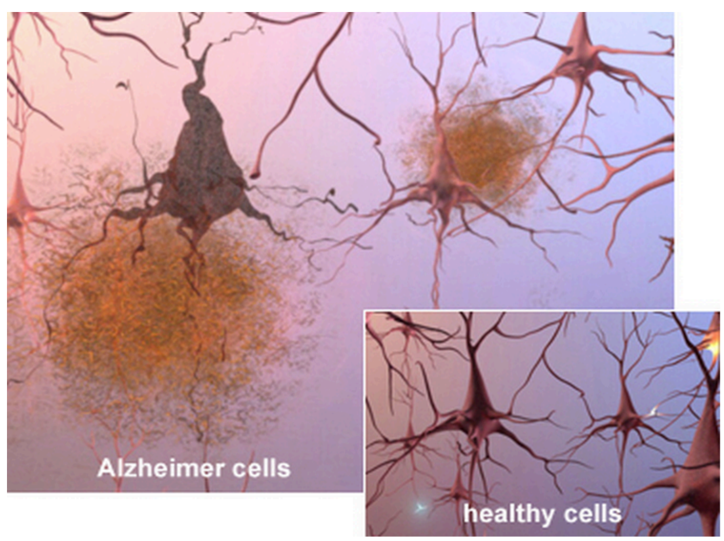

Figure 2. Alheimer's Cells Compared to Healthy Cells.

Alzheimer's disease is a type of dementia, classified by loss of brain function [2]. Common symptoms include memory loss, trouble with problem solving, confusion, and impaired judgment [2]. This disease is typically seen in older patients and gradually gets worse over time. One cause of the symptoms that Alzheimer's patients experience is reduced diffusion of ACh in the synaptic cleft [2]. Reduced diffusion is caused by abnormal clusters of protein fragments called plaques that build up on the branches of the neurons [2]. Plaques cause an increase in the tortuosity of the path that the ACh must follow to get from one cell to another [2]. This creates roundabout routes for ACh diffusion with contorted paths, dead-end spaces that trap molecules, and increased wall interactions [2]. Thus, increased tortuosity results in a decrease in diffusivity because it takes the ACh longer to travel from one neuron to another [2].

Mathematical Model

Assumptions

The mathematical model assumes that the diffusion of ACh occurs in a quiescent fluid, and the diffusivity constants account for the tortuosity and complete path that the ACh takes. In addition, according to this model, the ACh only moves in the x direction and starts diffusing at x=0, as seen in Figure 3. The particle cannot stay in the same spot over time and the probability of stepping left and right is equal. Particles are small enough in their surrounding area that an infinite domain can be assumed across the x-axis. Lastly, this model assumes that neurons are not destroyed due to Alzheimer's.

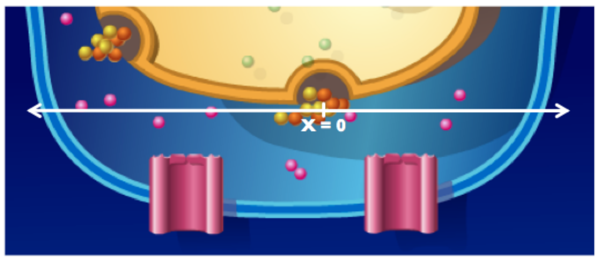

Figure 3. The axis of interest in the synaptic cleft.

Random Walk

Diffusion of ACh can be modeled by random walk by looking at the individual path that each molecule takes, and then graphing the path of the molecule with respect to time. Figure 4 illustrates this phenomenon.

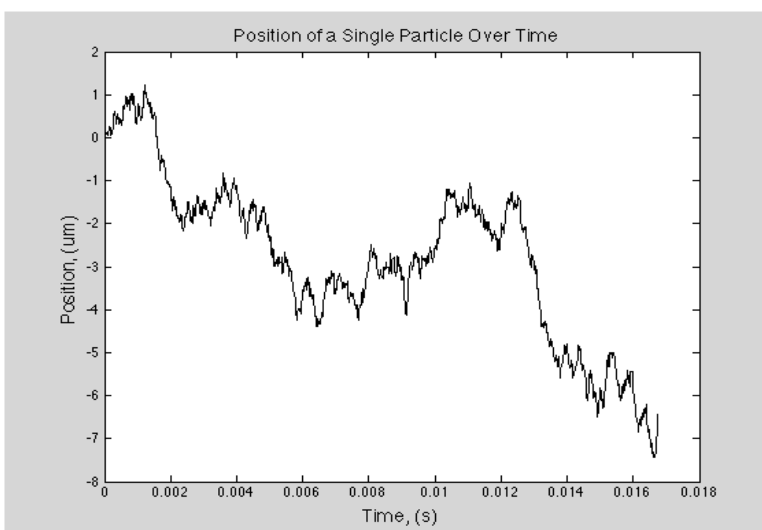

Figure 4. Random walk of a particle over time with 50/50 chance of stepping left/right.

For a more accurate model, random walk can be modeled with the Markov Process, which determines the probability, P, of a particle existing in a given space and time. It is described by the following equations:

$$P(x,t) = \sum_{n=-\infty}^{\infty} P(x \pm n\Delta x, t - \Delta t)$$

$$= aP(x + \Delta x, t - \Delta t) + \ bP(x - \Delta x, t - \Delta t)$$

where Δx is the position step, Δt is the time step, and a and b are the probabilities of a particle moving left and right respectively. Assuming a = b:

$$\boxed{P(x,t) = \frac{1}{2}P(x + \Delta x, t - \Delta t) + \frac{1}{2}P(x - \Delta x, t - \Delta t)}$$

This probability can be plotted versus position and time to model the chance of a particle being in a specific space at a specific time. The model follows a Gaussian distribution and can also be modeled by the 1-D diffusion equation [3].

Diffusion Equation

The derivation of the diffusion equation from the Markov Process is as follows:

$$P(x,t) - P(x, t - \Delta t) = \ \frac{1}{2}\left[\left(P(x + \Delta x, t - \Delta t) + P(x - \Delta x, t - \Delta t)\right)\right] - P(x, t - \Delta t)$$

$As\ \Delta t \to 0\ and\ \Delta x \to 0$

$$\Delta t \frac{\partial P}{\partial t} = \ \frac{1}{2}\Delta x^2 \frac{\partial^2 P}{\partial x^2}$$

$$\frac{\partial P}{\partial t} = \frac{1}{2}\frac{\Delta x^2}{\Delta t}\frac{\partial^2 P}{dx^2}$$

Let diffusivity, $D = \frac{\Delta x^2}{2\Delta t}$

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

This model is similar to the Markov Process and models the probability of a molecule being at a specific place at a specific time. This is the same result that Einstein proved can be used to model the diffusion of small particles [4].

<u>Solving the Analytical Solution</u>

This model simulates the release of ACh across the synapse. In order to simplify the calculations, the model will consider the release of a single vesicle. The diffusion equation models this release.

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

The instant the ACh is released from the vesicle will be considered the initial condition and the time is set equal to zero.

$$p(x,0) = g(x) = \delta(x), \ -\infty \le x \le \infty$$

This will model ACh over an infinite domain, which will be the boundary conditions for the model.

$$p(-\infty,t) = 0$$
$$p(\infty,t) = 0$$

In order to compare the diffusion equation to the random walk model, the diffusion equation must first be solved for the probability distribution. Since this is being modeled on an infinite domain Fourier's Transforms can be used.

$$P(\omega,t) = F\left[p(x,t)\right] = \int_{-\infty}^{\infty} p(x,t)e^{-j\omega x}dx$$

The definition of the Fourier Transform defines the first and second derivatives of a function in the Fourier domain as follows:

$$F\left[\frac{\partial}{\partial x}p(x,t)\right] = j\omega P(\omega,t)$$
$$F\left[\frac{\partial^2}{\partial x^2}p(x,t)\right] = \left(j\omega\right)^2 P(\omega,t) = -\omega^2 P(\omega,t)$$

These transforms are plugged back into the original equation, and the equation is solved for the transform of the probability distribution.

$$\frac{\partial}{\partial t}P(\omega,t) = -D\omega^2 P(\omega,t)$$
$$P(\omega,t) = P(\omega,0)e^{-D\omega^2 t}$$

Next the inverse Fourier transform is taken to convert the function from the Fourier domain, back into the time domain.

$$p(x,t) = F_x^{-1}\left[P(\omega,t)\right] = \frac{1}{2\pi}\int_{-\infty}^{\infty} P(\omega,t)e^{j\omega x}d\omega$$

Using this formula the probability distribution is found.

$$p(x,t) = \frac{1}{2\pi}\int_{-\infty}^{\infty} P(\omega,t)e^{-D\omega^2 t}e^{j\omega x}d\omega$$

The terms inside the integral are still in the Fourier domain. P(ω,0) is the Fourier transform of the initial condition.

$$P(\omega,0) = \int_{-\infty}^{\infty} p(x,0)e^{j\omega x}dx$$

$$P(\omega,0) = \int_{-\infty}^{\infty} g(x)e^{j\omega x}dx$$

$e^{-D\omega^2 t}$ is the Fourier transform of another function, h(x).

$$h(x) = F_x^{-1}(e^{-D\omega^2 t})$$
$$h(x) = \frac{1}{2\pi}\int_{-\infty}^{\infty} e^{-D\omega^2 t} e^{j\omega x} d\omega$$

Considering only the exponents the following simplifications can be made:

$$-D\omega^2 t + j\omega x = -Dt\left(\omega^2 + j\frac{x}{Dt}\omega - \frac{x^2}{4D^2t^2}\right) - \frac{x^2}{4Dt} = -Dt\left(\omega + \frac{jx}{2Dt}\right)^2 - \frac{x^2}{4Dt}$$

This is plugged back into h(x), and the substitution method is used to simplify the equation.

$$h(x) = \frac{1}{2\pi}\int_{-\infty}^{\infty} e^{Dt\left(\omega + \frac{jx}{Dt}\right)^2} e^{-\frac{x^2}{4Dt}} d\omega$$
$$y = \sqrt{Dt}\left(\omega + \frac{jx}{Dt}\right)$$
$$dy = \sqrt{Dt}\, d\omega$$
$$h(x) = \frac{1}{2\pi}\frac{1}{\sqrt{Dt}} e^{-\frac{x^2}{4Dt}} \int_{-\infty}^{\infty} e^{-y^2} dy$$

By Euler's method,

$$\int_{-\infty}^{\infty} e^{-y^2} dy = \sqrt{\pi}$$
$$h(x) = \frac{1}{\sqrt{4\pi Dt}} e^{-\frac{x^2}{4Dt}}$$

Convolution is now used to find a function for the probability distribution in the time domain.

$$p(x,t) = g(x) * h(x)$$

By definition:

$$p(x,t) = \int_{-\infty}^{\infty} g(x - x_0) h(x_0) dx_0$$

Plugging in $h(x) = \frac{1}{\sqrt{4\pi Dt}} e^{-\frac{x^2}{4Dt}}$ and g(x) = δ (x),

$$p(x,t) = \int_{-\infty}^{\infty} \delta(x - x_0) \frac{1}{\sqrt{4\pi Dt}} e^{-\frac{x_0^2}{4Dt}} dx_0$$
$$p(x,t) = \frac{1}{\sqrt{4\pi Dt}} \int_{-\infty}^{\infty} \delta(x - x_0) e^{-\frac{x_0^2}{4Dt}} dx_0$$

However, this is a rather complex integral to solve and would be more easily solved using the definition of the Laplace transform.

$$g * h = G \times H = (1) \times L^{-1}(H) = h(x)$$

Therefore,

$$p(x,t) = h(x)$$

$$\boxed{p(x,t) = \frac{1}{\sqrt{4\pi Dt}} e^{-\frac{x_0^2}{4Dt}}}$$

Results & Discussion

Model Comparison

The model is represented through various methods using MATLAB. The following constants are used:

$D_{healthy}$ = 800 um^2/sec and $D_{Alzheimer's}$ = 547 um^2/sec [5][6].

The three methods used are a macroscopic analytical solution, a macroscopic finite difference solution and a microscopic numerical random walk solution. Figures 5-7, respectively, depict these solutions for a healthy brain.

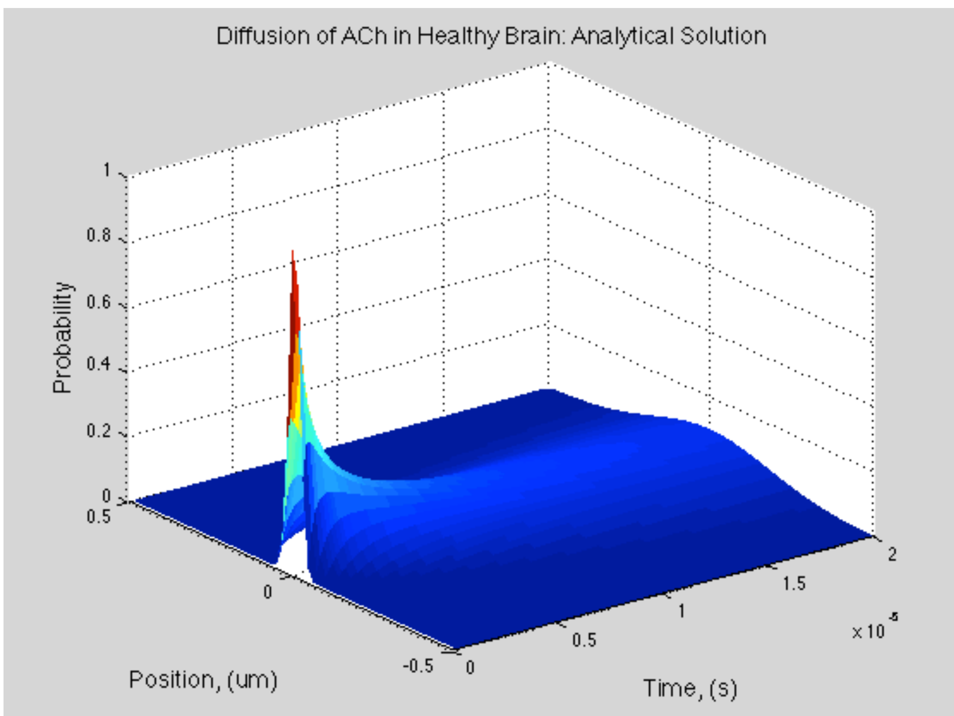

Figure 5. Analytical solution of diffusion of ACh across the synaptic cleft in a healthy brain.

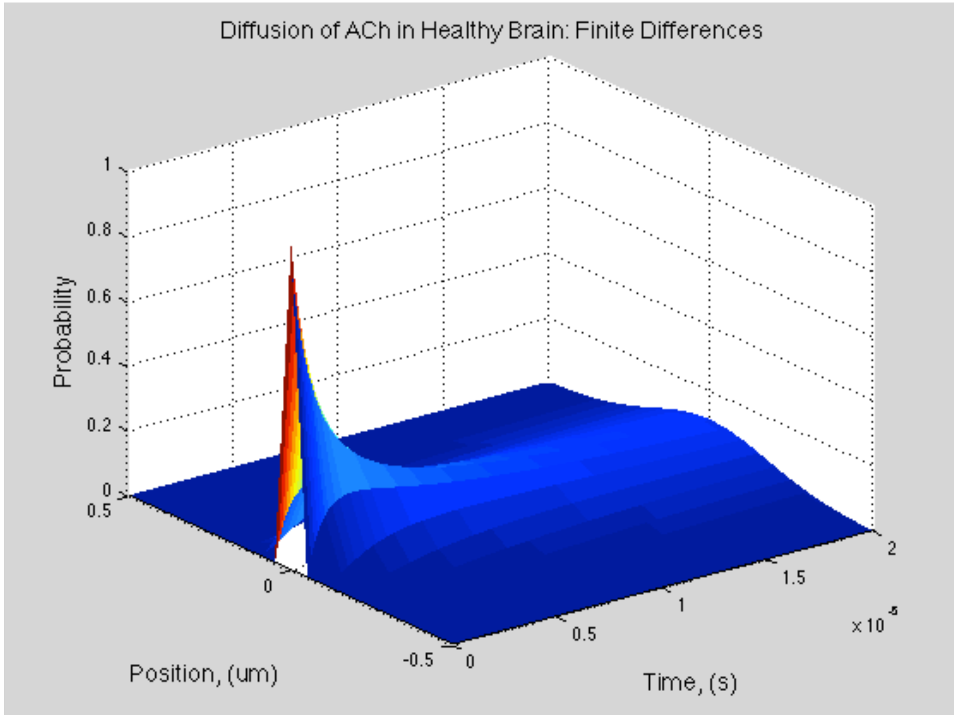

Figure 6. Finite difference solution of diffusion of ACh across the synaptic cleft in a healthy brain.

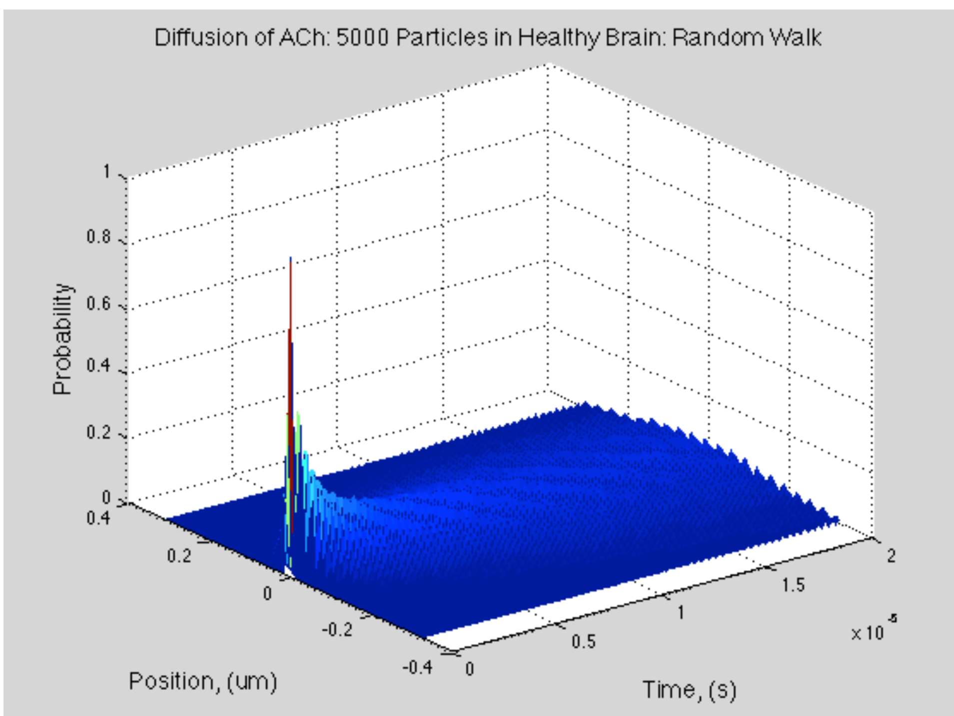

Figure 7. Random walk solution of diffusion of ACh across the synaptic cleft in a healthy brain.

These graphs model the probability distribution of ACh across the synaptic cleft. The initial impulse is modeled in all three figures. The analytical solution in Figure 5 depicts the distribution of the ACh over time. The bulk of the concentration diffuses almost instantaneously in a Gaussian distribution. The synaptic cleft is about 30 nm from the origin. With this model, ACh reaches the neuron within the first time step (1.67×10^{-7} seconds). Complete ACh diffusion is estimated to last about 2×10^{-4} seconds [7]. Due to the assumptions made, this model shows qualitative agreement with the ACh diffusion; however, it does not show quantitative agreement.

In comparison, the other methods also show qualitative agreement with ACh diffusion and the analytical solution. As seen in Figure 6, the finite difference solution does not as accurately depict the Gaussian distribution. This is because the finite difference approach is an approximation.

The random walk model is depicted in Figure 7. This model averages the probability of 5000 ACh particles randomly walking across the synaptic cleft. The solution appears more intermittent than the analytical solution. This is because the model calculates the probability distribution by counting the amount of particles in a defined increment of time and space across the domains and graphing the resulting histogram. This model indeed proves that the microscopic random walk method is equivalent to the macroscopic diffusion method.

Healthy Brain vs. Alzheimer's Brain

The analytical solution is the most accurate representation. This model is used to compare the model in a healthy brain and an Alzheimer's brain. Figures 8-9 depict this comparison.

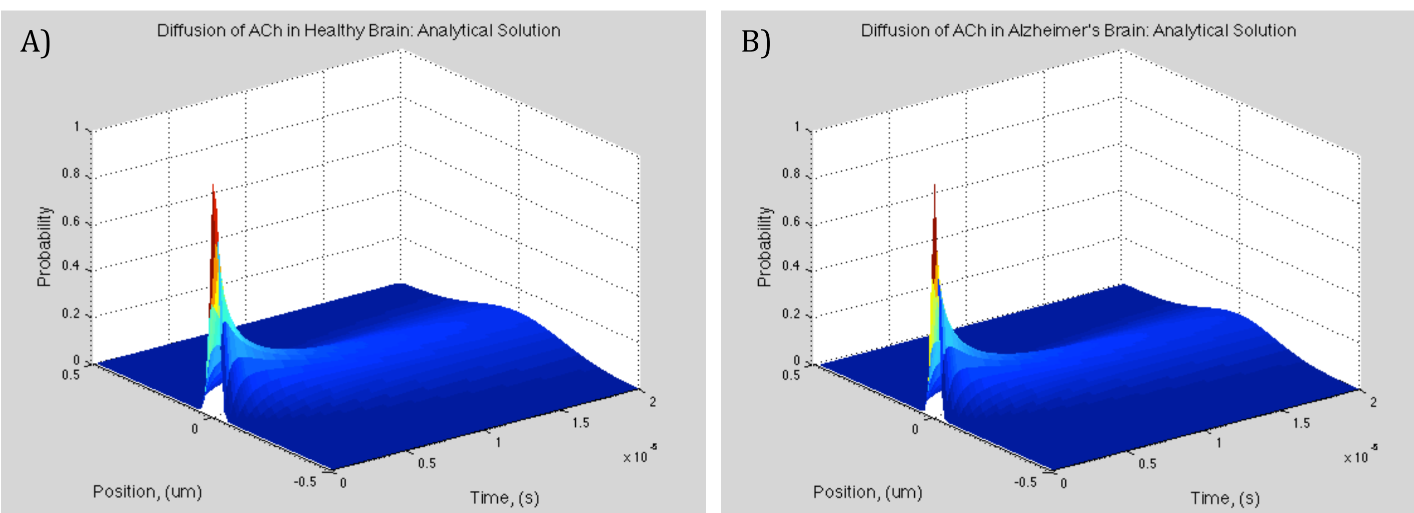

Figure 8. Analytical solution comparing ACh diffusion in a A) healthy brain B) Alzheimer's brain.

The Alzheimer's brain is modeled with a lower diffusivity than the healthy brain. The lower diffusivity is caused by the increase in tortuosity in the neuronal extracellular space. Over time, these graphs appear to be almost identical. However, the region of interest is only from -30 um to 30 um over the initial time steps. A comparison of the two probability distributions at the fourth time step (6.68×10^{-7} seconds) can be seen in Figure 9.

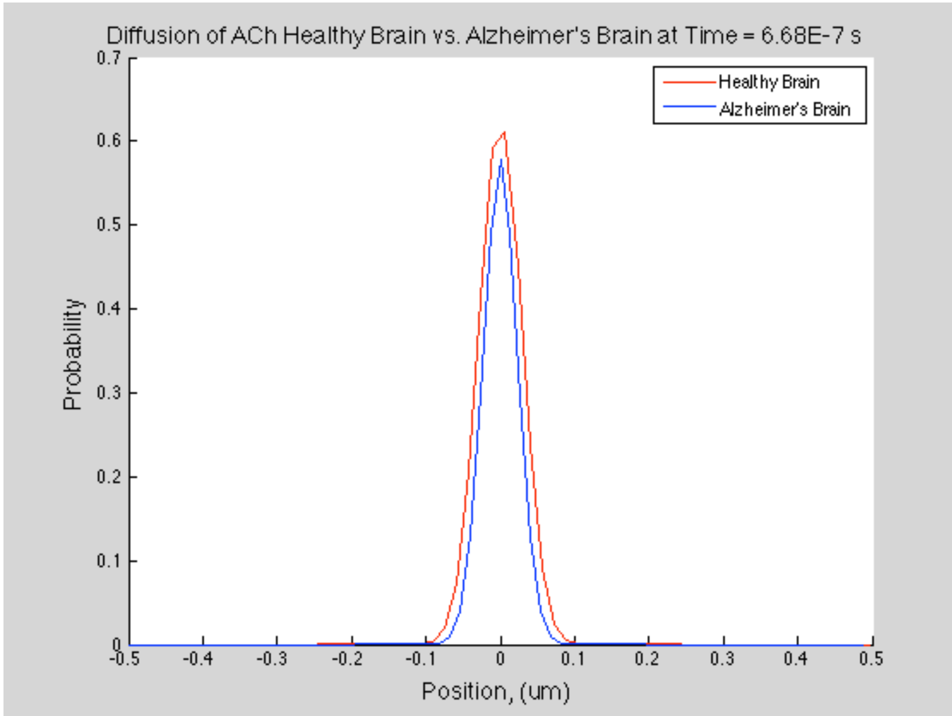

Figure 9. Comparison of ACh in a health brain versus an Alzheimer's brain at 6.68 x 10^7 seconds.

As expected, the ACh molecules in a healthy brain have a higher probability of reaching the synaptic cleft than the Alzheimer's brain. This probability difference is apparent across all times. Although this difference appears small, it has a large affect on functionality in Alzheimer's patients.

Conclusion

As seen in Figures 5-7, ACh diffusion across the synaptic cleft can be qualitatively modeled by a partial differential diffusion equation on an infinite domain. The analytical solution produces the most accurate results, depicting the Gaussian distribution of the ACh particles. In addition, Figure 7 depicts that the microscopic random walk of particles is equivalent to the macroscopic diffusion model. Finally, this model proves that increased tortuosity, leading to decreased diffusion, is one cause of decreased brain function in Alzheimer's patients.

Future Work

Although this model makes qualitative conclusions, quantitative analyses were inaccurate because of the assumptions made. In future models, all three dimensions could be considered in a non-quiescent fluid. This would better represent the full path the ACh travels and introduce a drift that the molecules experience in a non-quiescent fluid. In addition, the model could determine how severe a patient's Alzheimer's condition is by varying the diffusivities. A threshold of the diffusivity necessary to consider a brain unhealthy could be determined. Finally, the mechanism for ACh diffusion could be better represented by considering the concentration of ACh, the occurrence of its release, and the amount of ACh that undergoes reuptake.

Appendix A: References

[1] Synaptic Transmission. Columbia University. <http://www.columbia.edu/cu/psychology/courses/1010/mangels/neuro/transmission/transmission.html>.

[2] Alzheimer's Association. <www.alz.org>.

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Appendix B: MATLAB Code

Code for Analytical Solution:

```
%% constants
D1 = 800;
D2 = 547;
%% domain
dt = 1.67e-7;
tmesh = 0:dt:2e-5;
nt = length(tmesh);
%Normal brain
dx1 = sqrt(2*D1*dt);
xmesh1 = -0.5:dx1:0.5;
nx = length(xmesh1);
%% solution on infinite domain using Fourier
%analytical solution
sol_inf1 = (4*pi*D1*tmesh' * ones(1,nx)).^(-.5) .* exp(-(4*D1*tmesh).^(-
1)' * xmesh1.^2);
normalized1 = sol_inf1/max(abs(sol_inf1(:)));
figure(1)
surf(tmesh,xmesh1,normalized1','EdgeColor','none')
title('Diffusion of ACh in Healthy Brain: Analytical
Solution','FontSize',14)
xlabel('Time, (s)','FontSize',14);
ylabel('Position, (um)','FontSize',14);
zlabel('Probability','FontSize',14);

%Alzheimer's brain
dx2 = sqrt(2*D2*dt);
xmesh2 = -0.5:dx2:0.5;
nx = length(xmesh2);

% solution on infinite domain using Fourier
sol_inf2 = (4*pi*D2*tmesh' * ones(1,nx)).^(-.5) .* exp(-(4*D2*tmesh).^(-
1)' * xmesh2.^2);
normalized2 = sol_inf2/max(abs(sol_inf2(:)));
figure(2)
surf(tmesh,xmesh2,normalized2','EdgeColor','none')
title('Diffusion of ACh in Alzheimer''s Brain: Analytical
Solution','Fontsize',14)
xlabel('Time, (s)','FontSize',14);
ylabel('Position, (um)','FontSize',14);
zlabel('Probability','FontSize',14);

figure(3)
hold on
plot(xmesh1,normalized1(50,:),'r');
plot(xmesh2,normalized2(50,:),'b');
title('Diffusion of ACh Healthy Brain vs. Alzheimer''s Brain at Time =
6.68E-7 s','Fontsize',14)
xlabel('Position, (um)','FontSize',14);
ylabel('Probability','FontSize',14);
legend('Healthy Brain','Alzheimer''s Brain');
hold off
```

Code for Random Walk Analysis:

```
clear all;
clc;

D0 = 800;
dt = 1.674E-7;
step = 1000;
traj = 5000;
kick = sqrt(2*D0*dt);
endtime = step*dt-dt;
time = 0:dt:endtime;
p_l = 0.5;
p_r = 0.5;
xc = zeros(1,traj);
for j = 1:step
    p = rand(1,traj);
       for i=1:traj
          if j == 1
              xc(i) = 0;
          elseif p(i) < p_l
               xc(i)=xc(i)-kick;
          else
               xc(i)=xc(i)+kick;
          end
       end
   x = -(step*kick+kick/2)/50:kick:(step*kick+kick/2)/50;
   n = histc(xc,x);
   n = n(1:end-1)./traj;
   y(1:40,j) = n;
end

zplot = y';
xplot = -step*kick/50:kick:(step*kick/50)-kick;
yplot = 0:dt:endtime;

figure(1);
surf(yplot, xplot, y);
xlabel('Time, (s)');
ylabel('Position, (um)');
zlabel('Probability');
title('Probabilty of 5000 Particles in Healthy Brain: Random Walk');
y(:,121:1000) = [];

figure(2)
yplot2 = (0:dt:2E-5);
surf(yplot2,xplot,y,'EdgeColor','none');
title('Diffusion of ACh: 5000 Particles in Healthy Brain: Random
Walk','FontSize',14);
xlabel('Time, (s)','FontSize',14);
ylabel('Position, (um)','FontSize',14);
zlabel('Probability','FontSize',14);
```

Code for Finite Differences Solution:

```
D = 800;
dt = 1.67e-7;
dx = .05;
xmesh = -.5:dx:.5;
tmesh = 0:dt:2e-5;
nx = length(xmesh);
nt = length(tmesh);
stepsize = D * dt / dx^2;
sol_fd = zeros(nt, nx);
sol_fd(1, :) = (xmesh == 0);
for t = 1:nt-1
    for x = 2:nx-1
        sol_fd(t+1, x) = sol_fd(t, x) + stepsize * ...
            (sol_fd(t, x-1) - 2 * sol_fd(t, x) + sol_fd(t, x+1));
    end
end
figure(1)
surf(tmesh,xmesh,sol_fd','EdgeColor','none')
title('Diffusion of ACh in Healthy Brain: Finite
Differences','Fontsize',14)
xlabel('Time, (s)','FontSize',14);
ylabel('Position, (um)','FontSize',14);
zlabel('Probability','FontSize',14);
```

Code for Random Walk Example:

```
clear all;
clc;
D0 = 574;
dt = 1.674E-7;
step = 100000;
frames = step/100;
traj = 200;
kick = sqrt(2*D0*dt);
time(1:frames) = 0;
randx(1:frames) = 0;
for i = 1:traj
    xc(1:3) = 0;
    timet = 0;
    for j = 1:step
       timet = timet + dt;
       R = randn(1,3);
       xc = xc + kick*R;
       if rem(j,100) == 0
           time(j/100) = timet;
     randx(j/100) = xc(1);
       end
    end
end
figure (1)
plot(time(1:frames), randx(1:frames),'k');
xlabel('Time, (s)','FontSize',14);
ylabel('Position, (um)','FontSize',14);
title('Position of a Single Particle Over Time','FontSize',14);
```