Modeling Synaptic Transmission

TMA4195 — Mathematical Modeling (Fall 2022)

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1 Introduction

The objective of this project is to model synaptic transmission. The focus lies on what happens in the *synaptic cleft*, the region between two neurons that allows for passing signals between them. This mechanism is essential for our brain function. At the pre-synaptic neuron, also known as the axon terminal, neurotransmitters are released in response to an *action potential*, that is an electric signal. After this release, the neurotransmitters move across the synaptic cleft, where they interact with receptors located on the post-synaptic neuron, also known as the dendritic spine. The neurotransmitters essentially bind to free receptors and, when enough of these molecules are bound, a new signal is produced in the post-synaptic neuron. This signal will then lead to the same process in the next synapse and so on.

First we develop a simple mathematical framework for studying this process. Legg til approx. analytical løsning hvis vi får til dette også Then we try to solve the equations numerically, given some typical parameter values, in order to study some possible solutions. After this, the mathematical problem may be changed in several different ways, e.g. by changing the assumed geometry of the system, modeling clearance of neurotransmitters from the synaptic cleft or coupling the system with flow.

2 Modelling the Movement of Neurotransmitters

After the release of neurotransmitters at the pre-synaptic neuron, the signalling molecule moves across the synaptic cleft. This movement is most commonly modelled as free diffusion. The flux density of neurotransmitters, J_N, can be approximated using Fick's law of diffusion

$$J_N = -\alpha_N \nabla c_N,$$

where c_N is the concentration of neurotransmitters and α_N is a diffusion coefficient. Mass conservation in the absence of chemical reactions yields the diffusion equation

$$\frac{\partial c_N}{\partial t} = \alpha_N \nabla^2 c_N, \tag{1}$$

which describes how diffusion leads to a change in concentration with time. More specifically, the mass conservation equation on differential form reads

$$\frac{\partial c_N}{\partial t} + \nabla J_N = 0,$$

with no source or sink, since we assume an absence of chemical reactions when studying diffusion in isolation. Insertion of Fick's law yields

$$\frac{\partial c_N}{\partial t} - \nabla \alpha_N \nabla c_N = 0,$$

and assuming α_N is constant the equation simplifies to

$$\frac{\partial c_N}{\partial t} = \alpha_N \nabla \nabla c_N \implies \frac{\partial c_N}{\partial t} = \alpha_N \nabla^2 c_N,$$

which is the diffusion equation given above.

3 Modelling the Binding Process

As the neurotransmitters travel across the synaptic cleft, they eventually bind to free receptors which are fixed at the dendritic spine. We assume that the probability of a neurotransmitter binding to a receptor is a function of both the distance between them and the duration of time they are in proximity of each other. One natural way to model this behaviour is as a chemical reaction between neurotransmitters N and receptors R. However, as the receptors do not freely move around in the synaptic cleft Ω, but lie on a lower dimensional manifold Γ, we introduce a small artificial cleft Ω_ϵ such that $\Gamma \subset \Omega_\epsilon \subset \Omega$. The receptors are now defined to lie in Ω_ϵ where the proportion of free receptors at $x \in \Omega_\epsilon$ and time t is $P^R_{\Omega_\epsilon}(t,x) \in (0,1)$ Now we can model the binding process as a chemical reaction

$$R + N \xrightarrow{k} R{-}N,$$

where $R-N$ is a bound receptor. For simplicity, we assume that this chemical reaction is a net forward reaction. Let $f_N(t,x)$ be the probability density of neurotransmitters at position x at time t, and similarly for receptors, $f_R(t,x)$. We define $H(T)$ as the probability of a reaction occurring before a time T given that the neurotransmitter and receptor are at the same position, $x_N = x_R$. When $x_N \neq x_R$, the probability of a reaction occurring is weighted as a function of the distance, $g(|x_N - x_R|)$. Now the probability density of neurotransmitters at $t+\Delta t$ can be written as the probability density at t, times the probability that it has not reacted with any of the receptors in Ω_ϵ during Δt,

$$f_N(t+\Delta t, x) = f_N(t,x)\left(1 - \int_{\Omega_\epsilon} g(|x - x_R|)H(\Delta t) f_R(t, x_R) dx_R\right). \tag{2}$$

Notice that $f_R(t,x_R) = P^R_{\Omega_\epsilon}(t,x_R)$. As $\epsilon \to 0$ the amount of reactors stays constant, and the proportion of reactors in Ω_ϵ becomes a proportion on Γ, $P^R_\Gamma(t,x)$. Taking the limit $\epsilon \to 0$, Equation (2) can be written as

$$f_N(t+\Delta t, x) - f_N(t,x) = -f_N(t,x)\int_\Gamma g(|x - x_R|)H(\Delta t) P^R_\Gamma(t,x_R) dx_R.$$

As $H(0) = 0$ Hvorfor er dette viktig?Siden $H(\Delta t)/\Delta t = (H(\Delta t) - H(0))/\Delta t$, gir oss $H'(0)$, we can divide by Δt and take the limit $\Delta t \to 0$, giving

$$\frac{\partial}{\partial t} f_N(t,x) = -f_N(t,x)\int_\Gamma g(|x - x_R|)H'(0) P^R_\Gamma(t,x_R) dx_R.$$

Finally we assume $g(|x|) = \delta(x)$. Then the equation becomes

$$\frac{\partial}{\partial t} f_N(t,x) = -H'(0) f_N(t,x) P^R_\Gamma(t,x).$$

Let $[R]$ be a pseudo-concentration of receptors in Γ proportional to $P^R_\Gamma(t,x)$. Since the density of neurotransmitters is proportional to the concentration of the same substance, we reach the standard rate equation

$$\frac{\partial [N]}{\partial t} = -k[N][R],$$

where $[N]$ denotes the concentration of neurotransmitters.

4 Final Model

Our final (simple) mathematical model for synaptic neurotransmission, i.e. the sequence that covers the motion and activity of the neurotransmitters and receptors in the intercellular space, is found by composing the results from Sections 2 and 3. Notice that we assumed a net forward reaction in Section 3. More realistically, in the following we assume a chemical equilibrium of the form

$$R + N \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} R{-}N, \tag{3}$$

where $R-N$ denotes a bound receptor. There is in fact some probability that a bound receptor releases a neurotransmitter, and, vice versa, a probability that a neurotransmitter binds to the receptor, which is why this process is modelled by a reversible chemical reaction.

Conservation of mass of neurotransmitters gives the equation

$$\frac{\partial[N]}{\partial t} = \alpha_N \nabla^2[N] - k_1[N][R] + k_{-1}[R-N], \tag{4}$$

where $-k_1[N][R]$ is a sink, $k_{-1}[N-R]$ is a source and $\alpha_N \nabla^2[N]$ is the gradient of the flux of $[N]$. Similarly, conservation of mass of receptors gives the equation

$$\frac{\partial[R]}{\partial t} = -k_1[N][R] + k_{-1}[R-N], \tag{5}$$

where $-k_1[N][R]$ is a sink and $k_{-1}[N-R]$ is a source. The receptors do not diffuse, which explains the absence of a diffusion term in this equation. Finally, conservation of mass of bound receptors gives the equation

$$\frac{\partial[R-N]}{\partial t} = k_1[N][R] - k_{-1}[R-N], \tag{6}$$

where $-k_{-1}[N-R]$ is a sink and $k_1[N][R]$ a source. Thus, the final (simple) modelling equations we will study inside the artificial region Ω_ϵ are Equations (4), (5) and (6). Outside this region, in $\Omega \setminus \Omega_\epsilon$, i.e. in the region between the pre-synaptic neuron and the artificial region outside the post-synaptic neuron, there are no receptors. This means that we will simply study a special case of Equation (4) in this region, given by

$$\frac{\partial[N]}{\partial t} = \alpha_N \nabla^2[N], \tag{7}$$

because $[R] = [R-N] = 0$.

Eirik: Hadde kanskje vært nais å skrive noe her om geometrien på problemet (anta syllindrisk fasong på kløfta, inføre syllinderkoordinater, anta rotasjonssymmetri, og forklare dropping av θ-koordinaten. Kan eventuelt vie en helt egen seksjon til det.

5 Boundary Conditions

We deduce some boundary conditions based on the final model in the previous section. Subtracting Equation (5) from Equation (4) yields Notice that the system of equations given by (4), (5) and (6) can be reduced to a system of two equations. Subtracting Equation (5) from Equation (4) yields

$$\frac{\partial[N]}{\partial t} - \frac{\partial[R]}{\partial t} = \alpha_N \nabla^2[N]. \tag{8}$$

Moreover, adding Equation (6) and Equation (4) yields

$$\frac{\partial[N]}{\partial t} - \frac{\partial[R-N]}{\partial t} = \alpha_N \nabla^2[N]. \tag{9}$$

Finally, adding Equation (6) and Equation (5) yields

$$\frac{\partial[R]}{\partial t} + \frac{\partial[R-N]}{\partial t} = 0 \implies [R] + [R-N] = C(x), \tag{10}$$

where $C(x)$ is a constant function that does not depend on time. Inserting the expression into Equation (4) yields

$$\begin{aligned} \frac{\partial[N]}{\partial t} &= \alpha_N \nabla^2[N] - k_1[N][R] + k_{-1}(-[R] + C(x))) \\ &\Updownarrow \\ \frac{\partial[N]}{\partial t} &= \alpha_N \nabla^2[N] - k_1[N][R] - k_{-1}[R] + k_{-1}C(x), \end{aligned} \tag{11}$$

which is coupled to Equation (5) via

$$\begin{aligned} \frac{\partial[R]}{\partial t} &= -k_1[N][R] + k_{-1}(-[R] + C(x))) \\ &\Updownarrow \\ \frac{\partial[R]}{\partial t} &= -k_1[N][R] - k_{-1}[R] + k_{-1}C(x), \end{aligned} \tag{12}$$

Thus, alternatively, one could solve the coupled system of equations given by Equations (11) and (12), because the relation between the concentration of free and bounded receptors is given by Equation (10). The exact form of function $C(x)$ can be defined as a boundary condition.

Eirik: Hadde kanskje vært nais å skrive noe her om geometrien på problemet (anta syllindrisk fasong på kløfta, inføre syllinderkoordinater, anta rotasjonssymmetri, og forklare dropping av θ-koordinaten. Kan eventuelt vie en helt egen seksjon til det. Yes, enig i at dette hadde vært nice, spesielt mtp at vi begynner å prate om r og θ i neste avsnitt.

6 Scaling

Before moving on, the modelling equations should be scaled. The most important physical constants in this problem are summarized in Table 1. Concentration is only a meaningful concept on a macroscopic scale. On a molecular

Description	Variable	Value
Length of synaptic cleft	L	$15 \times 10^{-9}\,\mathrm{m}$
Radius of synaptic cleft	R	$0.22 \times 10^{-6}\,\mathrm{m}$
Diffusion coefficient	α_N	$8 \times 10^{-7}\,\mathrm{m^2\,s^{-1}}$
Density of receptors on dendritic membrane	ρ_R	$1 \times 10^{15}\,\mathrm{m^{-2}}$
Density of neurotransmitters on axon membrane	ρ_N	$33 \times 10^{15}\,\mathrm{m^{-2}}$
Forward reaction constant	k_1	$4 \times 10^{3}\,\mathrm{m^3\,mol^{-1}\,s^{-1}}$
Backward reaction constant	k_{-1}	$5\,\mathrm{s^{-1}}$

Table 1: The most important physical constants in the problem.

scale, the particles are not a continuous entity, and a moving average has to be introduced to make concentration a meaningful concept. In the r and θ directions, this is less of a problem, as we are dealing with a density of particles in these directions, and so the moving average has already been applied. However in the z-direction, it makes sense to introduce a *moving average characteristic size* Δz_{ma} (finn gjerne på et bedre navn på den her) Jeg synes dette navnet var ganske bra. We will set $\Delta z_{ma} = L/1000$, giving a *resolution* of 1000 different concentrations in the z-direction. Using this, we get

$$\begin{aligned} [R]_0 &= \frac{\rho_R}{\Delta z_{ma}} = 6.66 \times 10^{26}\,\mathrm{m^{-3}} \approx 110\,\mathrm{mol\,m^{-3}} \\ [N]_0 &= \frac{\rho_N}{\Delta z_{ma}} = 2.2 \times 10^{27}\,\mathrm{m^{-3}} \approx 3.6 \times 10^{3}\,\mathrm{mol\,m^{-3}} \end{aligned} \tag{13}$$

as the initial concentrations on the two boundaries. We can then define the scaled variables

$$\begin{aligned} \widehat{[N]} &= \frac{[N]}{[N]_0}, \\ \widehat{[R]} &= \frac{[R]}{[R]_0}, \\ \widehat{[R-N]} &= \frac{[R-N]}{[R]_0}. \end{aligned} \tag{14}$$

To find a scale for time, we insert the scales above into (4)

$$\begin{aligned} [N]_0 \frac{\partial \widehat{[N]}}{\partial t} &= [N]_0 \alpha_N \nabla^2 \widehat{[N]} - [N]_0 [R]_0 k_1 \widehat{[N]}\widehat{[R]} + [R]_0 k_{-1} \widehat{[R-N]} \\ \implies \frac{1}{[R]_0 k_1} \frac{\partial \widehat{[N]}}{\partial t} &= \frac{\alpha_N}{[R]_0 k_1} \nabla^2 \widehat{[N]} - \widehat{[N]}\widehat{[R]} + \frac{k_{-1}}{[N]_0 k_1} \widehat{[R-N]}. \end{aligned} \tag{15}$$

Er det første leddet til høyre for likheten i (15) korrekt? Tenker på gradienten. Se rød kommentar nederst. From this, we see that a reasonable time-scale is

$$\hat{t} = t[R]_0 k_1. \tag{16}$$

Under this scaling, the system of equations becomes

$$\frac{\partial \widehat{[N]}}{\partial \hat{t}} = \widehat{\alpha_N}\nabla^2\widehat{[N]} - \widehat{[N][R]} + \widehat{k_{-1}[R-N]}, \tag{17}$$

$$\frac{\partial \widehat{[R]}}{\partial \hat{t}} = -\widehat{[N][R]} + \widehat{k_{-1}[R-N]}, \tag{18}$$

$$\frac{\partial \widehat{[R-N]}}{\partial \hat{t}} = \widehat{[N][R]} - \widehat{k_{-1}[R-N]}, \tag{19}$$

where $\widehat{\alpha_N} = \frac{\alpha_N}{[R]_0 k_1}$ and $\widehat{k_{-1}} = \frac{k_{-1}}{[N]_0 k_1} \leq 10^{-7}$. Førstnevnte er vel ikke dimensjonsløs? Noe galt med enhetene til k_1 i tabellen over? Står noe litt annet i oppgaveteksten, men jeg skjønte ikke dette. EDIT: Tror det skyldes at det mangler en Δz_{ma}^2 i nevneren! (det mangler en length scale i gradienten). Da blir den dimensjonsløs. Ja shit stemmer, glemte å skalere de romlige dimensjonene. Var dog litt usikker på hvordan dette skulle gjøres, siden det er så stor forskjell på hvilken range r og z er i. Tenkte egentlig å bruke L som length scale, men da blir jo konstanten foran r-leddet veldig liten (perturbasjon?).

Eirik: Ser nå at den her skaleringen gjør at diffusjonskonstanten og $\widehat{k_{-1}}$ blir veldig små (typ $\leq 10^-9$), mens den tvinger $\widehat{k_1}$ til å være 1. Finnes sikkert en bedre måte å gjøre det på.

Når jeg tenker meg om, så består vel mesteparten av 'signaloverføringen' av diffusjonen, så det gir kanskje mer mening å skalere sånn at diffusjonskonstanten blir 1.

Har prøvd meg på en skalering som følger fremgangsmåte fra forelesning.

To scale the equation, let

$$\begin{aligned}
t^* &= t \cdot t_0 \\
z^* &= z \cdot z_0, \quad z_0 = 15 \cdot 10^{-9}\text{m} \\
r^* &= r \cdot r_0, \quad r_0 = 0.22 \cdot 10^{-6}\text{m} \\
[N]^* &= [N] \cdot [N]_0, \quad [N]_0 = \rho_N = 10^{15}\text{m}^2 \\
[R]^* &= [R][R]_0 \quad [R]_0 = \rho_R = 33 \cdot 10^{15}\text{m}^2 \\
[N-R]^* &= [N-R][N-R]_0, \quad [N-R]_0 = [N]_0 = \rho_N?
\end{aligned}$$

Hva tenker dere om å sette $[N-R]_0 = [N]_0$? Det blir vel maks antall $[N-R]$ vi kan ha?
Siden dette er tettheter vet jeg ikke helt? Vanskelig å se for seg
Ja $[N-R]_0 = [N]_0$ var min første tanke også, men jeg vet ikke om det kanskje er andre valg som er smartere. Det vil jo hvertfall gjøre at $[N]^* \in (0,1)$.

We have

$$\begin{aligned}
[N]^* &= [N]^*(r^*, z^*, t^*) = \rho_N[N](\frac{r^*}{r_0}, \frac{z^*}{z_0}, \frac{t^*}{t_0}) \\
[R]^* &= [R]^*(r_0, z_0, t_0) = \rho_R[R](\frac{r^*}{r_0}, \frac{z^*}{z_0}, \frac{t^*}{t_0}) \\
[N-R]^* &= [N-R]^*(r^*, z^*, t^*) = [N-R]_0[N-R](\frac{r^*}{r_0}, \frac{z^*}{z_0}\frac{t^*}{t_0})
\end{aligned}$$

$$\begin{aligned}
\frac{\partial [N]^*}{\partial t^*} &= \alpha\nabla[N]^* - k_1[N]^*[R]^* + k_{-1}[R-N]^* \\
\frac{\partial [N]^*}{\partial t^*} &= \frac{\alpha}{r^*}\frac{\partial}{\partial r^*}\left(r^*\frac{\partial [N]^*}{\partial r^*}\right) + \alpha\frac{\partial^2 [N]^*}{\partial (z^*)^2} - k_1[N]^*[R]^* + k_{-1}[R-N]^*
\end{aligned}$$

$$
\begin{aligned}
\frac{\partial [N]^*}{\partial t^*} &= \rho_N \frac{\partial [N]}{\partial t}\frac{1}{t_0} = \frac{\rho_N}{t_0}\frac{\partial [N]}{\partial t} \\
\frac{\partial [N]^*}{\partial r^*} &= \rho_N \frac{\partial [N]}{\partial r}\frac{1}{r_0} = \frac{\rho_N}{r_0}\frac{\partial [N]}{\partial r} \\
r^* &= r_0 \cdot r \\
r^*\frac{\partial [N]^*}{\partial r^*} &= r_0 \cdot r\frac{\rho_N}{r_0}\frac{\partial [N]}{\partial r} = \rho_N r\frac{\partial [N]}{\partial r} \\
\frac{\alpha}{r^*}\frac{\partial}{\partial r^*}\left(r^*\frac{\partial [N]^*}{\partial r^*}\right) &= \frac{\alpha}{r_0^2\cdot r}\frac{\partial}{\partial r}\left(\rho_N r\frac{\partial [N]}{\partial r}\right) = \frac{\alpha\rho_N}{r_0^2\cdot r}\left(\frac{\partial [N]}{\partial r} + r\frac{\partial^2 [N]}{\partial r^2}\frac{1}{r_0}\right) = \frac{\alpha\rho_N}{r_0^2\cdot r}\left(\frac{\partial [N]}{\partial r} + \frac{r}{r_0}\frac{\partial^2 [N]}{\partial r^2}\right) \\
\alpha\frac{\partial^2 [N]^*}{\partial (z^*)^2} &= \alpha\rho_N\frac{\partial^2 [N]}{\partial z^2}\frac{1}{z_0^2} = \frac{\alpha\rho_N}{z_0^2}\frac{\partial^2 [N]}{\partial z^2} \\
-k_1[N]^*[R]^* &= -\rho_N\rho_R k_1[N][R] \\
k_{-1}[N-R]^* &= [N-R]_0 k_1[N-R]
\end{aligned}
$$

Insert into model equation

$$
\begin{aligned}
\frac{\partial [N]^*}{\partial t^*} &= \frac{\alpha}{r^*}\frac{\partial}{\partial r^*}\left(r^*\frac{\partial [N]^*}{\partial r^*}\right) + \alpha\frac{\partial^2 [N]}{\partial z^2} - k_1[N][R] + k_{-1}[R-N] \\
\Rightarrow \frac{\rho_N}{t_0}\frac{\partial [N]}{\partial t} &= \frac{\alpha\rho_N}{r_0^2\cdot r}\left(\frac{\partial [N]}{\partial r} + \frac{r}{r_0}\frac{\partial^2 [N]}{\partial r^2}\right) + \frac{\alpha\rho_N}{z_0^2}\frac{\partial^2 [N]}{\partial z^2} - \rho_N\rho_R k_1[N][R] + [N-R]_0 k_{-1}[N-R] \\
\Leftrightarrow \frac{\partial [N]}{\partial t} &= \frac{t_0}{\rho_N}\frac{\alpha\rho_N}{r_0^2\cdot r}\left(\frac{\partial [N]}{\partial r} + \frac{r}{r_0}\frac{\partial^2 [N]}{\partial r^2}\right) + \frac{t_0}{\rho_N}\frac{\alpha\rho_N}{z_0^2}\frac{\partial^2 [N]}{\partial z^2} - \frac{t_0}{\rho_N}\rho_N\rho_R k_1[N][R] + \frac{t_0}{\rho_N}[N-R]_0 k_{-1}[N-R] \\
\Leftrightarrow \frac{\partial [N]}{\partial t} &= \frac{\alpha t_0}{r_0^2}\frac{1}{r}\left(\frac{\partial [N]}{\partial r} + \frac{r}{r_0}\frac{\partial^2 [N]}{\partial r^2}\right) + \frac{\alpha t_0}{z_0^2}\frac{\partial^2 [N]}{\partial z^2} - \rho_R t_0 k_1[N][R] + \frac{[N-R]_0 t_0}{\rho_N}k_{-1}[N-R] \\
&= \frac{\alpha t_0}{r_0^2}\frac{1}{r}\frac{\partial [N]}{\partial r} + \frac{\alpha t_0}{r_0^3}\frac{\partial^2 [N]}{\partial r^2} + \frac{\alpha t_0}{z_0^2}\frac{\partial^2 [N]}{\partial z^2} - \rho_R t_0 k_1[N][R] + \frac{[N-R]_0 t_0}{\rho_N}k_{-1}[N-R]
\end{aligned}
$$

$$
\frac{\partial [N]}{\partial t} = \frac{\alpha t_0}{r_0^2}\frac{1}{r}\frac{\partial [N]}{\partial r} + \frac{\alpha t_0}{r_0^3}\frac{\partial^2 [N]}{\partial r^2} + \frac{\alpha t_0}{z_0^2}\frac{\partial^2 [N]}{\partial z^2} - \rho_R t_0 k_1[N][R] + \frac{[N-R]_0 t_0}{\rho_N}k_{-1}[N-R] \tag{20}
$$

5 ways to balance the equation

$$
\begin{aligned}
t_0 &= \frac{r_0^2}{\alpha}, \quad \left[\frac{r_0^2}{\alpha}\right] = \frac{\mathrm{m}^2}{\mathrm{m}^2\mathrm{s}^{-1}} = \mathrm{s} \\
t_0 &= \frac{r_0^3}{\alpha}, \quad \left[\frac{r_0^3}{\alpha}\right] = \frac{\mathrm{m}^3}{\mathrm{m}^2\mathrm{s}^{-1}} = \mathrm{ms} \\
t_0 &= \frac{z_0^2}{\alpha}, \quad \left[\frac{z_0^2}{\alpha}\right] = \frac{\mathrm{m}^2}{\mathrm{m}^2\mathrm{s}^{-1}} = \mathrm{s} \\
t_0 &= \frac{1}{\rho_R k_1}, \quad \left[\frac{1}{\rho_R k_1}\right] = \frac{1}{\mathrm{m}^{-2}\mathrm{m}^3\mathrm{mol}^{-1}\mathrm{s}^{-1}} = \frac{\mathrm{s\ mol}}{\mathrm{m}} \\
t_0 &= \frac{\rho_N}{[N-R]_0 k_{-1}}, \quad \left[\frac{\rho_N}{[N-R]_0 k_{-1}}\right] = \frac{\mathrm{m}^{-2}}{\mathrm{m}^{-2}\mathrm{s}^{-1}} = \mathrm{s}
\end{aligned}
$$

Hvis enhent til k_{-1} er riktig. Prøver bare de med riktig dimensjon

First let $t_0 = \frac{r_0^2}{\alpha}$

$$
\frac{\partial [N]}{\partial t} = \frac{1}{r}\frac{\partial [N]}{\partial r} + \frac{1}{r_0}\frac{\partial^2 [N]}{\partial r^2} + \frac{r_0^2}{z_0^2}\frac{\partial^2 [N]}{\partial z^2} - \frac{r_0^2\rho_R}{\alpha}k_1[N][R] + \frac{[N-R]_0 r_0^2}{\rho_N \alpha}k_{-1}[N-R] \tag{21}
$$

with

$$\begin{aligned}
\frac{1}{r_0} &\approx 10^6 \\
\frac{r_0^2}{z_0^2} &\approx \frac{10^{-12}}{10^{-18}} = 10^6 \\
\frac{\rho_R r_0^2}{\alpha} k_1 &\approx \frac{10^{15}10^{-12}}{10^{-7}} k_1 = 10^{10} k_1 \\
\frac{r_0^2 [N-R]_0 k_{-1}}{\alpha \rho_N} &\approx \frac{10^{-12}}{10^{-7}10^{15}} [N-R]_0 k_{-1} = 10^{-20} [N-R]_0 k_{-1}
\end{aligned}$$

Next we try $t_0 = \frac{z_0^2}{\alpha}$

$$\frac{\partial [N]}{\partial t} = \frac{z_0^2}{r_0^2}\frac{1}{r}\frac{\partial [N]}{\partial r} + \frac{z_0^2}{r_0^3}\frac{\partial^2 [N]}{\partial r^2} + \frac{\partial^2 [N]}{\partial z^2} - \frac{z_0^2 \rho_R}{\alpha} k_1 [N][R] + \frac{[N-R]_0 z_0^2}{\rho_N \alpha} k_{-1} [N-R] \tag{22}$$

with

$$\begin{aligned}
\frac{z_0^2}{r_0^2} &\approx \frac{10^{-18}}{10^{-12}} = 10^{-6} \\
\frac{z_0^2}{r_0^3} &\approx \frac{10^{-18}}{10^{-18}} = 1 \\
\frac{\rho_R z_0^2}{\alpha} k_1 &\approx \frac{10^{15}10^{-18}}{10^{-7}} k_1 = 10^{4} k_1 \\
\frac{z_0^2 [N-R]_0 k_{-1}}{\alpha \rho_N} &\approx \frac{10^{-18}}{10^{-7}10^{15}} [N-R]_0 k_{-1} = 10^{-24} [N-R]_0 k_{-1}
\end{aligned}$$

Lastly we try $t_0 = \frac{\rho_N}{[N-R]_0 k_{-1}}$

$$\frac{\partial [N]}{\partial t} = \frac{\alpha \rho_N}{[N-R]_0 k_{-1} r_0^2}\frac{1}{r}\frac{\partial [N]}{\partial r} + \frac{\alpha \rho_N}{[N-R]_0 k_{-1} r_0^3}\frac{\partial^2 [N]}{\partial r^2} + \frac{\alpha \rho_N}{[N-R]_0 k_{-1} z_0^2}\frac{\partial^2 [N]}{\partial z^2} - \frac{\rho_R \rho_N}{[N-R]_0 k_{-1}} k_1 [N][R] + [N-R] \tag{23}$$

with

$$\begin{aligned}
\frac{\alpha \rho_N}{[N-R]_0 k_{-1} r_0^2} &\approx \frac{10^{-7}10^{15}}{10^{-12}} \frac{1}{[N-R]_0 k_{-1}} = 10^{22} \frac{1}{[N-R]_0 k_{-1}} \\
\frac{\alpha \rho_N}{[N-R]_0 k_{-1} r_0^3} &\approx \frac{10^{-7}10^{15}}{10^{-18}} \frac{1}{[N-R]_0 k_{-1}} = 10^{26} \frac{1}{[N-R]_0 k_{-1}} \\
\frac{\alpha \rho_N}{[N-R]_0 k_{-1} z_0^2} &\approx \frac{10^{-7}10^{15}}{10^{-18}} \frac{1}{[N-R]_0 k_{-1}} = 10^{-26} \frac{1}{[N-R]_0 k_{-1}} \\
\frac{\rho_R \rho_N}{[N-R]_0 k_{-1}} k_1 &\approx 10^{15}10^{15} \frac{k_1}{[N-R]_0 k_{-1}} = 10^{30} \frac{k_1}{[N-R]_0 k_{-1}}
\end{aligned}$$

Fra forelesning krever han at konstantene skal være << 1. Som vel enten er skaleringen $t_0 = \frac{z_0^2}{\alpha}$ eller $t_0 = \frac{1}{\rho_R k_1}$.

Fra forelesning i termisk sa han at "Molekylene har etter en tid t diffundert til en avstand proporsjonal med $\sqrt{Dt}$ D er diffusjonskoeffisienten".

7 Perturbation Analysis

Given the scaled system of equations, we try to find an analytical approximation to the system using perturbation theory. Beginning with Equation (18), we set $\widehat{\partial [R]} = \xi_0 + \nu\xi_1 + \nu^2\xi_2 + \mathcal{O}(\nu^3)$ and insert into the equation. Notice that we have defined $\nu := \widehat{k_{-1}}$ for ease of notation.

Tror ikke dette vil fungere pga coupling: prøver singular perturbation nedenfor i stedet. Usikker på om vi bør bruke alpha eller k som "liten" koeffisient.

Let $\nu := \widehat{k_{-1}} > 0$ for ease of notation. The problems when $\nu = 0$ and $\nu \to 0$ are qualitatively different, meaning that singular perturbation might be a good way to approximate an analytical solution to the system. A 0-order approximation to the outer solution can be found by setting $\nu = 0$, giving the system

$$\frac{\partial \widehat{[N]}}{\partial \hat{t}} = \widehat{\alpha_N}\nabla^2\widehat{[N]} - \widehat{[N]}\widehat{[R]}, \tag{24}$$

$$\frac{\partial \widehat{[R]}}{\partial \hat{t}} = -\widehat{[N]}\widehat{[R]}, \tag{25}$$

$$\frac{\partial \widehat{[R-N]}}{\partial \hat{t}} = \widehat{[N]}\widehat{[R]}. \tag{26}$$

Again, we see that the two last equations lead to (Dette kan man sikkert også se direkte dersom man skalerer to-sett systemet over først the relation $\frac{\partial \widehat{[R]}}{\partial \hat{t}} + \frac{\partial \widehat{[R-N]}}{\partial \hat{t}} = 0 \implies \widehat{[R]} + \widehat{[R-N]} = \hat{C}(x)$. Igjen, dette hjelper ikke så mye her.

Prøver å la alpha være liten også −− > Det tilsvarer ingen diffusion når alpha settes til 0. Representerer dette situasjonen der reaksjonene dominerer, dvs N har allerede diffundert over kløfta i en transient periode? Inner solution gir dermed denne transiente perioden?

Let $\mu := \widehat{\alpha_N} > 0$ for ease of notation. The problems when $\mu = 0$ and $\mu \to 0$ are qualitatively different, meaning that singular perturbation might be a good way to approximate an analytical solution to the system. A 0-order approximation to the outer solution can be found by setting $\mu = 0$, giving the system

$$\frac{\partial \widehat{[N]}}{\partial \hat{t}} = -\widehat{[N]}\widehat{[R]} + \widehat{k_{-1}}\widehat{[R-N]}, \tag{27}$$

$$\frac{\partial \widehat{[R]}}{\partial \hat{t}} = -\widehat{[N]}\widehat{[R]} + \widehat{k_{-1}}\widehat{[R-N]}, \tag{28}$$

$$\frac{\partial \widehat{[R-N]}}{\partial \hat{t}} = \widehat{[N]}\widehat{[R]} - \widehat{k_{-1}}\widehat{[R-N]}. \tag{29}$$

Subtracting the second equation from the first yields the reduction

$$\frac{\partial \widehat{[N]}}{\partial \hat{t}} - \frac{\partial \widehat{[R]}}{\partial \hat{t}} = 0 \implies \widehat{[N]} - \widehat{[R]} = D(x). \tag{30}$$

In addition, we see that $\widehat{[R]} + \widehat{[R-N]} = C(x)$, meaning that the outer solution can be found directly via the pre-defined functions C and D. Next we find the inner solution. Assume the boundary layer is $[0, \delta(\mu)]$, since the diffusion happens from the pre-synaptic neuron ($(t,x) = (0,0)$) to the post-synaptic neuron ($(t,x) = (t^*, z)$). We insert $N(\frac{t}{\delta(\mu)}, \mu), R(\frac{t}{\delta(\mu)}, \mu)$ and $Z(\frac{t}{\delta(\mu)}, \mu)$ into the system of equations, representing the outer solutions of $\widehat{[N]}, \widehat{[R]}$ and $\widehat{[R-N]}$ respectively, such that the system becomes

$$\frac{1}{\delta}\frac{\partial N}{\partial \hat{t}} = \mu\nabla^2 N - NR + \widehat{k_{-1}}Z, \tag{31}$$

$$\frac{1}{\delta}\frac{\partial R}{\partial \hat{t}} = -NR + \widehat{k_{-1}}Z, \tag{32}$$

$$\frac{1}{\delta}\frac{\partial Z}{\partial \hat{t}} = NR - \widehat{k_{-1}}Z. \tag{33}$$

Next we need to choose δ such that the equations are balanced. Dette gir ikke meg så mye når vi har både tid og romlig dimensjon. Perturbasjon gir kanskje ikke mening i dette tilfellet egentlig, siden diffusjonsleddet ikke påvirker hvordan N oppfører seg i tid?

After finding the inner solution, the uniform solution is the sum of the inner and the outer solutions subtracted by the limit of the matching condition.

8 1D Implementation

Eirik: Det her blir vel faktisk follow-up nummer 1 når jeg tenker meg om. Jeg kjører på med litt argumentasjon:

The typical radius of the synaptic cleft is $r_{\text{cleft}} = 0.22\,\mu\text{m}$, whereas the typical length is $L = 15\,\text{nm} \ll r_{\text{cleft}}$. We can therefore approximate the geometry of the synaptic cleft to be a cyllinder with infinite radius, without much loss

of generality. This geometrical reduction allows us to neglect end effects along the outer perimeter of the synaptic cleft. If we also assume that the release of neurotransmitters is uniform across the whole surface of the axon terminal, and similarly that the receptors are also distributed uniformly over the surface of the dendritic spine, then we get a system that is completely uniform in r, in addition to θ as already assumed. This reduces the system to a 1D diffusion problem.

We can therefore consider a simplified geometry with only one spatial dimension z. Then, all neurotransmitters are released at $z = 0, t = 0$, and all receptors lie at the other endpoint $z = L$, L being the length of the synaptic cleft. The modelling equations become

$$\frac{\partial [N]}{\partial t} = \alpha_N \frac{\partial^2 [N]}{\partial x^2} - k_1[N][R] + k_{-1}[R-N], \tag{34}$$

$$\frac{\partial [R]}{\partial t} = -\frac{\partial [R-N]}{\partial t} = -k_1[N][R] + k_{-1}[R-N]. \tag{35}$$

I.e., we have a given initial concentration of neurotransmitters at $x = 0$, and similarly for the unbound receptors at $x = L$. No receptors are bound at $t = 0$. As no more neurotransmitters or receptors enter the synaptic cleft after $t = 0$, it is natural to assume Neumann boundary conditions at the endpoints

$$\frac{\partial [N]}{\partial x}(0,t) = \frac{\partial [N]}{\partial x}(L,t) = 0. \tag{36}$$

To solve the system of equations numerically, we introduce a equispaced grid discretization along the z-axis, $z_0 = 0, z_1, , \ldots, z_K = L$, with $\Delta z = z_{i+1} - z_i$. We also discretize the time as $t_0 = 0, t_{n+1} = t_n + \Delta t, n = 0, 1, 2 \ldots$. The discretized concentrations are written as $[N]_k^n, [R]_k^n, [R-N]_k^n$ at z_k, t_n. As (35) is an ordinary differential equation, we solve it using forward Euler's method

$$[R]_k^{n+1} = [R]_k^n + \Delta t \cdot (-k_1[N]_k^n[R]_n^k + k_{-1}[R-N]_k^n),$$
$$[R-N]_k^{n+1} = [R-N]_k^n - ([R]_k^{n+1} - [R]_k^n).$$

After finding $[R]_k^{n+1}$ and $[R-N]_k^{n+1}$ we find $[N]_k^{n+1}$ by discretizing the reaction-diffusion equation (34) using the implicit Crank-Nicholson scheme given by

$$\frac{[N]_k^{n+1} - [N]_k^n}{\Delta t} = \frac{\alpha_N}{2(\Delta z)^2}[\left([N]_{k+1}^{n+1} - 2[N]_k^{n+1} + [N]_{k-1}^{n+1}\right) \tag{37}$$

$$+ \left([N]_{k+1}^{n} - 2[N]_k^{n} + [N]_{k-1}^{n}\right)] \tag{38}$$

$$- k_1 \left(\frac{[N]_k^{n+1} + [N]_k^n}{2}\right)\left(\frac{[R]_k^{n+1} + [R]_k^n}{2}\right) \tag{39}$$

$$+ k_{-1}\left(\frac{[R-N]_k^{n+1} + [R-N]_k^n}{2}\right), \tag{40}$$

for $k = 1, \ldots, K-1$. Instead of discretizing the Neumann boundary conditions fictitious grid points, we apply it directly obtaining an unconditionally stable scheme [1]

$$\frac{\partial^2 [N]_0^n}{\partial z^2} \approx \frac{1}{b(\Delta z)^2}([N]_2^n - [N]_1^n),$$
$$\frac{\partial^2 [N]_K^n}{\partial z^2} \approx -\frac{1}{b(\Delta z)^2}([N]_K^n - [N]_{K-1}^n),$$

where $b = \frac{1}{2} + \frac{\sqrt{3}}{3}$. On matrix form the system is written

$$A^n[N]^{n+1} = B^n[N]^n + C^n, \tag{41}$$

where

$$A^n = \begin{bmatrix} (1+W_0^n) & -\frac{V}{b} & & & & \\ -V & (1+W_1^n) & -V & & & \\ & \ddots & \ddots & \ddots & & \\ & & -V & (1+W_{K-1}^n) & -V & \\ & & & -\frac{V}{b} & (1+W_K^n) \end{bmatrix},$$

$$B^n = \begin{bmatrix} (1+Z_0^n) & \frac{V}{b} & & & & \\ V & (1+Z_1^n) & V & & & \\ & \ddots & \ddots & \ddots & & \\ & & V & (1+Z_{K-1}^n) & V & \\ & & & \frac{V}{b} & (1+Z_K^n) \end{bmatrix},$$

$$b = \frac{1}{2} + \frac{\sqrt{3}}{3},$$

$$C^n = \frac{\Delta t k_{-1}}{2}([R-N]_k^{n+1} + [R-N]_k^n),$$

$$[N]^n = [[N]_0^n \ [N]_1^n \ \cdots \ [N]_K^n]^T,$$

$$V = \frac{\Delta t \alpha_N}{2(\Delta z)^2},$$

$$W_k^n = \frac{\Delta t \alpha_N}{(\Delta z)^2} + \frac{\Delta t k_1}{4}([R]_k^{n+1} + [R]_k^n), \ k = 1, \ldots, K-1$$

$$W_0^n = W_K^n = \frac{\Delta \alpha_N}{b(\Delta z)^2} + \frac{\Delta t k_1}{4}([R]_k^{n+1} + [R]_k^n),$$

$$Z_k^n = -\frac{\Delta t \alpha_N}{(\Delta z)^2} + \frac{\Delta t k_1}{4}([R]_k^{n+1} + [R]_k^n), \ k = 1, \ldots, K-1,$$

$$Z_0^n = Z_K^n = -\frac{\Delta \alpha_N}{b(\Delta z)^2} + \frac{\Delta t k_1}{4}([R]_k^{n+1} + [R]_k^n).$$

To implement an example we choose parameter values as given in the assignment description, shown in table 1. The grid is discretized into $n_G = 100$ intervals. We choose the initial conditions as in (13), i.e., $[N]_0^0 = 360, [R]_{n_G}^0 = 11$. The evolution of bound receptors is shown in figure 1. Using these initial values makes the diffusion process happen very fast, much faster than the reaction, which can be seen in figure This can be seen as an argument for a geometrical reduction of the problem, removing the z-axis completely.

Kanskje noe av dette kan brukes? https://scipy-cookbook.readthedocs.io/items/CoupledSpringMassSystem.html

9 Numerical method

Ulrik: Noen tanker. Jeg er helt med på å følge fremgangsmåten i springer-artikkelen. Om vi skal kjøre på med et sylinder-grid, så tror jeg vi må ha en god del inspirasjon (dvs. kopiere hele fremgangsmåten, inkludert triksene i endepunktene, z_0, z_L). Alternativt så lager vi en mye enklere modell i 2D (eller 1D). Da slipper vi mye knot med detaljer i den numeriske implementeringen (tror jeg ihvertfall).

Then

$$\begin{aligned} \frac{\partial [N]}{\partial t} &= \alpha \nabla [N] - k_1 [N][R] + k_{-1}[R-N] \\ &= \frac{\alpha}{r}\frac{\partial}{\partial r}\left(r\frac{\partial [N]}{\partial r}\right) + \frac{\alpha}{r^2}\frac{\partial^2 [N]}{\partial \theta^2} + \alpha \frac{\partial^2 [N]}{\partial z^2} - k_1 [N][R] + k_{-1}[R-N] \\ &= \frac{\alpha}{r}\frac{\partial}{\partial r}\left(r\frac{\partial [N]}{\partial r}\right) + \alpha \frac{\partial^2 [N]}{\partial z^2} - k_1 [N][R] + k_{-1}[R-N] \end{aligned}$$

Assume $[N]$ is independent of θ. The concentration of N is the the same along a circle with radius r from the source. Let $[N]_{i,j}^n$ be an approximation to $[N](r_i, z_j, n\Delta t)$.
n = time

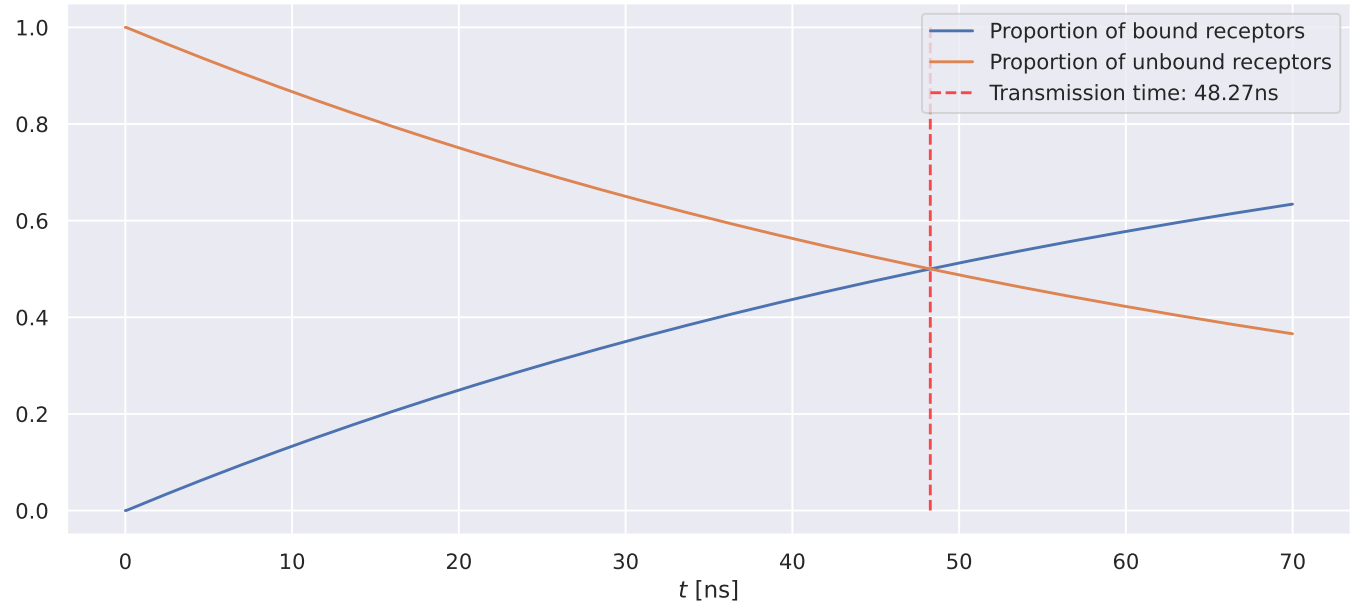

Figure 1: Evolution of bound receptors at the membrane using a one dimensional model. The modelling is done through a finite difference scheme with forward differencing in the time dimension, and Crank-Nicolson in the spatial dimension. Supposing the transmission happens when one half of the receptors are bound, we find the time to be around 50 nanoseconds.

i, j = position

$$
\begin{aligned}
\frac{[N]_{i,j}^{n+1} - [N]_{i,j}^{n}}{\Delta t} = & \frac{\alpha}{2r_i(\Delta r)^2}\left[r_{i+\frac{1}{2}}\left([N]_{i+1,j}^{n+1} - [N]_{i,j}^{n+1}\right) - r_{i-\frac{1}{2}}\left([N]_{i,j}^{n+1} - [N]_{i-1,j}^{n+1}\right)\right] \\
& + \frac{\alpha}{2r_i(\Delta r)^2}\left[r_{i+\frac{1}{2}}\left([N]_{i+1,j}^{n} - [N]_{i,j}^{n}\right) - r_{i-\frac{1}{2}}\left([N]_{i,j}^{n} - [N]_{i-1,j}^{n}\right)\right] \\
& + \frac{\alpha}{2(\Delta z)^2}\left[[N]_{i,j+1}^{n+1} - 2[N]_{i,j}^{n+1} + [N]_{i,j-1}^{n+1}\right] \\
& + \frac{\alpha}{2(\Delta z)^2}\left[[N]_{i,j+1}^{n} - 2[N]_{i,j}^{n} + [N]_{i,j-1}^{n}\right] \\
& - k_1\left(\frac{[N]_{i,j}^{n+1} + [N]_{i,j}^{n}}{2}\right)\left(\frac{[R]_{i,j}^{n+1} + [R]_{i,j}^{n}}{2}\right) \\
& + k_{-1}\left(\frac{[R-N]_{i,j}^{n+1} + [R-N]_{i,j}^{n}}{2}\right)
\end{aligned}
$$

Boundary conditions

$$
\begin{cases}
[N]_{i,j,k}^{0} = \text{Uniform distribution along surface of pre-synaptic neuron} \\
\vdots
\end{cases}
$$

Assume $[N]$ is independent of θ. The concentration of N is the the same along a circle with radius r from the source. Eirik: Ja jeg tenkte også denne antagelsen var fornuftig. Da kan man vel droppe indeks j i videre utledning? Alex: Han antok at "transition function" ved utledning av diffusion i slidsene var isotrop, så jeg tenker at dette høres fornuftig ut. Ulrik: På teams sist uke ble det diskutert litt initial values og boundary conditions. Oppsummert så kunne man gjøre litt som man ville, uniforme startverdier, point source, alt var "yes sure, you can do that!". Samme med grenseverdier, om man skulle ha Dirichlet eller Neumann. Neumann gir mest mening, men om man skulle modellert videre med "lekkasje" til andre neuroner kunne man prøve seg fram med Dirichlet.

Let δ_z^2 be the operator defined by $\delta_z^2[N]_{i,k}^n = [N]_{i,k+1}^n - 2[N]_{i,k}^n + [N]_{i,k-1}^n$. Similarly let δ_r and δ_r be defined as $\delta_r[N]_{i,k}^n = [N]_{i+1,k}^n - [N]_{i,k}^n$ and $\delta_{-r}[N]_{i,k}^n = [N]_{i,k}^n - [N]_{i-1,k}^n$ respectively.

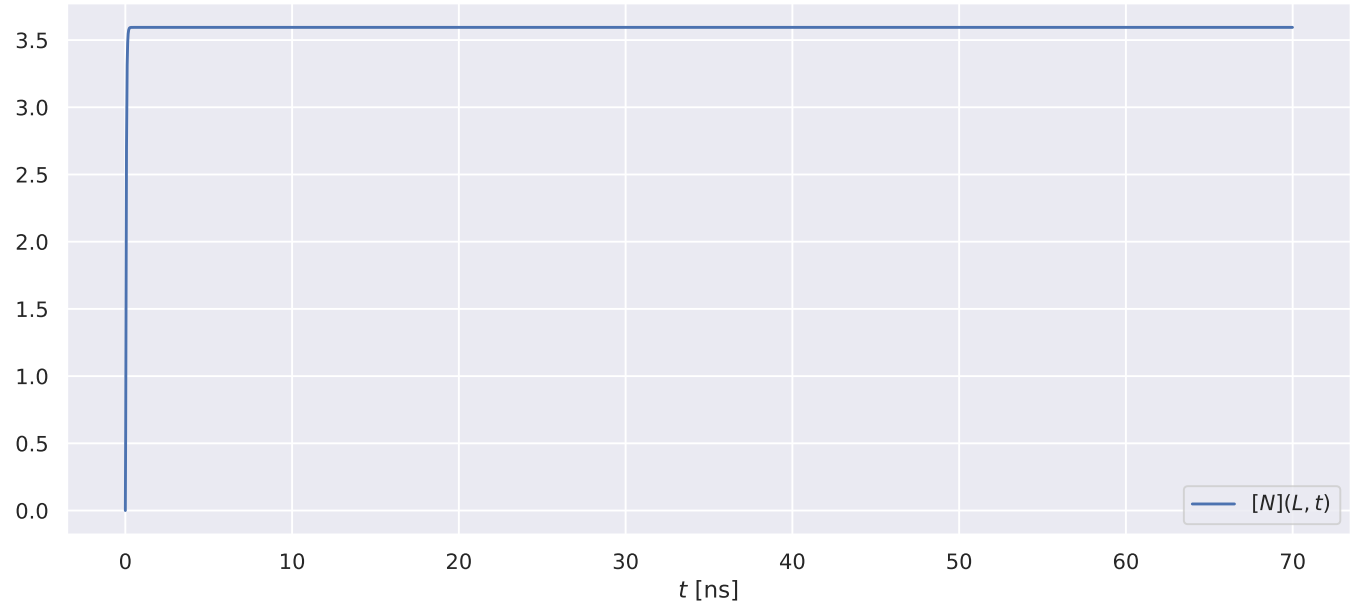

Figure 2: Concentration of neurotransmitters at the endpoint. As the concentration reaches a constant value quickly, the diffusion process is much faster than the binding of receptors.

$$\left[1 - \frac{\Delta t\alpha}{2r_i(\Delta r)^2} r_{i+\frac{1}{2}}\delta_r + \frac{\Delta t\alpha}{2r_i(\Delta r)^2} r_{i-\frac{1}{2}}\delta_{-r} - \frac{\Delta t\alpha}{2(\Delta z)^2}\delta_z^2 - \frac{\Delta t k_1}{2}\left(\frac{[R]_{i,j}^{n+1} + [R]_{i,j}^{n}}{2}\right)\right][N]_{i,j}^{n+1}$$
$$= \left[1 + \frac{\Delta t\alpha}{2r_i(\Delta r)^2} r_{i+\frac{1}{2}}\delta_r - \frac{\Delta t\alpha}{2r_i(\Delta r)^2} r_{i-\frac{1}{2}}\delta_{-r} + \frac{\Delta t\alpha}{2(\Delta z)^2}\delta_z^2 - \frac{\Delta t k_1}{2}\left(\frac{[R]_{i,j}^{n+1} + [R]_{i,j}^{n}}{2}\right)\right][N]_{i,j}^{n} + \Delta t k_{-1}\left(\frac{[R-N]_{i,j}^{n+1} + [R-N]_{i,j}^{n}}{2}\right)$$

9.1 RK to solve the differential equations for the chemical reactions

Kan bruke RK for å finne $[R]_{i,j}^{n}$, $[R]_{i,j}^{n+1}$, $[N-R]_{i,j}^{n}$ og $[N-R]_{i,j}^{n+1}$

$$\frac{\partial[N]}{\partial t} = -k_1[N][R] + k_{-1}[N-R]$$
$$\frac{\partial[R]}{\partial t} = -k_1[N][R] + k_{-1}[N-R]$$
$$\frac{\partial[N-R]}{\partial t} = k_1[N][R] - k_{-1}[N-R]$$

9.2 Procedure

1. Initiate a value of $[N]$ at time step $n+1$ to solve the chemical reaction differential equations.
2. Obtain values of $[N]$, $[R]$ and $[N-R]$ at time step $n+1$ by using RK method
3. Insert the values for $[N]$, $[R]$ and $[N-R]$ into the big equation

Eirik: Ok så tanken er en "alternerende" løser, som bytter mellom å finne bidraget fra kjemisk reaksjon i neste tidssteg ved å bruke konsentrasjonene for nåværende tiddsteg i en RK, og så bruker dette bidraget i crank-nicholson for å finne konsentrasjonene ved neste tidssteg? Det gir vel forsåvidt mening, men jeg har lite peiling på stabiliteten på en sånn approach. Karen: Ja stemme, det va det eg mente. Tror det e sånn de har gjort det i denne: https://link.springer.com/content/pdf/10.1007/s10827-010-0289-5.pdf. Der har de et teorem som sie "The finite difference scheme, Eqs. (27a)– (27c), with the initial and boundary conditions, Eqs. (14a)–(16b), is unconditionally stable with respect to the initial condition and source term.". men hvis me har litt anderledes ligninger så må me jo sjekke

om det gjelde for oss og. Og ja vet ikkje om dette e beste måten/funke ennå. Ulrik: Dag foreslår òg Crank-Nicholson i forumet pga. stabilitet.
Karen: Skulle me starta med å droppe z-koordinaten? liksom $\varepsilon \to 0$ eller blir det feil?

Eirik: Tror vi må beholde z-koordinaten, for ellers blir det vel som å si at bredden på den synaptiske kløfta er 0? (som kanskje er mer likt første follow-up oppgave?) Jeg ser forsåvidt ikke helt hvordan man kan ta høyde for $\epsilon \to 0$ tho. Den eneste ideen jeg hadde var å la k_1 og k_{-1} være avhengig av z, type

$$\hat{k}_1(i,j,k) = \begin{cases} k_1 & k = 0 \\ 0 & k \geq 1 \end{cases}$$

og tilsvarende for k_{-1}. Da får vi modellert at reaksjonen mellom R og N kun skjer inni Ω_ϵ, samt at hvis man lar antallet grid points i z-retning gå mot uendelig, så vil det bli som om $\epsilon \to 0$. Dette gjør jo k-ene ganske lite glatte da, så om det fucker med stabiliteten, det vet jeg ikke. Karen: enig!

10 Kode som kanskje kan hjelpe

Alex: har ikke gått gjennom denne koden foreløpig, men kanskje den kan hjelpe. Fant fra numdiff.

```
def calc_sol(x, t, order, theta, plot = False):
    """
    order = 1: Use first oder disc. on BC.
    order = 2: Use second order disc. on BC.
    theta = 1: Backward Euler.
    theta = 1/2: Crank Nicolson (Trapezoidal Rule).
    """
    M = len(x)-1
    N = len(t)-1

    # Construct Q.
    data = np.array([np.full(M+1, 1), np.full(M+1, -2), np.full(M+1, 1)])
    diags = np.array([-1, 0, 1])
    Q = spdiags(data, diags, M+1, M+1,format='lil')
    if order == 1:
        Q[0,:3] = [-1,0,1]
        Q[-1,-3:] = [1,0,-1]
    elif order == 2:
        Q[0, 1] = Q[-1, -2] =  2
    Q = Q.tocsr()

    sol = np.zeros((N+1,M+1))
    sol[0,:] = initial(x)

    k = t[1]-t[0]
    h = x[1]-x[0]
    r = k/h**2

    lhs = identity(M+1) - theta*r*Q
    b = identity(M+1) + (1-theta)*r*Q
    for n in range(N):
        rhs = b @ sol[n,:]
        sol[n+1,:] = spsolve(lhs,rhs)

    return sol
```

11 Muligens nyttige kilder

- https://en.wikipedia.org/wiki/Reaction%E2%80%93diffusion_system

- https://www-m6.ma.tum.de/~kuttler/script_reaktdiff.pdf
- https://www.uni-muenster.de/imperia/md/content/physik_tp/lectures/ws2016-2017/num_methods_i/rd.pdf
- https://kluedo.ub.uni-kl.de/frontdoor/deliver/index/docId/5960/file/mastersthesis_blandfort.pdf
- https://iopscience.iop.org/article/10.1088/0034-4885/64/7/202/pdf
- https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1282074/pdf/biophysj00061-0065.pdf
- https://pdf.sciencedirectassets.com/271059/1-s2.0-S0166223600X00252/1-s2.0-S0166223696200505/main.pdf?X (crosstalk etc)

Dette ligner veldig på oppgaven vår, men har ikke tilgang: https://online.ucpress.edu/abt/article-abstract/81/6/435/
Denne ser ganske lik ut som oppgaven vår: https://isn.ucsd.edu/courses/beng221/problems/2013/project-11-Modellir
Ser lovende ut: https://link.springer.com/content/pdf/10.1007/s10827-010-0289-5.pdf
Dokumentasjon til MRST, som han fyren bruker i matlab kode sin https://www-sintef-no.translate.goog/contentassets/
Kode fra fyren bruker løsere fra MRST hos Sintef, veldig unyttig spør du meg.

klasse **NonLinearSolver** *(varargin)*

Generalisert Newton-lignende ikke-lineær løser

Synopsis:

```
solver = NonLinearSolver()

solver = NonLinearSolver('maxIterations', 5)
```

Beskrivelse:

NonLinearSolver-klassen er en generell ikke-lineær løser basert på Newtons metode. Den er i stand til å velge tidstrinn og kutte basert på konvergenshastigheter og kan utvides via underklassing eller modulære lineære løsere og tidstrinnklasser.

Konvergens håndteres av PhysicalModel-klassen. NonLinearSolver reagerer ganske enkelt basert på hva modellen rapporterer når det gjelder konvergens for å sikre et visst nivå av innkapsling.

Parametere: Ingen.–

Returnerer: En NonLinearSolver-klasseforekomst klar til bruk.

Se også

`simulateScheduleAD`, `LinearSolverAD`, `SimpleTimeStepSelector`

total water content of brain tissue gray matter is about 85% (Katzman and Pappius, 1973), i.e., $\alpha + \beta = 0.85$. Assuming $\alpha = 0.2$ (Rice and Nicholson 1991), then $\beta = 0.65$ and the volume fraction of the solids, $u_s/(u_o + u_i + u_s)$, is 0.15.

Equation for behavior of DA in extracellular space

There are many ways to derive the partial differential equation describing the relation between diffusion and uptake. Here a simple approach is taken based on the specific spherical geometry appropriate to this problem.

A spherical iontophoresis electrode of radius r_0 (cm) emits a flux of DA, J_0 (μmol cm^{-2} s^{-1}). The real iontophoresis electrode has a radius of 1–2 μm, and the tip is a disk, because it is the cut end of a glass capillary tube. Such a boundary condition introduces unnecessary complexity without adding anything to the problem, because the detailed structure of the electrode tip plays a negligible role in the solution when measurements are made a few micrometers away, as they always are in practice. On the other hand, the point source used satisfactorily in analytical solutions to linear iontophoresis problems (e.g., Nicholson and Phillips, 1981) is inappropriate for the numerical solution to be developed here.

Consider a spherical shell at a distance r from the center of the emitting electrode (Fig. 1). The thickness of the shell is δr, the areas of the inner and outer surfaces of the shell are $A(r)$, and $A(r + \delta r)$, and the fluxes on the inner and outer surfaces of the shell are $J(r)$ and $J(r + \delta r)$, respectively. Then, performing a mass balance on the flux through the volume element of the spherical shell:

$$A(r)\delta r \frac{\partial c}{\partial t} = A(r)J(r) - A(r + \delta r)J(r + \delta r) \qquad (3)$$

approximating $A(r + \delta r)$ and $J(r + \delta r)$ with Taylor expansions and neglecting terms in δr^2 and higher:

$$A(r + \delta r) \approx A(r) + \frac{\partial A}{\partial r}\delta r; \quad J(r + \delta r) \approx J(r) + \frac{\partial J}{\partial r}\delta r$$

so that Eq. 3 becomes (writing A and J for $A(r)$ and $J(r)$, respectively, and again neglecting terms in δr^2)

$$A \frac{\partial c}{\partial t} = -\left(A \frac{\partial J}{\partial r} + J \frac{\partial A}{\partial r}\right) = -\frac{\partial (AJ)}{\partial r}. \qquad (4)$$

The required relation between flux and concentration can be described by Fick's first law recast appropriately for a porous medium. The justification for the form used has been the subject of discussion (e.g., Aris, 1975; Nicholson and Phillips, 1981), but in essence it is necessary to recognize that the flux is driven by the extracellular concentration gradient in the interstices of the extracellular space, $\delta c_e^o/\delta r$. It is assumed that within the narrow clefts between cells, diffusion is governed by the free diffusion coefficient D (cm^2 s^{-1}). The effect of the obstructed extracellular space is accounted for by a modified diffusion coefficient, $\alpha D/\lambda^2$, where λ (non-

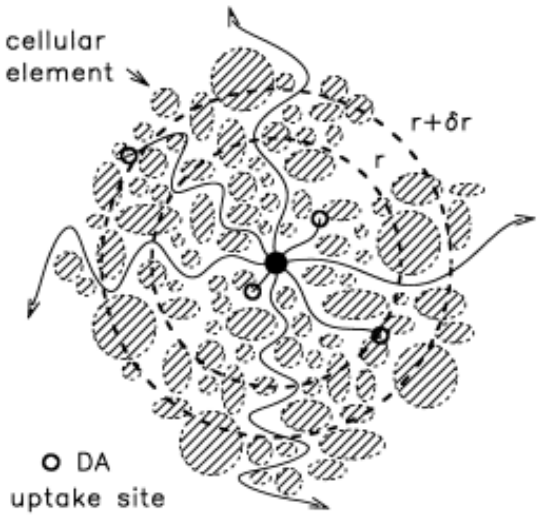

FIGURE 1 Some concepts used in this paper. The brain extracellular microenvironment consists of the spaces between cellular elements (cell bodies, fibers, dendrites, glial processes). The elements are depicted here by the broken ellipses. A microelectrode, assumed to be a small sphere and indicated by the central black circle, releases DA by iontophoresis. The DA is constrained both by the reduced volume fraction (α) of the extracellular space relative to the whole volume and the tortuosity (λ). The tortuosity is shown here in cartoon form as the wiggling lines emanating from the source electrode. The wiggles are caused by the hindrance of the diffusing particles by the cellular elements. Diffusing molecules are captured by uptake sites (*thick open circles*) located primarily in presynaptic terminals. To develop a mass-balance of the macroscopic behavior of the diffusing DA molecules, a thin shell of thickness δr is inscribed in the tissue at a distance r from the center of the releasing electrode.

dimensional) is the tortuosity. Tortuosity is a measure of the extent to which diffusing particles are hindered by the presence of obstructions, in the form of cells or their extensions (see Nicholson and Phillips (1981) for more detail). It is also frequently convenient to define an apparent diffusion coefficient $D^* = D/\lambda^2$. Then

$$J = -\alpha D^* \frac{\partial c_e^o}{\partial r}, \quad \text{hence} \quad \frac{\partial J}{\partial r} = -\alpha D^* \frac{\partial^2 c_e^o}{\partial r^2}. \qquad (5)$$

Combining Eqs. 4 and 5 and noting that $A = 4\pi r^2$ and $\partial A/\partial r = 8\pi r$

$$\frac{\partial c}{\partial t} = \alpha D^* \left(\frac{\partial^2 c_e^o}{\partial r^2} + \frac{2}{r}\frac{\partial c_e^o}{\partial r}\right). \qquad (6)$$

It remains to define the time derivative on the left-hand side of Eq. 6. From Eqs. 1 and 2, this can be written:

$$\frac{\partial c}{\partial t} = \alpha \frac{\partial c_o^o}{\partial t} + \frac{\partial c_i}{\partial t} \qquad (7a)$$

$$\text{or} \quad \frac{\partial c}{\partial t} = \alpha \frac{\partial c_o^o}{\partial t} + \beta \frac{\partial c_i^i}{\partial t}. \qquad (7b)$$

12 Model

A possible model for the synaptic neurotransmission, i.e. the sequence that covers the motion and activity of the neurotransmitters and receptors in the intercellular space, is based on a *reaction-diffusion system*. It is assumed that the neurotransmitters "move" via two different processes. First, they diffuse across the synaptic cleft, following the diffusion equation

$$\mathbf{N}_t = k\nabla^2\mathbf{N}, \tag{42}$$

where k is a diffusion constant and $\mathbf{N}(\mathbf{x}, t)$ is a vector function describing the number of neurotransmitters N at position $\mathbf{x}$ at time t. Second, the binding process between neurotransmitters and receptors is modeled as a reversible chemical reaction

$$\mathrm{R} + \mathrm{N} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \mathrm{R{-}N}, \tag{43}$$

where R represents receptors on the post-synaptic neuron, N the neurotransmitters emitted from the pre-synaptic neuron, k_1 a rate (probability) of binding of neurotransmitters and k_{-1} a rate (probability) that a bound receptor releases a neurotransmitter. This chemical reaction can be modeled by the equations

$$\frac{\mathrm{d}[N]}{\mathrm{d}t} = -k_1[N][R] + k_{-1}[R-N], \tag{44}$$

$$\frac{\mathrm{d}[R]}{\mathrm{d}t} = -k_1[N][R] + k_{-1}[R-N], \tag{45}$$

where $[\cdot]$ represents the concentration of a substance. In total, the reaction diffusion process takes the form

$$\frac{\mathrm{d}\mathbf{N}}{\mathrm{d}t} = k\nabla^2\mathbf{N} - k_1[N][R] + k_{-1}[R-N]. \tag{46}$$

DIMENSJONER?

Define the vector $\mathbf{Y} = \begin{pmatrix} N & R \end{pmatrix}^T$, such that the equation may be written as

$$\frac{\mathrm{d}\mathbf{Y}}{\mathrm{d}t} = D\nabla^2\mathbf{Y} - K_1\mathbf{Y} + K_{-1}\mathbf{Y} \tag{47}$$

$$= \begin{pmatrix} D_N & 0 \\ 0 & D_R \end{pmatrix}\nabla^2\mathbf{Y} - k_1\begin{pmatrix} 1 & 1 \\ 1 & 1 \end{pmatrix}\mathbf{Y} + k_{-1}\begin{pmatrix} 1 & 1 \\ 1 & 1 \end{pmatrix}\mathbf{Y}, \text{ FEIL.} \tag{48}$$

is a two-component reaction diffusion system.

Using the "General form of reaction rate equation" the chemical reaction can instead be modeled by the equations

$$K = -k_1[N][R] + k_{-1}[R-N], \tag{49}$$

$$\frac{\mathrm{d}[R]}{\mathrm{d}t} = K, \text{ Left side} \tag{50}$$

$$\frac{\mathrm{d}[N]}{\mathrm{d}t} = K, \text{ Left side} \tag{51}$$

$$\frac{\mathrm{d}[R-N]}{\mathrm{d}t} = -K, \text{ Right side} \tag{52}$$

$$\tag{53}$$

Perhaps a more correct reaction diffusion equation for the neurotransmitters is

$$\frac{\mathrm{d}[N]}{\mathrm{d}t} = \alpha_N\nabla^2[N] - k_1[N][R] + k_{-1}[R-N], \tag{54}$$

when in $\Omega(\epsilon)$. Similarly, the reaction diffusion equation for the receptors when in $\Omega(\epsilon)$ is Jeg tror ikke det er diffusjon av $[R]$, da vil ligningene være gyldige i hele Ω, ikke bare i Ω_ϵ, siden $[R] = [R-N] = 0$ utenfor Ω_ϵ.

$$\frac{\mathrm{d}[R]}{\mathrm{d}t} = \alpha_R\nabla^2[R] - k_1[N][R] + k_{-1}[R-N], \tag{55}$$

while the reaction diffusion equation for the "bounded chemical" is

$$\frac{\mathrm{d}[R-N]}{\mathrm{d}t} = k_1[N][R] - k_{-1}[R-N]. \tag{56}$$

Thus we have three equations in $\Omega(\epsilon)$. When in the domain from the pre-synaptic neuron to the beginning of $\Omega(\epsilon)$, there only exists neurotransmitters, meaning that we are looking at a simple diffusion equation of the form

$$\frac{\mathrm{d}[N]}{\mathrm{d}t} = \alpha_N \nabla^2[N], \tag{57}$$

assuming that α_N is constant throughout the synaptic cleft Er dette en ok assumption? Virker litt vel forenklende kanskje, men vet ikke om den er nødvendig engang. De har hvertfall gjort det i det ene prosjektet som er linket nederst (Modeling Diffusion Process of Neurotransmitter Across Synapse) Denote by c_N, c_R and c_{R-N} the concentrations of N, R and $R-N$ respectively.

Let the synaptic cleft be denoted by Ω. In order to be able to use these equations we will define a volumetric domain $\Omega(\epsilon)$ where the receptors are detached from the membranes. This area is defined by the thickness ϵ. Inside this domain, the equations can correctly be used. Then, $\epsilon \longrightarrow 0$ will give the modeling equations we are looking for. Define $c(t,x)$, $[c(t,x)] = \mathrm{mol\,m^{-3}}$ as the concentration of neurotransmitters in the synaptic cleft (Ω). In addition, define a pseudo-concentration of free receptors in $\Omega(\epsilon)$, $P(t,x) \in (0,1)$. P thus represents the fraction of receptors that are free at a position x on the post-synaptic neuron, when $\epsilon \longrightarrow 0$. Then the equation becomes

$$\frac{\mathrm{d}c}{\mathrm{d}t} = \alpha_N \nabla^2 c - k_1 c[R] + k_{-1}[R]c^{-1}, \tag{58}$$

which is our modeling equation Need to remove the $[R]$ using P somehow. I think this will depend on the geometry chosen for the synaptic cleft. Read what is written in continuation.

13 Three-dimensional Geometry

In our first model, we assume that the synaptic cleft is shaped like a cube. In continuation, in order to make this more realistic, we could model it as a cylinder instead. Let ρ_R represent the density of receptors on the membrane. We assume that ρ_R is constant, $\rho_R = 1000\,\mathrm{\mu\,m^{-2}}$, according to the values shown in the project description. Defining the synaptic cleft as a cube, means that the pre- and post-synaptic clefts are cubes as well. Thus, let $P(t,x) = \rho_R \cdot A\epsilon$, where A is the area of the surface on the post-synaptic cleft and ϵ is the height of $\Omega(\epsilon)$. Thus, the equation is

$$\frac{\mathrm{d}c}{\mathrm{d}t} = \alpha_N \nabla^2 c - k_1 c\rho\epsilon A + k_{-1}\rho\epsilon A c^{-1}, \tag{59}$$

where A is the cross-sectional area of the post-synaptic neuron. Får ikke dimensjonene til å stemme helt. Når $\epsilon \longrightarrow 0$ får vi kun en diffusjonsligning, så noe mangler åpenbart.

Kan det tenkes at man har to ulike regimer: synaptic cleft Ω hvor $[R] = 0$, og post-synaptic cleft Ω_ϵ hvor $[R] > 0$. Deretter krever man at $[N]$ er kontinuerlig i overgangen, og ender opp med ligningene våre. Til slutt lar man ϵ gå til null.

Syns dette ↑ høres fornuftig ut. Da får man altså kun diffusjon av [N] utenfor Ω_ϵ, mens innenfor vil [N] påvirkes av både diffusjon og reaksjon med reseptorene. Men hva med [R] innenfor Ω_ϵ? Reseptorene står vel fast på cellemembranen, og vil derfor ikke diffusere? Men i slidesene er vel hele poenget med innføringen av den "pseudo-konsentrasjonen" å også modellere [R] med diffusjon?

Jeg skjønner det som at $[R]$ er pseudo-konsentrasjonen. Vi modellerer opptaket av neurotransmittere av reseptorer som en kjemisk reaksjon mellom to konsentrasjoner (noe det ikke faktisk er), men da trenger vi en "konsentrasjon" av reseptorene. Om $\epsilon \to 0$ er noe som vi kun tenker oss skjer for at modellen skal ligne virkeligheten, eller om vi faktisk skal ta en grenseverdi i utledningeng, er jeg usikker på. I artiklene som nevnes under bryr de seg ikke så mye om dette, og bare kjører på med $[R]$. Jeg (Ulrik) tror de endelige modelleringsligningene er (4), (5) og (6).

(Eirik) Enig, bortsett fra at [R] vel ikke diffuserer. Også (57) i tillegg da, sammen med [R]=0 og [R-N]=0, for å modellere konsentrasjonene utenfor Ω_ϵ.

Noen flere tanker. Jeg fikk snakket med Xavier igår. Han sa at vi ikke skal trenge å definere geometrien for å utlede ligningene. Vi må anta konstant mengde reseptorer, ikke konstant konsentrasjon i Ω_ϵ. Jeg tenker at enten så holder det å si at $P_{\Omega_\epsilon}(x,t) \to_{\epsilon\to 0} P_\Gamma(x,t)$, eller så må vi utlede det tilsvarende slide 8-9 (Chemical reactions) med vår definerte pseudo-konsentrasjon (om det gir mening). Tenker å Blir ikke det bare det samme som "standard rate equation" da? Jeg skjønner heller ikke hvordan vi kan anta konstant mengde reseptorer i Ω_ϵ og klare å relatere dette til konsentrasjonen uten å definere geometrien først. Skal vi da komme fram til noen ligninger for

mengen stoff i stedet for konsentrasjon? I artikkelen her bruker de sylinderkoordinater til å lage en reaction diffusion eqn.https://link.springer.com/content/pdf/10.1007/s10827-010-0289-5.pdf

If we discard terms of order 3 or higher, and assume that the reaction between the receptors and neurotransmitters only take place when $z = 0$, so that $\delta_z k_1 = k_1$ and $\delta_z k_{-1} = k_{-1}$ (dette er noe sloppy notasjon, bør kanksje fikses), we get

$$\left[1 - \frac{\Delta t\alpha}{2r_i(\Delta r)^2} r_{i+\frac{1}{2}}\delta_r + \frac{\Delta t\alpha}{2r_i(\Delta r)^2} r_{i-\frac{1}{2}}\delta_{-r} - \frac{\Delta t k_1}{2}\left(\frac{[R]_{i,j}^{n+1} + [R]_{i,j}^{n}}{2}\right)\right]\left[1 - \frac{\Delta t\alpha}{2(\Delta z)^2}\delta_z^2\right][N]_{i,j}^{n+1}$$
$$= \left[1 + \frac{\Delta t\alpha}{2r_i(\Delta r)^2} r_{i+\frac{1}{2}}\delta_r - \frac{\Delta t\alpha}{2r_i(\Delta r)^2} r_{i-\frac{1}{2}}\delta_{-r} - \frac{\Delta t k_1}{2}\left(\frac{[R]_{i,j}^{n+1} + [R]_{i,j}^{n}}{2}\right) + \Delta t k_{-1}\left(\frac{[R-N]_{i,j}^{n+1} + [R-N]_{i,j}^{n}}{2}\right)\right]\left[1 + \frac{\Delta t\alpha}{2(\Delta z)^2}\delta_z^2\right][$$

we can then split this scheme into a two-step process, by introducing an intermediate $[N]_{i,k}^{*}$. This gives

$$\left[1 - \frac{\Delta t\alpha}{2r_i(\Delta r)^2} r_{i+\frac{1}{2}}\delta_r + \frac{\Delta t\alpha}{2r_i(\Delta r)^2} r_{i-\frac{1}{2}}\delta_{-r} - \frac{\Delta t k_1}{2}\left(\frac{[R]_{i,j}^{n+1} + [R]_{i,j}^{n}}{2}\right)\right][N]_{i,j}^{*} = \left[1 + \frac{\Delta t\alpha}{2(\Delta z)^2}\delta_z^2\right][N]_{i,j}^{n}$$

$$\left[1 - \frac{\Delta t\alpha}{2(\Delta z)^2}\delta_z^2\right][N]_{i,j}^{n+1}$$
$$= \left[1 + \frac{\Delta t\alpha}{2r_i(\Delta r)^2} r_{i+\frac{1}{2}}\delta_r - \frac{\Delta t\alpha}{2r_i(\Delta r)^2} r_{i-\frac{1}{2}}\delta_{-r} - \frac{\Delta t k_1}{2}\left(\frac{[R]_{i,j}^{n+1} + [R]_{i,j}^{n}}{2}\right) + \Delta t k_{-1}\left(\frac{[R-N]_{i,j}^{n+1} + [R-N]_{i,j}^{n}}{2}\right)\right][N]_{i,j}^{*}$$

$$\frac{dN*}{dx*} = \frac{N_0 dN}{x_0 dx} \tag{60}$$

$$x* = x_0 x, \qquad N^*(x*) = N^*(\frac{x}{x_0}) = N_0 N \tag{61}$$

$$dx^* = x_0 dx, \qquad dN^* = N_0 dN \tag{62}$$

$$\frac{d}{dx^*}\left(\frac{N_0 dN}{x_0 dx}\right) = \frac{d}{dx^*}\frac{dN*}{dx*} = \frac{d^2 N*}{d(x^*)^2} \tag{63}$$

References

[1] Abdul Khaliq et al. "A new 3D mass diffusion–reaction model in the neuromuscular junction". In: *Journal of Computational Neuroscience* 30.3 (2010), pp. 729–745. DOI: 10.1007/s10827-010-0289-5.