Modeling a synaptic transmission,
Mathematical modeling

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1 Introduction

In this report, we start by showing a 3D Monte Carlo simulation of Brownian motion as a first model for the diffusion of neurotransmitters. Next, modeling equations are derived for the initial model, as well as the expanded model which includes glia cells. After this, mathematical modeling is used to obtain a rough estimate of the time used to transmit a signal. This is followed by several attempts at solving a 1D model of the problem, and then a 2D model.

2 Proof of concept: Monte Carlo simulation

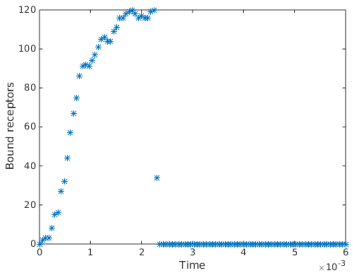


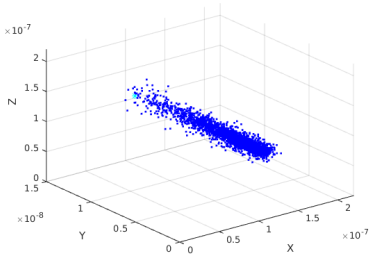
Figure 1: Number of bound receptors based on time.

In order to make the problem simple enough to use a Monte Carlo simulation method, we postulate a few assumptions:

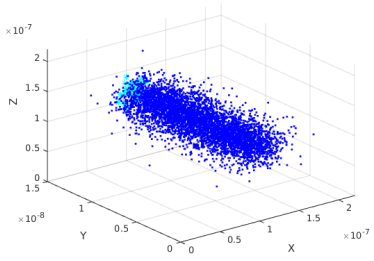
- We start with all 5000 neurotransmitters in one point, on the middle of the axon wall.
- The probability of a neurotransmitter binding to a receptor is linearly dependent on how many receptors are available.
- All neurotransmitters disconnect from the receptors when the signal is triggered.
- Once the signal is triggered, glia cells are taken into account and start to clean up.

- Neurotransmitters released from glia cells are marked as inactive and can again bond to the axon wall.
- All probabilities of connecting a neurotransmitter to anything is dependent on the distance between the neurotransmitter and for example the dendritic wall.
- We assume that the signal is triggered and passed on to the dendritic wall when we meet 80 percent coverage of the receptors.

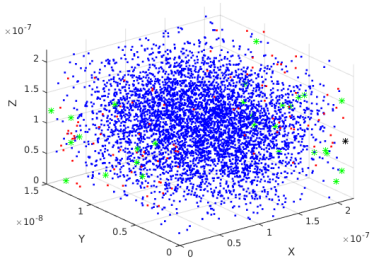
As we can see in figure 1, the time before the synapse fires is around 2 ms. This is however higly dependent upon what constants we choose. An actual plot of what the simulation looks like is presented in figure 2. As for further studies, we deemed the simulation method not very easy to use (and extremely computationally expensive), so we instead turned to more traditional numerical mathematical modeling.



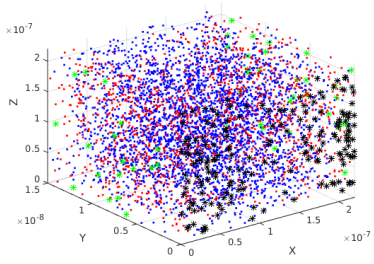
(a) Some time has passed, a few neurotransmitters are bound to receptors.



(b) A large number of bounded neurotransmitters, dendrite almost ready to fire.



(c) Dendrite has fired, glia cells have started to clean up the synaptic cleft.



(d) More time has passed, the first deactivated neurotransmitters has returned to the axon.

Figure 2: Monte Carlo simulation of the synaptic cleft. Active neurotransmitters are blue, inactive ones are red. Bounded neurotransmitters is indicated by a $*$ symbol and cyan is bound to receptors, green is bound to glia cells (transporters) and black ones have returned to the axon.

3 Deriving the modeling equations

Diffusion equation

Given the equations from the task [2], we quickly conclude that the diffusion of the neurotransmitters can be modeled by

$$\frac{dc}{dt} = \kappa \nabla^2 c \tag{1}$$

$$\nabla c \cdot n = g(t, c), \tag{2}$$

with the last equation being the Neumann boundary condition. In the equations, c is the concentration of neurotransmitters, κ is the diffusion constant and $g(t, c)$ is a boundary flux.

3.1 The binding process

First we look at the reversible chemical reaction

$$\mathrm{R} + \mathrm{N} \rightleftharpoons \mathrm{RN}, \tag{3}$$

where R is the number of receptors and N is the number of neurotransmitters. The reaction rates are k_1 to the right and k_2 to the left, being respectively the probability for the reactions to occur in their direction. We get 3 ODE's from this chemical reaction:

$$\frac{d[\mathrm{R}]}{dt} = -k_1[\mathrm{R}][\mathrm{N}] + k_2[\mathrm{RN}]$$

$$\frac{d[\mathrm{N}]}{dt} = -k_1[\mathrm{R}][\mathrm{N}] + k_2[\mathrm{RN}]$$

$$\frac{d[\mathrm{RN}]}{dt} = k_1[\mathrm{R}][\mathrm{N}] - k_2[\mathrm{RN}],$$

where [R], [N] and [RN] are the concentrations of the receptors, neurotransmitters and the bound product of them. We may consider [N][R] the probability of a neurotransmitter meeting an unoccupied receptor, and k_1 the probability of the binding reaction happening. Likewise for k_2. Next, we insert c for [N]. Introducing P^R as the probability of a receptor being unoccupied, and $(1 - P^R)$ as the probability that the neurotransmitter is attached to the receptor leads to the following simplification [1] of the above ODE's:

$$\frac{dc}{dt} = -k_1 c P^R + k_2(1 - P^R) \tag{4}$$

$$\frac{dP^R}{dt} = -k_1 c P^R + k_2(1 - P^R). \tag{5}$$

3.2 Glia cells

$$\mathrm{T} + \mathrm{N} \rightleftharpoons \mathrm{TN} \rightarrow \mathrm{N}_{\mathrm{inactive}} + \mathrm{T}.$$

Here, we define k_3, k_4, k_5 as the reaction rates of first rightward, first leftward, second rightward reactions.

Similarly to the binding process, we get the following set of equations:

$$\begin{aligned}\kappa\nabla c \cdot n &= -k_3 c P^T + k_4(1 - P^T)\\ \frac{dP^T}{dt} &= -k_3 c P^T + (1 - P^T)(k_4 + k_5).\end{aligned}$$

Combining these equations, we get

$$\begin{aligned}\kappa\nabla c \cdot n &= -c(k_1 P^R + k_3 P^T) + k_2(1 - P^R) + k_4(1 - P^T)\\ \frac{dP^R}{dt} &= -c k_1 P^R + k_2(1 - P^R)\\ \frac{dP^T}{dt} &= -c k_3 P^T + (k_4 + k_5)(1 - P^T).\end{aligned}$$

4 Modeling a time scale

We wanted to find a scaling for time in order to get a feel about the time it takes before a signal is transmitted. In order to do that, we use the diffusion equation

$$\frac{\partial c^*}{\partial t^*} = \kappa\nabla^2 c^*. \tag{6}$$

Since we were given a radius and a height, we chose to use cylindrical coordinates. Thus ∇^2 becomes

$$\nabla^2 f = \frac{1}{r^*}\frac{\partial}{\partial r^*}\left(r^*\frac{\partial f}{\partial r^*}\right) + \frac{1}{(r^*)^2}\frac{\partial^2 f}{\partial \phi^2} + \frac{\partial^2 f}{\partial (z^*)^2}.$$

We scale the equation so that

$$\begin{aligned}c^* &= Cc\\ r^* &= Rr\\ z^* &= Lz\\ t^* &= Tt.\end{aligned}$$

With the scaling, the equation becomes

$$\frac{\partial Cc}{\partial Tt} = \kappa\left(\frac{1}{Rr}\frac{\partial}{\partial Rr}\left(Rr\frac{\partial Cc}{\partial Rr}\right) + \frac{1}{(Rr)^2}\frac{\partial^2 Cc}{\partial \phi^2} + \frac{\partial^2 Cc}{\partial (Lz)^2}\right).$$

We assume that the neurotransmitters are released in the centre of the axon. Due to rotational symmetry, c becomes independent of ϕ. Since $R >> h$, it follows that $1/R^2 << 1/L^2$, and we assume $1/R^2 \approx 0$. After these simplifications the equation becomes

$$\frac{1}{T}\frac{\partial c}{\partial t} = \kappa\frac{1}{L^2}\frac{\partial^2 c}{\partial z^2}.$$

To simplify, we set all derivatives to be ~ 1, and obtain

$$\frac{1}{T} = \kappa\frac{1}{L^2}.$$

Solving for T gives us a timescale

$$T = \frac{L^2}{\kappa} = \frac{(15 \cdot 10^{-9}\text{m})^2}{0.3 \cdot 10^{-12}\text{m}^2/\text{s}} = 0.75\text{ms}.$$

This is by no means a correct time for the signal to be transmitted, but we could guess that the real time will be of order 1ms.

5 1D Model

Let us look at the easiest possible model of the synaptic cleft; a 1D model. Assume the neurotransmitters diffuse along a line, released from the axon terminal and arriving at the dendritic spine. When the neurotransmitters attach and detach to the receptors, we model it as a total flux J of neurotransmitters leaving or entering the domain. Further, we assume that when the neurotransmitters are within a small distance ϵ of the dendritic spine, they are close enough to react with the receptors.

The number of receptors on one membrane is $\text{R} \approx \gamma_R \cdot \pi r^2 \approx 152$, where γ_R is the density of receptors and r is the radius of the synaptic cleft [2]. $\text{N} = 5000$ as before. Let Ω be the line between 0 and L.

Now, look at the area near the dendritic spine. Let Ω_ϵ be a small area close to L with width ϵ, see Figure 3. Let $\gamma_{N\epsilon}(t)$ be the density of neurotransmitters in Ω_ϵ, γ_R the density of receptors in the area ϵ, and $P^R(t)$ be the probability that one receptor is available. With reaction constants k_1 and k_2, the flux can be expressed as

$$J(t) = k_1 \gamma_{N\epsilon}(t) \gamma_R P^R(t) - k_2 \gamma_R (1 - P^R(t)).$$

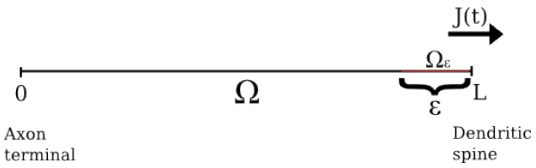


Figure 3: Model of the synaptic cleft in one dimension

5.1 Initial values and boundary conditions

Initial values:

$$c(x,0) = \begin{cases} \text{N} & \text{if } x = 0 \\ 0 & \text{elsewhere} \end{cases}$$

Neumann boundary conditions:

$$c_x(0,t) = 0,$$
$$c_x(L,t) = J(t).$$

The homogeneous Neumann boundary condition at $x = 0$ comes from the physical explanation that neurotransmitters cannot go back through the axon terminal.

5.2 Scaling of variables

We use the same scaling as in section 4 and replace in the unscaled diffusion equation (6) such that

$$\frac{\mathrm{N}}{T}\frac{\partial c}{\partial t} = \kappa\frac{\mathrm{N}}{L^2}\frac{\partial^2 c}{\partial x^2} \Rightarrow \frac{\partial c}{\partial t} = \eta\frac{\partial^2 c}{\partial x^2}, \qquad \eta = \kappa\frac{T}{L^2}.$$

Using the values $L = 15 \cdot 10^{-9}$, $T = 10^{-3}$ and $\kappa = 0.3 \cdot 10^{-12}$, we get the resulting value $\eta = 4/3$.

5.3 Numerical scheme

Using Crank-Nicholsons method, we obtain

$$(1 - \frac{k}{2h^2}\delta_x^2)C_m^{n+1} = (1 + \frac{k}{2h^2}\delta_x^2)C_m^n,$$

where k and h are the time and space steps, respectively. Adding Neumann boundary conditions to the system, we expand the numerical scheme to involve boundary points, and an additional term such that the resulting scheme becomes

$$\left(I - \frac{r}{2}A\right)C^{n+1} = \left(I + \frac{r}{2}A\right)C^n + \frac{k}{2}(d^n + d^{n+1}),$$

where $r = \frac{k}{h^2}$,

$$A = \begin{pmatrix} -3/2h & 2h & -h/2 & & \\ 1 & -2 & 1 & & \\ & \ddots & \ddots & \ddots & \\ & & 1 & -2 & 1 \\ & & -3/2h & 2h & -1/2h \end{pmatrix}, C = \begin{pmatrix} C_0 \\ C_1 \\ \vdots \\ C_M \\ C_{M+1} \end{pmatrix}, d = \begin{pmatrix} 0 \\ 0 \\ \vdots \\ 0 \\ J(t) \end{pmatrix}.$$

The result of this scheme is visualized in figure 4.

5.4 Expanding our method with glia cells

Modeling the equation in one dimension is done by considering the points a and b, and the line between them. In this case, a is the axon side and b is the dendrite side. Due to this, the boundary conditions for a and b differ. For a, we have

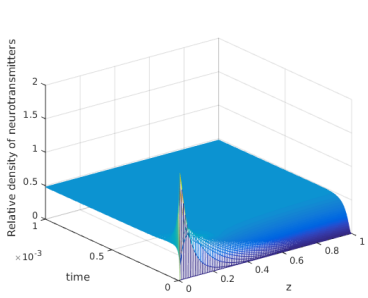
$$\kappa\nabla c = -k_3 c P^T + k_4(1 - P^T),$$

and for b we have

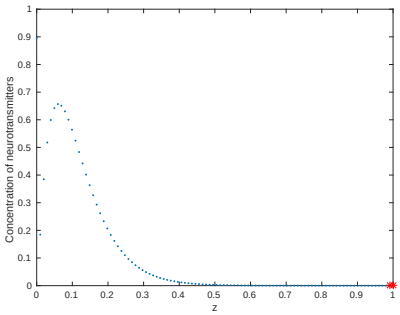
$$\kappa\nabla c = -k_1 c P^R + k_2(1 - P^R).$$

The next step is to combine these boundary conditions with the modeling equation to form a set of ODE's.

Using the finite element method the final system of equations then becomes



(a) Distribution of neurotransmitters on a line over time. $k_1 = 10$, $k_2 = 1$, $\Delta t = 0.001$, $\Delta z = 0.01$.



(b) Distribution of neurotransmitters on a line at a certain time. The red dots in the right corner marks Ω_ϵ.

Figure 4: Distribution of neurotransmitters on a line using the Matlab script $dim1.m$.

$$
\begin{aligned}
M\dot{C}(t) = &- KC(t) - k_3 Q^a(P_a^T(t))C_1(t) + \left[k_4(1 - P_a^T(t))\right] d^a \\
&- k_1 Q^b(P_b^R(t))C_N(t) + \left[k_2(1 - P_b^R(t))\right] d^b \\
\frac{\partial P_a^T(t)}{dt} &= -ck_3 P_a^T(t) + (k_4 + k_5)(1 - P_a^T(t)) \\
\frac{\partial P_b^R(t)}{dt} &= -ck_1 P_b^R(t) + k_2(1 - P_b^R(t)),
\end{aligned}
$$

where $P_a^T(t)$ defines the probability that a transporter in side a is available and $P_b^R(t)$ defines the probability that a receptor in side b is available at time t. M is the problem mass matrix and K is the problem stiffness matrix. C is the concentration of neurotransmitters at all internal nodes.

The system was found by Jörg Henrik Holstad [1] and was solved by combining into one large system and solved by using Matlab's ode45.

A plot using N = 6 internal nodes is shown in figure 5. More realistic constant values could be trued here as well.

The 2D scheme from [1] was also tried, but as shown in figure 6 we couldn't get the scheme to be stable.

6 2D model

Two models for a 2-dimensional scheme are proposed. The first considers height and width, while the second considers width and depth. The main difference is that in the first model, the neurotransmitters need to travel a distance before reaching the receptors. While in the second model the neurotransmitters and receptors start side by side.

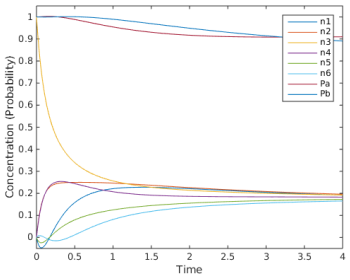
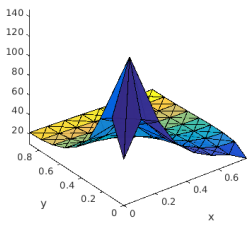
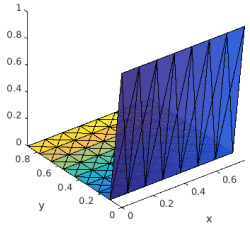


Figure 5: Solving the one dimensional case using the element method and Matlab's ode45 using the constants $a = 0$, $b = 8$, $N = 6$, $\kappa = 3$, $k_1 = k_2 = k_3 = k_4 = k_5 = 0.5$, $P_a^T(0) = P_b^R(0) = 1$, $C(0) = [0, 0, 1, 0, 0, 0]$.



(a) 2D solution at time 0.3 in a rectangular domain.



(b) Initial condition in a rectangular domain.

Figure 6: Our try to solve the 2D model with the finite element method and Matlab's ode45. We recognize that the scheme is numerically unstable and blows up.

6.0.1 Numerical scheme

We use the finite difference method to discretize the modeling equation (1), with boundary conditions (4) and (5).

$$C_{j,k}^{i+1} = C_{j,k}^{i} + \frac{\Delta t}{2}\Bigg[\kappa\Big(\frac{C_{j+1,k}^{i} - 2C_{j,k}^{i} + C_{j-1,k}^{i}}{(\Delta y)^2} + \frac{C_{j,k+1}^{i} - 2C_{j,k}^{i} + C_{j,k-1}^{i}}{(\Delta x)^2}\Big) - k_1 C_{j,k}^{i} P_{j,k}^{i} + k_2(1 - P_{j,k}^{i})\Bigg] \tag{7}$$

$$P_{j,k}^{i+1} = P_{j,k}^{i} + \Delta t\Big[- k_1 C_{j,k}^{i} P_{j,k}^{i} + k_2(1 - P_{j,k}^{i})\Big], \tag{8}$$

where i is points in time, and j, k are points in space. Δt, Δx, Δy are step length in time, width and height or depth, respectively.

6.1 Height and width

6.1.1 Domain, initial and boundary values

We consider the synaptic cleft a square with height L and width $2R$. We assume initially that the neurotransmitters are uniformly distributed on the axon terminal, at height $y = L$, and the receptors are uniformly distributed on the dendritic spine, $y = 0$. We also assume that the surface of the dendritic spine is covered by an extracellular fluid with thickness ϵ as presented in the 1D case in figure 3.

Like in the 1D-model, the neurotransmitters in this area can only react with unoccupied receptors.

6.1.2 Results

Using the 5-point-formula in equation (7), what was proposed in 6.1.1 was attempted, but the system was numerically unstable. Therefore, it will not be included in this report.

6.2 Width and depth

6.2.1 Domain, initial and boundary values

Initially we chose a random point where we released all the neurotransmitters. The initial function for the concentration of neurotransmitters is zero everywhere except from that point. On the boundary we assumed that the particles could freely diffuse outside of the domain.

To simplify the diffusion equation we neglect the height of the synaptic cleft. Furthermore, we chose to view the resulting disc as a square with size $4R^2$, due to the difficult nature of the Laplacian in cylindrical coordinates. We assume that the receptors are equally distributed over the square.

If the number of bounded receptors doesn't change over a time interval Δt, we assume equilibrium and that a signal is being transmitted.

6.2.2 Results

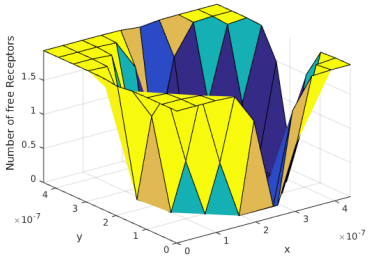
The program *dim2.m* was used with values given in [2], with $k_1 = 10^4$, $k_2 = 10$, and

- number of steps in x- and y-direction, $n_x = n_y = 10$
- number of time steps $n_t = 4 \cdot 10^5$, simulated over 1 second

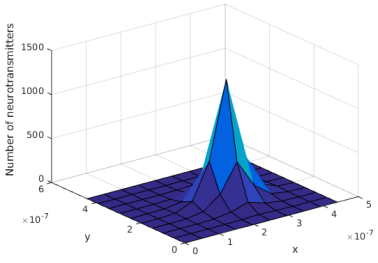
This results in a signaling time of $t_s = 33.8$ms. The following figures show the distribution of neurotransmitters and free receptors at the signaling time.

6.2.3 Discussion

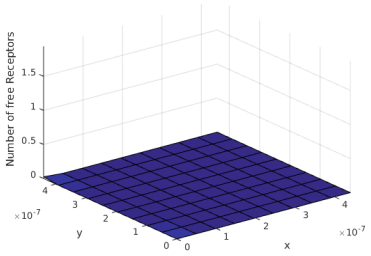
As we can see from figure 7c, practically all receptors are bounded at this time, so this may be considered an upper bound for the signaling time. This is a two dimensional model, and thus lacks a certain accuracy.



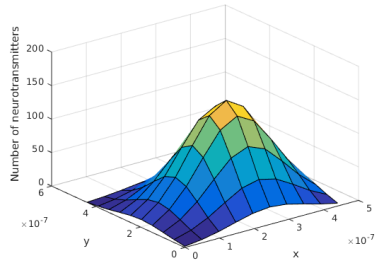
(a) Distribution of free receptors at 5 ms.



(b) Distribution of neurotransmitters at 5 ms.



(c) Distribution of free receptors at signal time.



(d) Distribution of neurotransmitters at signal time.

Figure 7: Simulation of the synaptic cleft at different times. This model is in 2 dimensions, ignoring height. In (a) and (c) the z-axis represents the number of free receptors. In (b) and (d) it represents the number of neurotransmitters. Signaling time is 33.8 ms.

References

[1] Jörg Henrik Holstad, *Modellering av Diffusjon av Nevrotransmittere i den Ekstracellulære Væsken*. 2011.
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