NEUROTRANSMITTER RELEASE IN THE BRAIN

Problem 3 Report

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1. Problem Description

1.1. Introduction

The human brain consists of around 100 billion neurons each making 1000-10,000 synaptic connections. The activity of the brain is electrical but the connections between neurons are primarily chemical, across a specialised structure called the synapse. At the synapse, vesicles containing neurotransmitter fuse with the cell membrane and release their contents into the synaptic cleft. The transmitter molecules (typically 10,000-100,000 molecules per vesicle in our systems) diffuse across the synaptic cleft, where some of them engage with receptors triggering another wave of electrical activity in the post synaptic cell, while the remainder are taken back up by membrane bound transporter proteins so they can be broken down or re-packaged. It is of interest experimentally to measure how this process changes with age or drugs. For example, do aging or drugs affect the concentration of neurotransmitter released from the vesicles and the rate of re-uptake?

1.2. Experimental measurements

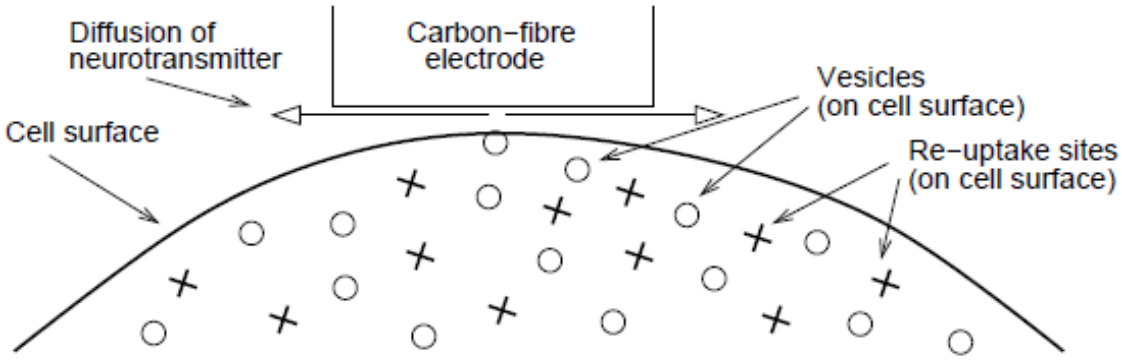


Figure 1

This release of the neurotransmitter can be detected using microelectrodes, with a typical experimental set-up as shown in Figure 1. The neurotransmitter molecules are oxidised electrochemically at the surface of the electrode, which results in an electric current. A typical current profile detected from the brain of a snail (Lymnaea stagnalis) is shown in *Figure 2*,

from data provided by Dr. O'Hare (Imperial College London). The spikes correspond to neurotransmitter-release events.

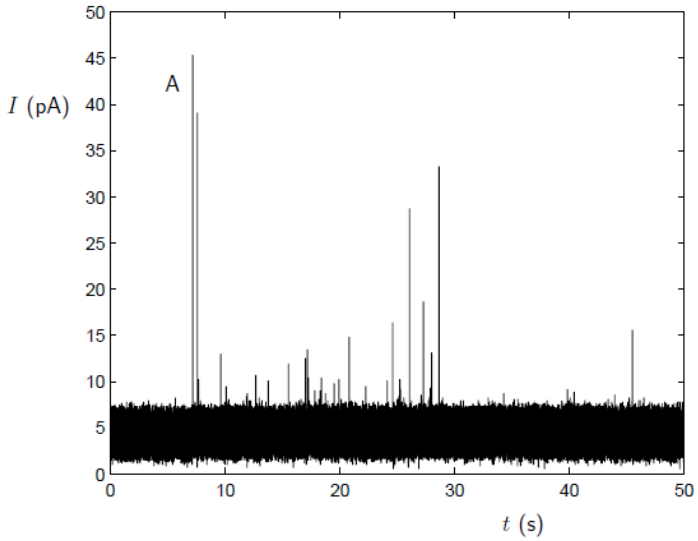


Figure 2

We would like to be able to relate the size of the spikes in current response back to key parameters of the process, such as the total concentration released from the vesicle and the rate of re-uptake. This requires a theoretical model.

The scheme of work will be the following:

- ✓ Introduction of the problem
- ✓ Partial differential equation model of vesicle release, re-uptake and oxidation at the electrode:
  - ➢ Governing equation (diffusion process).
  - ➢ Boundary conditions.
  - ➢ Initial condition.
  - ➢ Problem transformations:
    - ❖ Non-dimensional problem
    - ❖ 1-D problem
- ✓ Analytical solution of the model.
- ✓ Numerical solution of the model.
- ✓ Comparison to experimental results. Further work.

2. Introduction of the problem

As we said, we want to study the current produced by neurotransmitter molecules in terms of key parameters of the process, such as the total concentration released from the vesicle and the rate of re-uptake.

The neuron is divided in two membranes: pre-synaptic and the post-synaptic. We used an electrode in the post-synaptic membrane to obtain flow current data.

In the synapse, a vesicle full of molecules of serotonin breaks when it goes through the pre-synaptic membrane and liberates the molecules. Most of them go to the receptor and some are re-up taken into the pre-synaptic membrane.

The electrode makes a redox reaction

$$OX + e^- \underset{k_f}{\overset{k_b}{\Leftrightarrow}} RED$$

Therefore, the serotonin is reduced and becomes another chemical substance. The electrons liberated in the reaction cause the electrical current.

Our objective is to find the mathematical model which gives us this rate of current response. It will depend on:

- ✓ The reuptake constant.
- ✓ The number of molecules.
- ✓ The chemical reaction.
- ✓ The rate of diffusion.

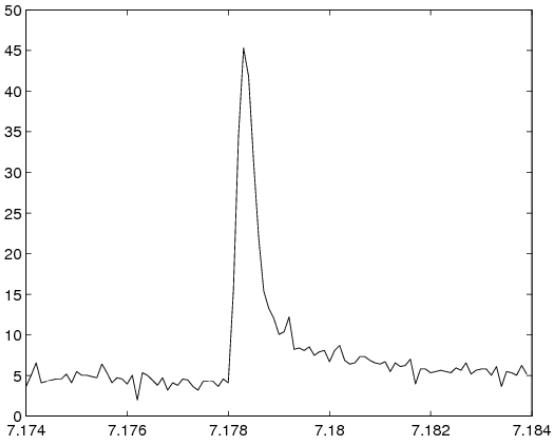


Figure 3: Electrical current

3. Mathematical model

3.1. Partial differential equation. Domain definition

The problem is analogous to a diffusion process, and therefore it can be modelled by using the diffusion equation:

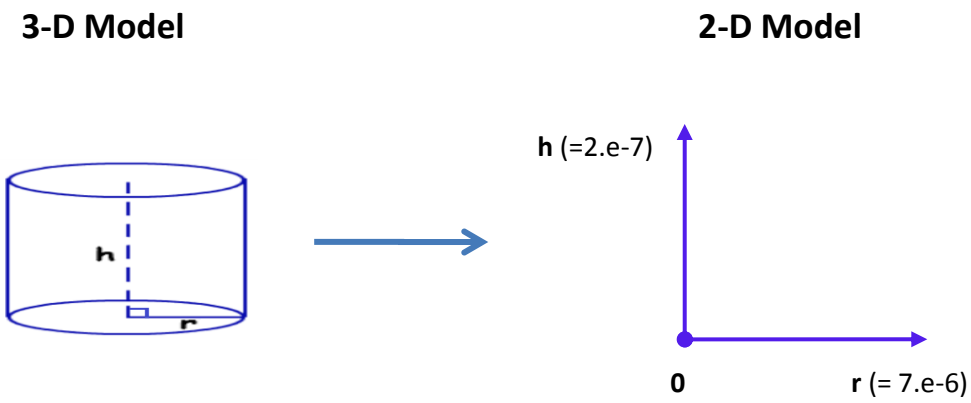
$$\frac{\partial C}{\partial t} = D \cdot \nabla^2 C$$

Where:

- ✓ C is the concentration of serotonin.
- ✓ D is the diffusion constant.

Experimental results show that these constants can be dependent of some variables as the age or the use of some drugs such as antidepressants.

Our domain will be a cylinder, whose base is the electrode and the top is the post-synaptic membrane. Because of the symmetry, we can consider de model as 2-Dimmensional, so we will not eliminate the angle θ.



In our experiment, the distance between the pre-synaptic membrane and the electrode is $2 \cdot 10^{-7} m$, and the radio of the electrode is $7 \cdot 10^{-6} m$.

After reducing the problem to a 2-D model, we obtain the following partial differential equation:

$$\frac{\partial C}{\partial t} = D \cdot \left(\frac{\partial^2 C}{\partial r^2} + \frac{1}{r}\frac{\partial C}{\partial r} + \frac{\partial^2 C}{\partial z^2} \right)$$

The boundaries of our domain are:

$$z \in [a,\ b] \text{ with } b - a = 2 \cdot 10^{-7} m$$

$$r \in [0,\ 3.5 \cdot 10^{-6}]$$

Once the partial differential equation is solved, we use the obtained value of C to calculate its partial derivate with respect to z in the base of cylinder. With this derivate we calculate the current intensity:

$$I = nFD \int_0^{\infty} \int_0^{2\pi} \left. \frac{\partial C}{\partial z} \right|_{z=a} r dr d\theta$$

Where F is the Faraday's constant and n is the number of electrons transferred.

3.2. Boundary conditions

The boundary conditions are:

- We have $C = 0$ when $z = a$ because the potential of the electrode is high enough to make the reaction only in one direction. Therefore, at that boundary the concentration of serotonin is zero.
- We have $C \to 0$ when $r \to \infty$. That's because we considerer the release of vesicle is produced in $r = 0$, $z = b$ so it doesn't get to the farthest points. We can make this assumption because the high of the cylinder is much smaller than its radious.
- We have $-\frac{\partial C}{\partial z} = kC$ when $z = b$ because we assume the reuptake rate is proportional to the concentration (first order chemical reaction).
- We have $\frac{\partial C}{\partial r} = 0$ because of the symmetry.

3.3. Initial condition

Our initial condition will be the following one:

$$C(r,z,0) = \frac{C^*\delta(r)\delta(z-b)}{r},$$

where delta is the Dirac delta function, and Q is the number of moles of serotonin released from the vesicle.

This means that, at the initial time, all the serotonin is concentrated at one single point and it is all released from this point at t=0. We can make this assumption because the size of the vesicle is so much smaller than the size of the electrode, and the release process is so much faster than the diffusion process.

3.4. Problem transformations

3.4.1. Non-dimensional problem

We make the following changes of variables to construct an equivalent non-dimensional problem:

- $C = \frac{2Q}{\pi(b-a)^3}\hat{C}$
- $z = a + (b-a)\hat{z}$
- $r = (b-a)\hat{r}$
- $t = \frac{(b-a)^2}{D}\hat{t}$
- $I = \frac{2QnFD}{\pi(b-a)^2}\hat{I}$
- $k = \frac{D}{b-a}\hat{k}$

After the changes of variables described before, we obtain a new problem that is dimensionless:

$$\frac{\partial \hat{C}}{\partial \hat{t}} = \nabla^2 \hat{C} = \frac{\partial^2 C}{\partial r^2} + \frac{1}{r}\frac{\partial C}{\partial r} + \frac{\partial^2 C}{\partial z^2}$$

With the following boundary conditions:

- $\frac{\partial \hat{C}}{\partial \hat{r}} = 0 \qquad \hat{r} = 0$
- $\hat{C} = 0 \qquad \hat{z} = 0$
- $\hat{C} \to 0 \qquad \hat{r} \to \infty$
- $\frac{\partial \hat{C}}{\partial \hat{z}} = \hat{k}\hat{C} \qquad \hat{z} = 1$

In this dimensionless model we can consider that $r \in [0, \infty)$ because the horizontal dimension is much bigger than the vertical one.

Our non-dimensional initial condition is:

$$\hat{C}(\hat{z}, 0) = \pi \frac{\delta(\hat{r})}{\hat{r}} \delta(\hat{z} - 1) \; if \; \hat{t} = 0$$

And the current has is defined by the following expression:

$$\hat{I} = \int_0^{\infty} \int_0^{2\pi} \left. \frac{\partial \hat{C}}{\partial \hat{z}} \right|_{\hat{z}=0} \hat{r} d\hat{r} d\theta$$

The two main reasons we transform the problem are:

- ✓ We reduce the number of parameters.
- ✓ We make it robust to changes of sizes, and we can easily see what are the variables that have an actual influence in the system.

3.4.2. 1-D Problem

We can define a new function $\bar{C}$ that does not depend on r but just on the height z and on time by integrating along r and using the boundary condition $C \to 0$ as $r \to \infty$.

$$\bar{C}(\hat{z},\hat{t}) = \int_0^{\infty}\int_0^{2\pi} \hat{C}(\hat{r},\hat{z},\hat{t})\hat{r}d\hat{r}d\hat{\theta}$$

The new unknown, $\bar{C}$, satisfies the one-dimensional equation with just two boundary conditions – the ones related to $\hat{z}$, and a simpler initial condition.

Then our expression of the main equation becomes:

$$\frac{\partial \bar{C}}{\partial \hat{t}} = \frac{\partial^2 \bar{C}}{\partial \hat{z}^2}$$

And the boundary conditions become:

- $\bar{C} = 0 \quad if \quad \hat{z} = 0$
- $-\frac{\partial \bar{C}}{\partial \hat{z}} = \hat{k}\bar{C} \quad if \quad \hat{z} = 1$

We can get rid of the $\frac{\delta(r)}{r}$ part in the initial condition:

$$\bar{C}(\hat{z},0) = \pi\delta(\hat{z}-1) \qquad \hat{t} = 0$$

Derivating along $\hat{z}$ we found the new expression for the current:

$$\hat{I} = \left.\frac{\partial \bar{C}}{\partial \hat{z}}\right|_{\hat{z}=0}$$

4. Analytical solution

By using the method of separation of variables, we can find the analytical solution of the one-dimensional problem. We consider $\bar{C}(\hat{z},\hat{t})$as a product of two functions, each depending in only one variable:

$$\bar{C}(\hat{z},\hat{t}) = Z(\hat{z})T(\hat{t})$$

Thus we can represent the main equation of the problem

$$\frac{\delta\bar{C}}{\delta\hat{t}} = \frac{\delta^2\bar{C}}{\delta\hat{z}^2}$$

as

$$ZT' = Z''T$$

We divided each term by *ZT* so we can separate it in two problems, one related to *Z* and one related to *T*.

$$\frac{Z''}{Z} = \frac{T'}{T} = -\lambda_n$$

The two problems are:

$$T' + \lambda_n T = 0 \qquad \bar{t} > 0$$

$$Z'' + \lambda_n Z = 0 \qquad \hat{z} \in [0,1]$$

First we solve the problem in *Z*, obtaining:

$$Z_n(\hat{z}) = \alpha \sin(\lambda_n \hat{z})$$

And then we solve the problem in *T*:

$$T_n(\hat{t}) = \beta e^{-\lambda_n^2 \hat{t}}$$

So we can write $\bar{C}(\hat{z},\hat{t})$ as an infinite Fourier series:

$$\bar{C} = \sum_{n=1}^{\infty} A_n \sin(\lambda_n \hat{z})\, e^{-(\lambda_n^2 \hat{t})}$$

If we take into account the boundary conditions in $\hat{z} = 1$ and substitute them in the new expression:

$$-\frac{\partial \bar{C}}{\partial \hat{z}} = \hat{k}\bar{C} \quad \leftrightarrow \quad -\sum_{n=1}^{\infty} A_n \cos(\lambda_n)\, e^{-(\lambda_n^2 \hat{t})} = \hat{k} \sum_{n=1}^{\infty} A_n \sin(\lambda_n)\, e^{-(\lambda_n^2 \hat{t})}$$

An expression for λ_n is easily found:

$$\lambda_n = -\hat{k} \cdot \tan(\lambda_n)$$

We can find the value of A_n making $\hat{t} = 0$ in the expression for $\bar{C}(\hat{z},\hat{t})$ and imposing the initial condition:

$$\sum_{n=1}^{\infty} A_n \sin(\lambda_n \hat{z}) = \pi\delta(\hat{z} - 1)$$

So we obtain:

$$A_n = \frac{-\lambda_n \sin(\lambda_n)}{\cos(\lambda_n)\sin(\lambda_n) - \lambda_n}$$

The whole expression for $\bar{C}(\hat{z},\hat{t})$ becomes:

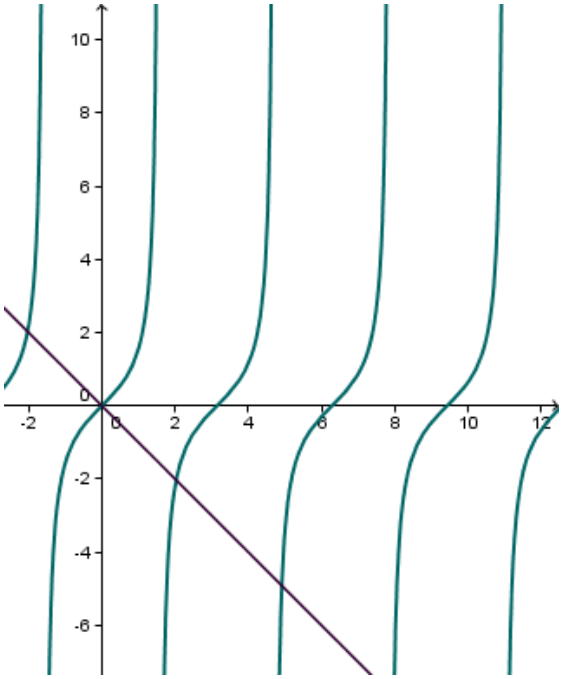
$$\bar{C} = \sum_{n=1}^{\infty} \frac{-\lambda_n \sin(\lambda_n)}{\cos(\lambda_n)\sin(\lambda_n) - \lambda_n} \sin(\lambda_n \hat{z})\, e^{-(\lambda_n^2 \hat{t})}$$

We derive to find the expression for the current:

$$\hat{I} = \left.\frac{\partial \bar{C}}{\partial \hat{z}}\right|_{\hat{z}=0} \leftrightarrow \hat{I} = \sum_{n=1}^{\infty} \frac{-\lambda_n^2 sin(\lambda_n)}{cos(\lambda_n)\, sin(\lambda_n) - \lambda_n} e^{-\lambda_n^2 t}$$

In order to represent the current, we want to calculate the minimum number of terms from the series we need to do so. Having the equality $\lambda_n = -\hat{k} \cdot \tan(\lambda_n)$, we intersect the functions $f(\lambda) = -\frac{\lambda}{\hat{k}}$ and $g(\lambda) = \tan(\lambda)$ to have a general idea of the intervals in which the roots will move.

We choose $\widehat{\boldsymbol{k}} = \mathbf{1}$ to draw the intersection in GeoGebra:



We can appreciate that $\left(n - \frac{1}{2}\right)\pi < \lambda_n < n\pi$.

Also considering that as $n \to \infty$, $\left|\frac{-\lambda_n^2 sin(\lambda_n)}{cos(\lambda_n)\, sin(\lambda_n) - \lambda_n}\right| \approx \lambda_n$, it's possible to narrow the inner term in the current expression like this:

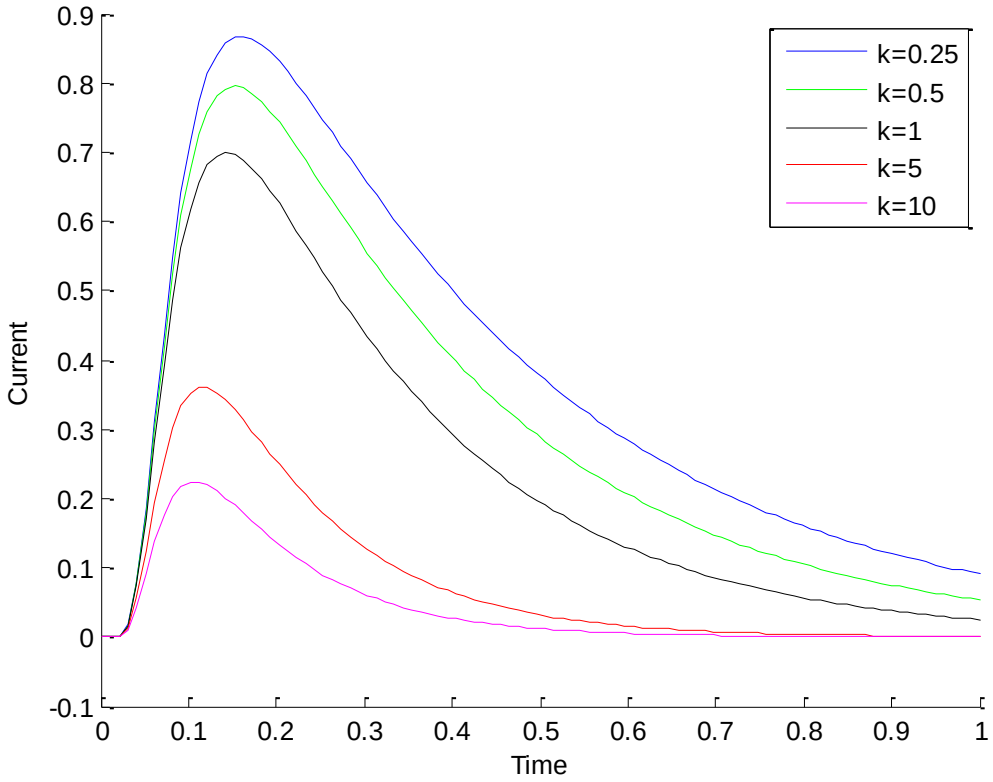
$$\left|\frac{-\lambda_n^2 sin(\lambda_n)}{cos(\lambda_n)\, sin(\lambda_n) - \lambda_n} e^{-\lambda_n^2 t_0}\right| < n\pi e^{\left(n-\frac{1}{2}\right)^2 \pi^2 t_0}$$

The only thing left is fixing a precision to represent the current, e.g. 10^8, and imposing the following equality:

$$n\pi e^{\left(n-\frac{1}{2}\right)^2 \pi^2 t_0} = 10^8$$

Solving it will give us the minimal number of roots we need to represent the current. For example, for k=1, the number of necessary roots is at least 50. After that, we substitute to obtain the expression of the current.

The following graph represents the current for different values of K. As we can see, as *k* decreases, the current increases.



Experimental data show that the rate of the reaction is smaller in old age, so you need bigger vesicles that can contain larger amounts of molecules to counter the decreasing rate of uptake to the pre-synaptic membrane. For example, k=0.25 could correspond to an old person or to someone who has use drugs such as antidepressants.

5. Numerical solution

By using finite differences and the Euler implicit method, we can find a numerical approximation of the solution for the 2-dimensional problem:

$$\frac{\partial C}{\partial t} = \frac{\partial^2 C}{\partial r^2} + \frac{1}{r}\frac{\partial C}{\partial r} + \frac{\partial^2 C}{\partial z^2}$$

To do this we do a discretization of the domain into a mesh of equidistant points and we use the boundary equations we defined earlier

- $\frac{\partial C}{\partial r} = 0$
- $-\frac{\partial C}{\partial z} = kC$

and approximation of the partial derivates at the points in the mesh

- $\frac{\partial^2 C}{\partial z^2} = \frac{C_{i,j+1} - 2C_{i,j} + C_{i,j-1}}{h^2}$
- $\frac{\partial^2 C}{\partial r^2} = \frac{C_{i+1,j} - 2C_{i,j} + C_{i-1,j}}{h^2}$
- $\frac{1}{r}\frac{\partial C}{\partial r} = \frac{1}{r}\frac{C_{i+1,j} - C_{i-1,j}}{2h}$; $\frac{\partial C}{\partial z} = \frac{C_{i,j+1} - C_{i,j-1}}{2h}$

We also have to take into account the Neumann boundary conditions in the main matrix which are more complicated. We implement them as it follows:

- ✓ **r = 0; z ≠ 0**

  In this case, the boundary condition is $\frac{\partial C}{\partial r} = 0$ and it becomes this equation

$$\frac{\partial C}{\partial t} = \frac{2\partial^2 C}{\partial r^2} + \frac{\partial^2 C}{\partial z^2} = \frac{4C_{i+1,j} - 6C_{i,j} + C_{i,j+1} + C_{i,j-1}}{h^2}$$

- ✓ **r ≠ 0; z = 1**

In this case, the boundary condition is $-\frac{\partial C}{\partial z}=kC$ and it becomes this equation

$$\frac{\partial C}{\partial t} = \frac{\partial^2 C}{\partial z^2} + \frac{1}{r}\frac{\partial C}{\partial r} + \frac{\partial^2 C}{\partial r^2} == \frac{(-4 - 2hk)C_{i,j} + 2C_{i,j-1} + C_{i+1,j} + C_{i-1,j}}{h^2} + \frac{1}{r}\frac{C_{i+1,j} - C_{i-1,j}}{2h}$$

We can see ***k*** in the matrix.

- ✓ **r = 0; z = 1**

And finally, in this case, the boundary condition are $\frac{\partial C}{\partial r}$= 0 and $-\frac{\partial C}{\partial z}=kC$ and it becomes this equation

$$\frac{\partial C}{\partial t} = \frac{2\partial^2 C}{\partial r^2} + \frac{\partial^2 C}{\partial z^2} = \frac{4C_{i+1,j} - (6 + 2hk)C_{i,j} + 2C_{i,j}}{h^2}$$

We can see ***k*** in the matrix too.

We implement the rest of points in the main matrix using normal finite differences as it follows:

$$\frac{\partial C}{\partial t} = \frac{\partial^2 C}{\partial z^2} + \frac{1}{r}\frac{\partial C}{\partial r} + \frac{\partial^2 C}{\partial r^2} == \frac{C_{i,j+1} - 4C_{i,j} + C_{i,j-1} + C_{i+1,j} + C_{i-1,j}}{h^2} + \frac{1}{r}\frac{C_{i+1,j} - C_{i-1,j}}{2h}$$

Our initial condition

$$\hat{C}(\hat{z},0) = \pi \frac{\delta(\hat{r})}{\hat{r}} \delta(\hat{z}-1)$$

is hard to implement numerically, so we use the Green Function of this expression

$$C_{ij}^{0} = 2\pi \frac{1}{4(\pi t_0)^{\frac{3}{2}}} e^{\frac{1}{4t_0}(-r^2-(z-1)^2)}$$

to define it in an equivalent way.

With our Matlab code we can see that in this system our initial condition is

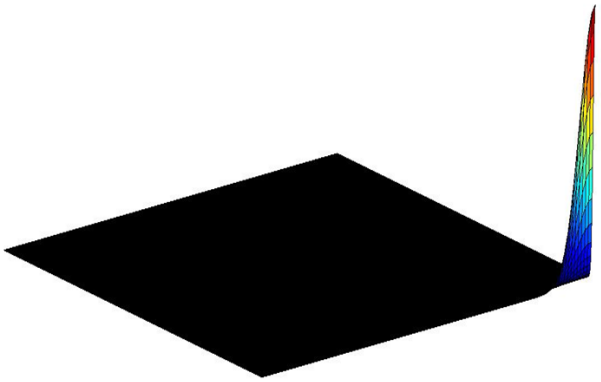


Figure 4

Although we have found troubles with small step seizes, our numerical solution is quite similar to the analytical one. The following graph represents current calculated analytically and numerically with ***k=1***.

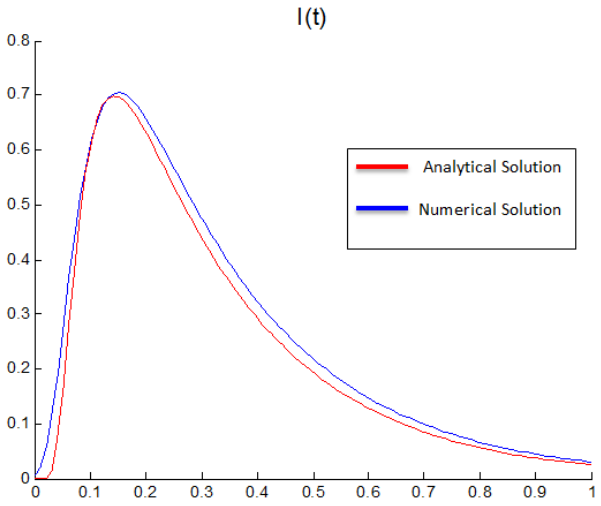


Figure 5

To complete, the next graphs represents the concentration of serotonin (*C*)

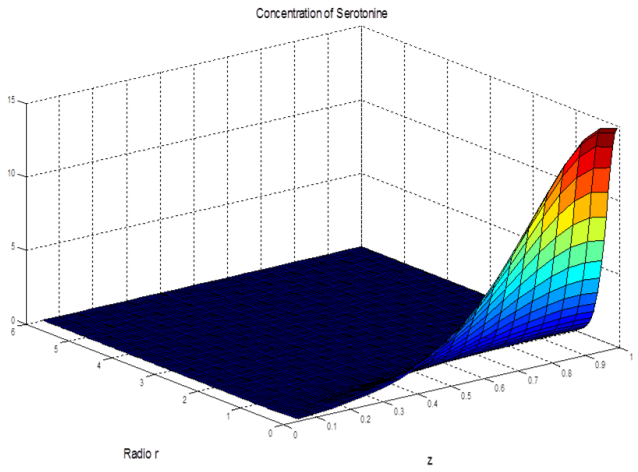


Figure 6

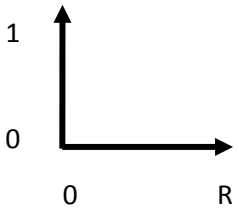
We can see how vesicle breaks and release serotonin molecules in the point *z=1, r=0*. That's why the points close to that "*breaking points*" are higher than the rest.

After the initial time and due to the diffusion process, serotonin goes to the rest of points and the graph decreases.

In order it solve it we have to choose a finite maximum value of r. We chose

$$R > 6 \cdot \sqrt{t_{MAX}} \rightarrow \boxed{R = 6}$$

We consider $0 \leq r \leq R$,



where R is defined by the before equation. It means that there is no time for the serotonin molecules to arrive to the point $r = R$, so in this boundary the concentration of serotonin is zero.

6. Conclusions

- ✓ We can adapt a model based on the diffusion equation to this problem.
- ✓ We can simplify the model to solve it both analytically and numerically
- ✓ The analytical and numerical solutions agree

7. Further Work. Comparison to experimental results

For further work we would have wanted to fit the model to actual experimental data. For that we would have to go back to the model with the parameters:

$$I = \frac{2QnFD}{\pi(b-a)^2} \sum_{n=1}^{\infty} A_n \left(\frac{k(b-a)}{D} \right) e^{-\lambda_n^2 \left(\frac{k(b-a)}{D} \right) \frac{(b-a)^2}{D} t_0}$$

We would need to fit the diffusion constant D, the number of moles of serotonin Q, the separation between the membrane and the electrode (b-a) (which can be easily measured) and the reuptake rate k.

Annex: MATLAB code

```
% Numerical 2-Dimensional
clear all
close all
clc
% For example:
dt=0.01; h=0.05; Time=1;

% Parameters:
t0=0.001;
K=1;
R=6*floor(sqrt(Time));

% By finite differences
n=(Time-t0)/dt;
n2=1/h;
n3=R/h;

% Temporal discretization
t=linspace(t0,Time,n);

% Spatial discretization
X=linspace(0,R,n3+1);
Y=linspace(0,1,n2+1);


% Initial conditions (u0)
for i=1:(n3)
    for j=2:n2+1
        AUX1=2*pi/(4*pi*t0)^(3/2);
        u0(i,j-1)=AUX1*exp(1/(4*t0)*(-X(i)^2-(Y(j)-1)^2));
    end;
end;
figure(1)
surf(u0)
u0=reshape(u0',1,(n2)*(n3));
axis off
pause

% Matrix A

for i=1:n2
    aii(i)=-6;
    aij(i)=1;
    aij_(i)=1;
    aij1(i)=4;
    aij2(i)=0;
end;
for i=n2+1:n2*n3
    aii(i)=-4;
    aij(i)=1;
    aij_(i)=1;
    aij1(i)=1;
    aij2(i)=1;
end;
for i=2*n2:n2:n2*n3
```

```
    aii(i)=-2*(2+h*K);
    aij_(i)=2;
    aij(i)=0;
    aij1(i)=1;
    aij2(i)=1;
end;

for i=(n2+1):n2:(n2*n3-n2+1)
    aij_(i)=0;
end

A = spdiags([[aij2((n2+1):end) ones(1,n2)]' ...
    [aij_(2:end) 1]' aii' [1 aij(1:end-1)]' ...
    [ones(1,n2) aij1(1:end-n2)]'], [-n2 -1:1 n2],n2*n3,n2*n3);

A(n2,:)=0;
A(n2,n2)=-6-2*h*K;
A(n2,n2-1)=2;
A(n2,2*n2)=4;

unos = ones(1,n2*n3);

Aaux = spdiags([-unos' unos'], [-n2 n2], n2*n3,n2*n3);
Aaux(1:n2,:)=0;

for i=n2+1:n2*n3
    module=ceil(i/n2);
    Aaux(i,:)=Aaux(i,:)*(1/X(module));
end

A = 1/h^2*A+1/(2*h)*Aaux;

u=u0;

for k=1:n+1
    % Implicit euler method
    u=(eye(n2*n3)-dt*A)\u';
    u=u';
    matrizu0=reshape(u,n2,n3);

    figure(1)
    surf(Y(2:end), X(2:end), matrizu0');
    ylabel('Radio r','FontSize',14)
    xlabel('z','Fontsize',14)
    title('Concentration of Serotonine','FontSize',14)
    axis([0 1 0 6 0 25])

    % Current
    for i=1:n3
        Derivada(i)=-(matrizu0(2,i)-4*matrizu0(1,i))/(2*h);
    end

    Corriente(k)=h*trapz(Derivada.*X(1:end-1));
```

```
pause(0.0001)
end;

% current variation (t)
figure(3)
hold on
plot(t,Corriente(1:end-1))
title('I(t)', 'FontSize', 14 )

% Analytical solution
k=1;
n=fzero(@(m) m*pi*exp(-pi^2*(m-1/2)^2*0.001)...
    -10^(-8),1/sqrt(0.001));
epsilon=1e-10;
x0=(pi/2):pi:(pi/2)+(n)*pi;
for i=1:n
    Lambda(i)=fzero(@(lambda) lambda+k*tan(lambda),...
        [x0(i)+epsilon,x0(i)+pi/2+epsilon]);
end
Lambda=sort(Lambda);

t = linspace(0.001,1,100);
suma = zeros(1,length(t));
for i=1:n
    suma=suma-(Lambda(i)^2*sin(Lambda(i))/...
        (cos(Lambda(i))*sin(Lambda(i))-Lambda(i)))...
        *exp(-Lambda(i)^2*t);
end

plot(t,suma,'r');
```