TMA4195 Mathematical Modelling

Synaptic Neurotransmission, Fall 2022

Group 12: Christian O. Moen, Sebastian Hiller, Frida S. Aase, Justus Pete Renger and Petter Nøst

November 23, 2022

Contents

1 Introduction

In this project, we will propose a model for the synaptic neurotransmission that occurs in the synaptic cleft between neurons in the brain. Synaptic neurotransmission occurs when two neurons attach to each other. In the process, neurotransmitters are released by one neuron, called the presynaptic neuron, and can bind to the receptors of the other neuron, the postsynaptic neuron. We can think of this process as occurring in two steps. First, the neurotransmitters are released by the presynaptic neuron and diffuse in the synaptic cleft. When the neurotransmitters get close enough to the receptors, they may bind to the receptors on the membrane of the postsynaptic process. This is a reversible chemical reaction and is the second step in the process.

We will present several models for this system and simulation results from them. The first model is, as the synaptic cleft, a full three dimensional model of the system. We model the system with closed boundaries so no neurotransmitters may leave the synaptic cleft. In this model, we simulate the release of 5000 neurotransmitters in a point. This is thought to be a good approximation for one synaptic vesicle popping and

releasing all its neurotransmitters. We present our simulation results from this model and give some details of the numerical scheme used to solve the modeling equations and the implementation of it.

In the three dimensional simulations, we find that the time until the diffusion has resulted in a homogeneous concentration in the whole synaptic cleft, is several orders of magnitude lower than the time until transmission. Because of this, and the geometry of the cleft, we propose a geometric reduction of the system. The geometric reduction corresponds to the cleft being modeled as a plane. For the reduced system, we propose a numerical scheme that we implement. From this model, we estimate the time of transmission using closed boundaries and the release of neurotransmitters from one vesicle pop.

As a further improvement of the model, we take into account the transportation of neurotransmitters out of the synaptic cleft that is performed by glia cells. Because the neurotransmitters now can leave the synaptic cleft, a total of 5000 neurotransmitters is no longer sufficient to get a transmission. Therefore, we simulate a constant flux of neurotransmitters into the synaptic cleft. With this system, we try to estimate the time of transmission, now being dependent on the input flux of neurotransmitters. Therefore, we estimate the total amount of neurotransmitters needed to achieve transmission. Lastly, we propose some improvements left as future work.

2 Three dimensional model

2.1 Modeling equation

We start by presenting the modeling equation for the transmission process occurring in the synaptic cleft. Let the neurotransmitter concentration at time t and position $\mathbf{x} = (x, y, z) \in \mathbb{R}^3$ in the synaptic cleft be denoted by $n(t, \mathbf{x})$. We assume that the neurotransmitters diffuse in the synaptic cleft. In addition, the neurotransmitters bind to the receptors located on the cell membrane. The chemical binding reaction that takes place is

$$\mathrm{R} + \mathrm{N} \underset{k_{\mathrm{off}}}{\overset{k_{\mathrm{on}}}{\rightleftharpoons}} \mathrm{R{-}N}. \tag{1}$$

Here, R denotes the receptors, N denotes the neurotransmitters, and R−N is the bound receptor. Moreover, $k_{\mathrm{on}} = 4 \cdot 10^6 \ \mathrm{mol}^{-1}\,\mathrm{L}\,\mathrm{s}^{-1}$ is the reaction constant in the binding reaction, and $k_{\mathrm{off}} = 5\,\mathrm{s}^{-1}$ is the reaction constant in the reaction where a bound receptor releases a neurotransmitter ([Ray]). We denote by $r(t, \mathbf{x})$ the concentration of free receptors and by $b(t, \mathbf{x})$ the concentration of the bound receptors R−N in the synaptic cleft.

The neurotransmitter concentration is controlled by a diffusion-reaction equation. The receptors and the bound receptors cannot diffuse, they remain at the membrane of the postsynaptic cleft at all times, and therefore they are modeled by a reaction equation. Thus, the three concentrations are the solution of the following system of partial differential equations

$$n_t = \kappa \Delta n - k_{\mathrm{on}} n \cdot r + k_{\mathrm{off}} b, \tag{2}$$
$$r_t = -k_{\mathrm{on}} n \cdot r + k_{\mathrm{off}} b, \tag{3}$$
$$b_t = \ \ k_{\mathrm{on}} n \cdot r - k_{\mathrm{off}} b, \tag{4}$$

where $\kappa = 8 \cdot 10^{-7} \mathrm{m}^2/\mathrm{s}$ is the diffusion constant and $\Delta = \frac{\partial^2}{\partial x^2} + \frac{\partial^2}{\partial y^2} + \frac{\partial^2}{\partial z^2}$ is the Laplace operator. By subscript t, we denote the partial derivative with respect to time, i.e. $\partial/\partial t$. The total number of free receptors, bound receptors, and neurotransmitters at time t is, respectively,

$$R(t) = \int r(t, \mathbf{x}) d\mathbf{x}, \qquad B(t) = \int b(t, \mathbf{x}) d\mathbf{x}, \qquad \text{and} \qquad N(t) = \int n(t, \mathbf{x}) d\mathbf{x}.$$

Denote the fraction of bound receptors at time t as $P(t) = B(t)/R(0)$. In our simulations, we assume the minimal fraction of bound receptors necessary to trigger a transmission to be 0.5. So to find the transmission time t^*, we find the first time point where the fraction of bound receptors surpasses 0.5, i.e,

$$t^* = \arg\min_t P(t) \geq 0.5. \tag{5}$$

2.2 Geometrical model

We model the synaptic cleft as a rectangular cuboid, where the height corresponds to the height of the synaptic cleft $h = 15\,\text{nm}$, and the width and length determine the surface area of the neuron's membranes. The surface area of the synaptic cleft in this project is proposed circular with radius $r = 0.22\,\mu\text{m}$. But as an approximation, this will be modeled as a square with sides $2r$. This is in order to use a rectangular grid when solving the differential equations using finite difference methods. A sketch of this geometrical model is shown in Figure 1.

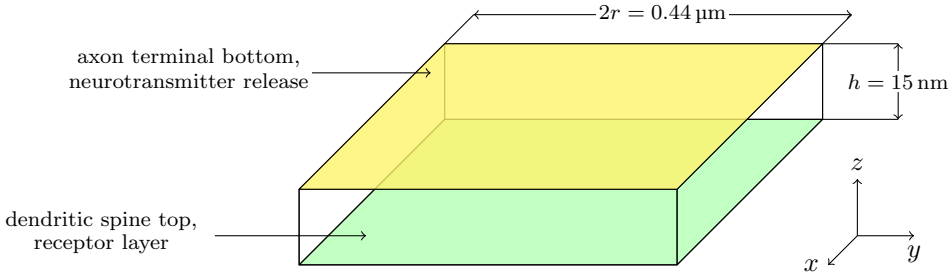


Figure 1: Abstract model of the synaptic cleft. Not to scale.

2.3 Numerical scheme

We propose two finite difference methods for solving the modeling equations (2)-(4); forward Euler and Crank Nicholson. As we will further develop the model, we do not go into the detail of the numerical scheme for this preliminary model. The details of the scheme for the final model are given in Section 4. For both methods, we use an equally spaced quadratic grid in the xy-plane with the same number of grid points in each direction. We use 30 times fewer grid points in the z-direction because $2r/h \approx 30$.

The Forward Euler method is an explicit first order finite difference method with stability criterion

$$\kappa \Delta t \left(\frac{1}{(\Delta x)^2} + \frac{1}{(\Delta y)^2} + \frac{1}{(\Delta z)^2} \right) < \frac{1}{2}, \tag{6}$$

where $\Delta t, \Delta x, \Delta y$ and Δz are the step sizes used in the numerical method for, respectively, t, x, y, and z. The Crank-Nicholson method, on the other hand, is unconditionally stable but has a higher computational complexity because it is an implicit method.

To model a synaptic cleft with zero neurotransmitter flux out of the cleft, we use Neumann boundary conditions. The Neumann boundary condition is that the concentration flux of neurotransmitters at the boundaries of the synaptic cleft is zero. Thus, the system is modeled such that no neurotransmitters can leave the synaptic cleft. We simulate one synaptic vesicle popping, which corresponds to 5000 neurotransmitters being released. All 5000 neurotransmitters are placed at the point in the center of the grid at the surface of the presynaptic neuron - the yellow surface in Figure 1. In addition, the initial receptor distribution on the postsynaptic neuron's membrane is uniform over the surface (the green surface in Figure 1) with a density of receptors on the membrane $1000\,\mu\text{m}^{-2}$. Initially, there are no bound receptors in the system.

2.4 Simulations

Because of the numerical instability of the forward Euler method, and the computational complexity of Crank-Nicholson, estimating the time until transmission requires a lot of computational power. The problem with the forward Euler method is that the step size Δt must be very small in order to satisfy the stability criterion (6) without simultaneously reducing the granularity of the grid in the spatial dimensions by too much.

The chemical reaction occurs on the postsynaptic neuron's membrane. To get a better understanding of what occurs on this surface, we calculate the total number of free receptors, bounded receptors, and neu-

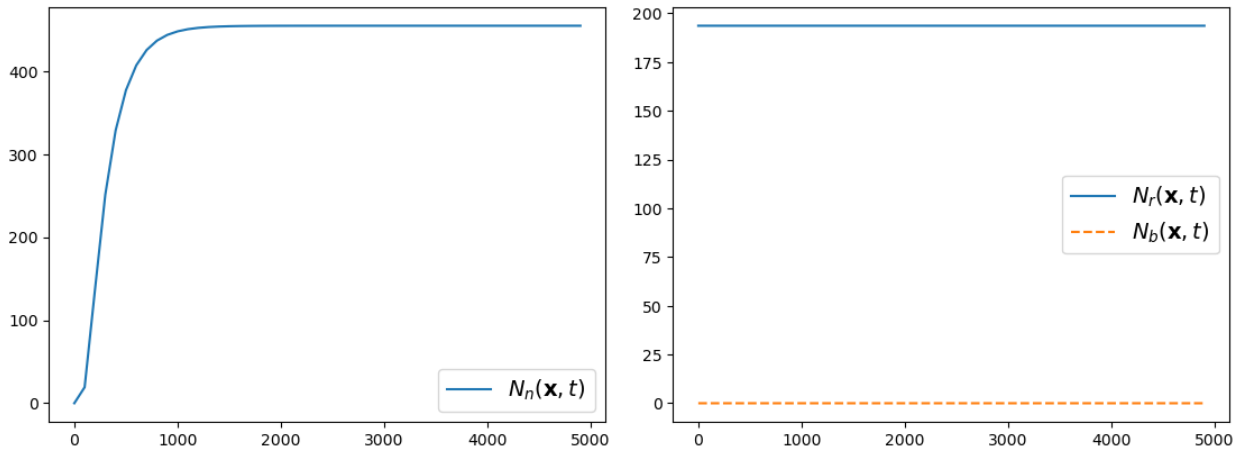


Figure 2: The graph of the total number of neurotransmitters N_n on the membrane of the postsynaptic cell is plotted to the left as a function of iterations in the time domain. On the right, we see the same plot, but this time the graph of the number of free and bound receptors is plotted. The graph of the number of free receptors is the blue, solid line, whereas, the graph of the bounded receptors is the orange, dashed line.

rotransmitters on this surface as a function of iterations from the numerical simulations using the forward Euler method. The graphs of these three sizes are plotted in Figure 2. The number of neurotransmitters on the postsynaptic neuron's membrane converges after approximately 1000 iterations in time. The number of neurotransmitters then corresponds to the number which gives a homogeneous concentration in the whole synaptic cleft. In the simulations, we used 11 grid points in the z-direction, therefore, the homogeneous concentration corresponds to there being 1/11th of the total number of neurotransmitters in each layer, i.e., $5000/11 \approx 454.5$ in each layer. Thus, the diffusion process has reached its stable state. At this time, the number of bounded receptors is less than one. Note that since the number of bounded receptors in the layer will be the sum of the concentration b over the surface, it is possible to have non-integer values for the total number of bounded receptors in the numerical model. Since forward Euler is unstable if (6) is not met, we cannot increase the step size Δt by more, thus to simulate until the transmission time we would have to simulate for a large number of iterations which increases the computational time significantly.

Physically, we can think of the process taking place in two steps. Step one is that the neurotransmitters diffuse, and reach the membrane of the postsynaptic neuron. Before a sufficiently large number of neurotransmitters have reached the surface where the free receptors are located, no reaction can take place. When there is a sufficiently high concentration of neurotransmitters on the postsynaptic membrane, the reactions will start.

Our results imply that the time it takes for the concentration of neurotransmitters to become homogeneous is very little compared to the time until half the receptors have bounded. In Figure 2 there is less than one bound receptor. Thus, the time until the transmission is much larger than the endpoint in these simulations. Hence, the time it takes for the neurotransmitters to reach the membrane of the postsynaptic neuron is negligible in comparison to the time from then until the transmission occurs. In addition, the height of the synaptic cleft is much smaller than the radius of the membrane ($h \ll r$). Because of this, it seems reasonable to model the whole synaptic cleft as a two dimensional surface, where we neglect the height of the synaptic cleft. This corresponds to the membrane of the presynaptic and postsynaptic neurons being in the same plane. This will significantly reduce the computational complexity of the model since we can reduce the spatial dimensional by one.

Note that even though we have implemented the Crank-Nicholson method for this system, the computational complexity of it was too high to yield any results for the three dimensional geometrical model. However, since the Crank-Nicholson method is unconditionally stable, we will use it to model the reduced geometrical model, where the whole synaptic cleft is modeled as a plane rather than a cuboid, which will be the topic of

the next section.

3 Geometrically reduced model

In this section we will discuss the geometrical reduction from three to two spatial dimensions. We still model the synaptic cleft with closed walls so that no neurotransmitters can leave the system.

3.1 Geometrical reduction and the determination of the initial neurotransmitter distribution

In the previous section, we have established a physical reasoning and computational necessity for a reduction from the three dimensional problem to a two dimensional simplification. Physically speaking we reduce our synaptic cleft to the postsynaptic membrane. In terms of our modeling equations (2)-(4), this does not require many changes. We simply use the two dimensional Laplace operator and reduce the spatial dimension of the concentrations by one. In order to keep the grid for the numerical scheme simple we keep modeling the membrane as a square with length $0.44\,\mu m$. The concentration of receptors is still uniformly distributed on this square with density $1000\,\mu m^{-2}$.

In the 2D model, we can't simulate the diffusion of the neurotransmitters from the axon terminal to the postsynaptic membrane since these are now located in the same plane. Therefore, to take into account the diffusion process that has occurred, we must determine an initial distribution of neurotransmitters on the postsynaptic membrane. The initial distribution should be similar to how the neurotransmitter concentration was on the postsynaptic membrane when the full model was used.

We now discuss how to choose the initial neurotransmitter concentration for simulating one synaptic vesicle popping in the 2D model. In the previous section, the simulation results suggested that a homogeneous concentration of neurotransmitters was reached at a time when there was less than one bound receptor when simulating one synaptic vesicle popping. This suggests that the diffusion process is much faster than the reaction process. At the time of transmission, when half the receptors are bound, there will remain ca. 4900 neurotransmitters in the synaptic cleft. And since the diffusion process is very fast, the concentration of neurotransmitters will remain approximately homogeneous and the number of neurotransmitters in the final layer will be almost constant; before the reaction, it is 5000/11 and after it is approximately 4900/11. Because of this, we argue that we can use that the number of neurotransmitters that reach the final layer is 1/11th of the total number of neurotransmitters when modeling a synaptic vesicle popping. Therefore, in the 2D model, when simulating one synaptic vesicle popping, we use 500 as the initial number of neurotransmitters. Moreover, we start with the neurotransmitters distributed over a circle with radius $0.22\,\mu m$ and center in the middle of the postsynaptic membrane, as shown in Figure 5. The concentration is highest in the middle of the circle and decreases as a function of the distance from the center. This is explained in more detail in Section 4.2 where the full model including the glia cells is presented.

3.2 Numerical scheme

To solve the system of differential equations we use Crank-Nicholson method with Neumann conditions of zero flux out of the system. The implementation can be seen in the Appendix. Since the spatial dimensions are now reduced by one, the computational complexity of the Crank-Nicholson method is significantly reduced. Therefore, the problems we faced in the three dimensional problems are no longer an issue.

3.3 Simulations

We use the implementation of the numerical scheme to estimate the time of transmission. The time of transmission is when half the receptors are bound. The total number of free receptors, bound, and neurotransmitters are plotted in Figure 3 as a function of time. From the plots we see that the time of transmission in this system is found to be $t = 3.7 \cdot 10^{-7}$s. As a next step, we will take into account the effect of glia cells.

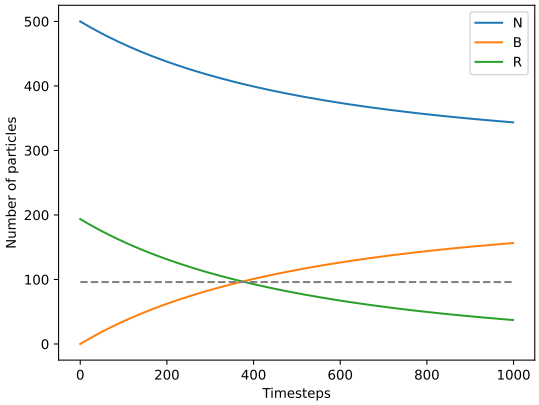


Figure 3: The total number of neurotransmitters is plotted in blue, the total number of bound receptors is seen in green and the number of free receptors is seen in green as a function of the number of iterations in time in the numerical scheme.

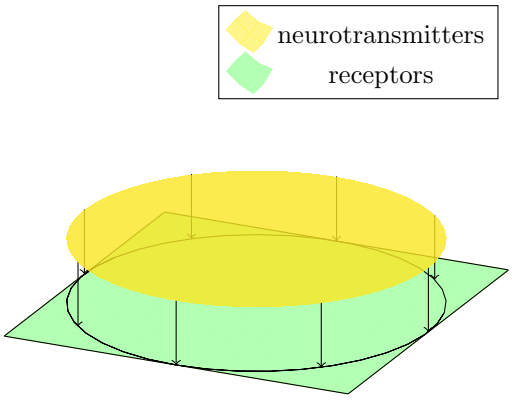


Figure 4: Schematic model of neurotransmitters (yellow, top layer) reaching the membrane (green, bottom layer).

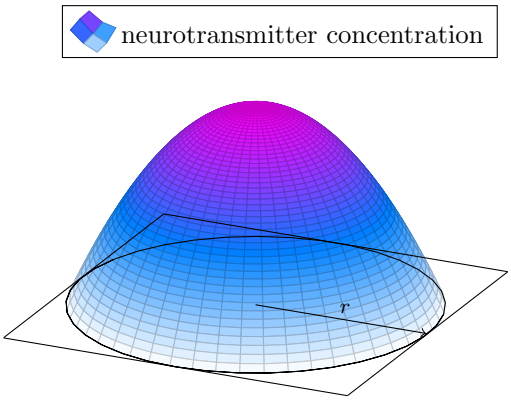


Figure 5: Initial distribution of neurotransmitters on the postsynaptic neuron's membrane.

4 Glia cell and the clearance of synaptic cleft

In this section, we discuss how to model the edges of our simulation to allow neurotransmitters to be "lost". This is motivated by the fact that at the edge boundaries of the synaptic cleft, there are glia cells that facilitate the transportation of neurotransmitters out of the synaptic cleft. This is an important process that allows the neuron to be reset and get ready for future transmissions. We integrate this in the geometrically reduced model from the previous section.

4.1 Numerical scheme

For modeling, two approaches come to mind. The first method is to model the sides of our rectangular cuboid in the same way we modeled the bottom. To achieve this one would add a new reactant to all the sides. This reactant would represent the glia cells and have a very high density and reaction constant. Such that every density of neurotransmitters that reaches those layers would instantly react and disappear from the simulation.

The second approach would be to simply model the sides as open in the finite difference calculations. This method is what we decide to implement as it is computationally less intensive and doesn't involve "inventing" density and reaction constants for the glia cells. This is implemented using Crank-Nicolson (CN) with Dirichlet boundary conditions on each of the equations (2), (3) and (4). The two dimensional CN stencil of an equation of the form $u_t = \kappa\Delta u + f(u)$ is given by

$$\begin{aligned}\frac{u_{i,j}^{n+1} + u_{i,j}^{n}}{\Delta t} = \frac{\kappa}{2\Delta x\Delta y}(&u_{i+1,j}^{n+1} + u_{i-1,j}^{n+1} + u_{i,j+1}^{n+1} + u_{i,j-1}^{n+1} - 4u_{i,j}^{n+1} \\ &+ u_{i+1,j}^{n} + u_{i-1,j}^{n} + u_{i,j+1}^{n} + u_{i,j-1}^{n} - 4u_{i,j}^{n} + f(u_{i,j}^{n})),\end{aligned} \tag{7}$$

where $f(u_{i,j}^n) = f(n_{i,j}^n, r_{i,j}^n, b_{i,j}^n) = -k_{\text{on}} n_{i,j}^n r_{i,j}^n + k_{\text{off}} b_{i,j}^n$ is the function containing the reaction terms. Define $\sigma := \Delta t\kappa/2\Delta x\Delta y$ and move the $n+1$ terms to the left hand side and the n terms to the right. Furthermore, let $\boldsymbol{U}^n = [u_{1,1}^n, u_{1,2}^n, ..., u_{1,l}^n, u_{2,1}^n, ..., u_{k,l}^n]^T$ for timestep n and number of grid points k and l in x and y direction of the membrane, respectively. Then, equation (7) can be written in matrix form as a system of linear equations with general structure $\mathbf{A}\boldsymbol{U}^{n+1} = \mathbf{B}\boldsymbol{U}^n + f(\boldsymbol{U}^n)$, where the block matrices $\mathbf{A}$ and $\mathbf{B}$ correspond to the stencil

$$\begin{aligned}&-\sigma(u_{i-1,j}^{n+1} + u_{i,j-1}^{n+1}) + (1+4\sigma)u_{i,j}^{n+1} - \sigma(u_{i+1,j}^{n+1} + u_{i,j+1}^{n+1}) \\ =&\sigma(u_{i-1,j}^{n} + u_{i,j-1}^{n}) + (1-4\sigma)u_{i,j}^{n} + \sigma(u_{i+1,j}^{n} + u_{i,j+1}^{n}) + f(u_{i,j}^{n}).\end{aligned} \tag{8}$$

Since the receptors are assumed stationary, that is, no diffusion of the receptors, equations (3) and (4) are approximated by $\boldsymbol{r}^{n+1} = \boldsymbol{r}^n + f(\boldsymbol{u}^n)$ and $\boldsymbol{b}^{n+1} = \boldsymbol{b}^n - f(\boldsymbol{u}^n)$ respectively. The glia cells are modeled by having a Dirichlet boundary condition corresponding to a neurotransmitter concentration of zero along the boundary, depicting how the glia cells consume everything outside the grid.

4.2 Influx of neurotransmitters

When neurotransmitters can leave the synaptic cleft, it is suggested by [MZ99] that a single synaptic vesicle pop often isn't enough for transmission. It is not clear how exactly the neurotransmitters leave the axon terminal. As a simplification, we have decided to use a constant (in time) flux $n_{in}(\mathbf{x})$ onto the postsynaptic membrane to model the average amount of neurotransmitters that reach the postsynaptic layer.

In our physical understanding it seems more likely for neurotransmitter to emerge from the middle of the axon terminal. Hence we adjust the spatial distribution of the flux $n_{in}(\mathbf{x})$ accordingly. Given a point $\mathbf{x}$ in the circular membrane in polar coordinates, i.e. $\mathbf{x} = x_r e^{ix_\varphi}$, we set the flux per timestep as

$$n_{in}(\mathbf{x}) = n_{in}(x_r e^{ix_\varphi}) = r^2 - x_r^2,$$

which has the same form as the initial neurotransmitter distribution we used in the previous section, as seen in Figure 5.

4.3 Simulations

The system is initialized with a flux of 20 neurotransmitters per timestep, with a timestep of size $\Delta t = 5 \cdot 10^{-9}$s. The concentrations are distributed as seen in the plots in the first column of Figure 6, which coincide with the initial distributions mentioned before. After a certain time, t_e, the flux of neurotransmitters into the boundary layer and the flux out due to glia cell transportation becomes equal. The distribution of n, b and r at such an equilibrium is shown in the middle column of the same figure. From this point on, the distribution of n remains the same disregarding the small variation due to neurotransmitter receptor binding; the plot in (b) is after 193 iterations in time, whereas the plot in (c) is after 624 iterations. We see that the concentration of neurotransmitters is constant after the equilibrium time (b) until the transmission time (c). The distribution of b and r at the time of transmission is shown in 6f and 6i. We estimate the transmission time to be $3.12 \cdot 10^{-6}$s.

We will now try to vary the magnitude of the flux to see how it affects the system.

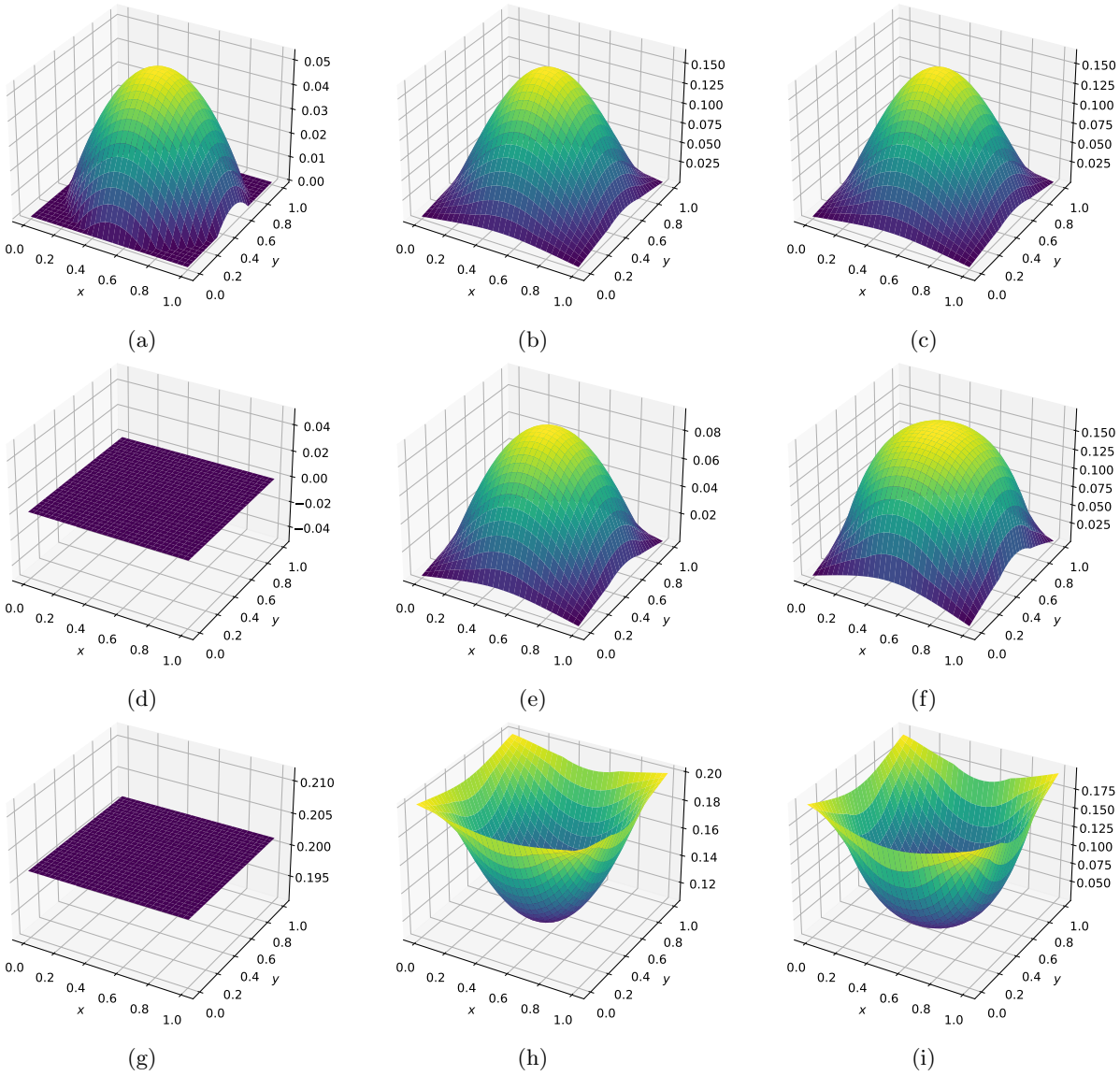
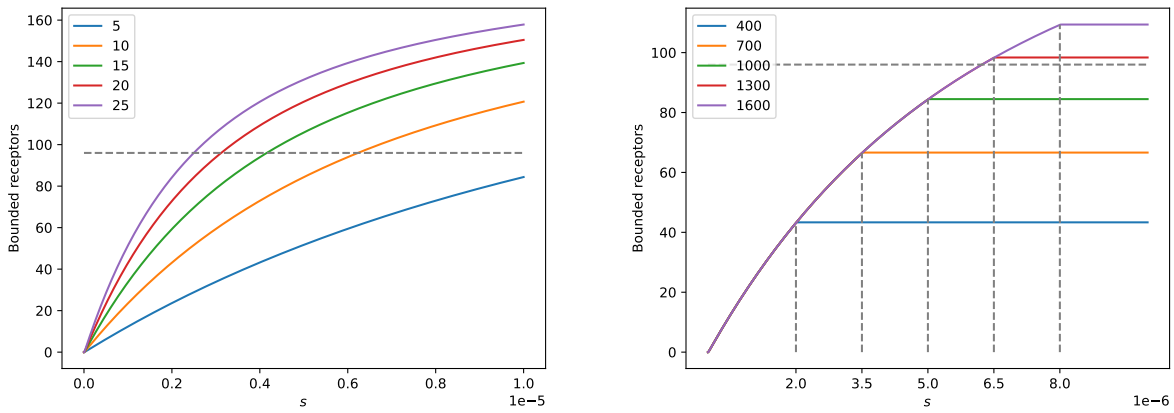


Figure 6: The concentration distribution of for n, b and r from top to bottom when $t = 0$ (first column), when the change in number of neurotransmitters is small $\delta N \ll 1$ (equilibrium with flux out of the sides) (middle column), and when signal is transmitted (last column).

Figure 7a shows the number of bound receptor $B(t)$ as a function of time for input fluxes of varying magnitude. We see that the effect of having a lower flux magnitude is to delay the transmission time. However, we find that the transmission will take place if we simulate for a long enough time period. Even with very low flux magnitude we find that it amounts to a transmission, but then we get into timescales of seconds, which don't seem to make sense for times of transmission between neurons in the brain. This suggests that the flux only impacts the time of transmission, not the occurrence.

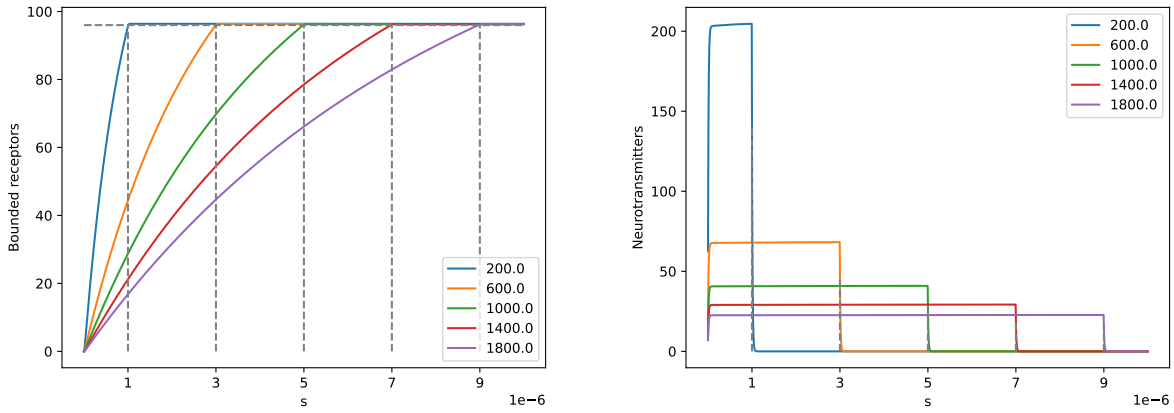
Next, instead of adding neurotransmitters at all timesteps, we consider what happens when a constant flux into the system stops at varying iteration numbers. This means that the total number of neurotransmitters entering the system varies. From the plot in Figure 7b we see that when the flux of neurotransmitters stops, the number of bounded receptors no longer increases. To get a transmission for this given value of flux, a little less than $10 \cdot 1300 = 13000$ neurotransmitters is needed.



(a) (b)

Figure 7: The number of bounded receptors $B(t)$ when flux per timestep is varying, (a), and for constant flux equal 10 with varying times for when influx is terminated, (b). Legend show flux per timestep (a) and timestep for flux termination (b).

The example in Figure 6 transmitted a signal when the total of $624 \cdot 20 = 12480$ neurotransmitters had been emitted into the cleft. As an example, we therefore fix the total number of neurotransmitters $N = 12500$ which we send in to the cleft over a varying number of timesteps T_i, such that the total number of neurotransmitters per timestep into the cleft is $N_i = N/T_i$. The graphs of the number of bound neurotransmitters from varying the number of time steps are seen in Figure 8a. We see further results suggesting that for a signal to be transmitted we only need to consider a certain amount of N released into the cleft, specifically, $N \approx 12500$. This may be due to the relatively fast diffusion of neurotransmitters. As seen in Figure 8b, the neurotransmitters diffuse out of the cleft almost immediately after the flux in is terminated, leaving no more neurotransmitters to bond.



(a) (b)

Figure 8: The total number of B (8a) and N (8b) for a constant number of neurotransmitters $N = N_i \cdot T_i$ released into the cleft with flux N_i per timestep for a total of T_i timesteps .

We see that the total amount of bound receptors seem to remain constant after the termination of influx. This makes sense due to the reaction coefficient to bind is orders of magnitude larger than the coefficient to unbind. To now model a potential second transmission, the bound neurotransmitters first have to leave

the receptors to start with an empty synaptic cleft. As we do not know the time until a new "set" of neurotransmitters will release, we do not know if they have enough time to unbind from the receptors and leave the cleft. This might suggest that the model is flawed and another mechanism is needed for neurotransmitter clearance.

5 Coupling with flow

To further improve the simulation one could take the flow of the underlying media into account. This movement acts on the neurotransmitters by pushing them into a certain direction with a constant force. Simulating this could be done in multiple ways. In our case, it is natural to again slightly change our finite difference matrix. This time by adding a direction dependent weight to neighboring cells. If this is done consistently for all entries the result is a wind-like drift of neurons. Another way would be to change our diffusion equation to account for this constant force.

References

[MZ99] Svoboda K Mainen ZF, Malinow R, *Synaptic calcium transients in single spines indicate that NMDA receptors are not saturated*, Nature **399** (1999), 151–155.

[Ray] Xavier Raynaud, *TMA4195 - Mathematical Modeling (Fall 2022). Modeling Synaptic Transmission*, Note: We refer to the project description from the course to use some of the numerical values given there. It was downloaded from: https://wiki.math.ntnu.no/tma4195/2022h/project.

6 Appendix

All the code used in this project can be seen in our git repository https://github.com/kikkan/TMA4195/tree/main.