Synaptic Transmission

Erfan Baradarantohidi

February 25, 2024

1 Introduction

Communication of neurons with each other, neurons with muscles or with glands at synapses, and the transfer of a signal from the axon terminal of one neuron to the next neuron is called *synaptic transmission* [1]. While there are two major types of synapses, chemical and electrical, here we focus on modeling the dynamics of chemical synapses. release of neurotransmitter into **synaptic cleft** has following general mechanism:

- Arrival of the action potential at the axon terminal
- Depolarization of the terminal membrane
- Opening of the voltage-gated Ca^{2+} channels
- Fusion of **vesicles** containing neurotransmitter with the membrane at the synapse
- Release of the transmitter by exocytosis into the synaptic cleft

Figure 1 shows a schematic of this process. In this project, a dynamical system of equations that models this process is analyzed and simulated.

This project is defined as the final project of the seminar, *Current Topics in Computational Neuroscience* at TU Berlin and Prof. Dr. Sprekeler's supervision.

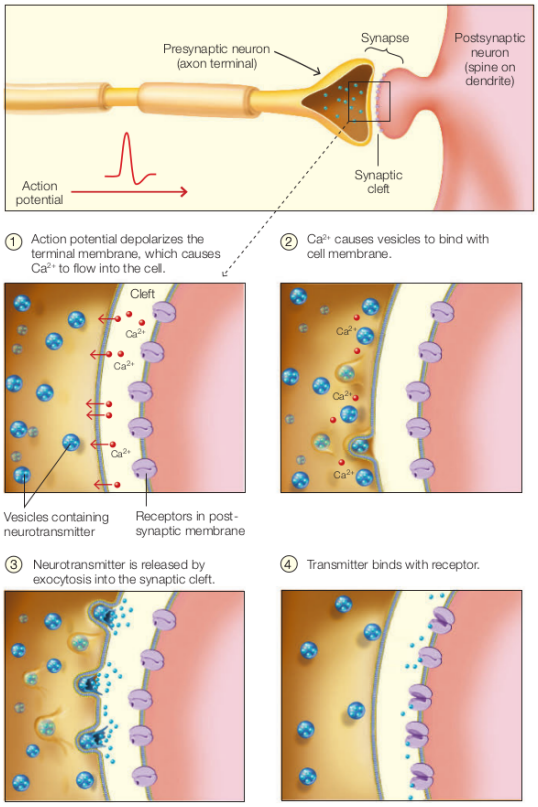

Figure 1: Neurotransmitter release at the synapse, into the synaptic cleft

2 Mathematical Modeling

A leaky integrator is used to model the influx of the Ca^{2+}, $\dot{\mathbf{C}}(t)$, due to the depolarization of the terminal membrane, caused by the input action potential. We can assume the arrival of the scaled action potential $\mathbf{R_1 I}(t)$ is the input to the system that causes the influx. R_1 is the Ca^{2+} influx rate. In the absence of input, the system decays to e^{-1} of initial concentration differences (if $\neq 0$), in time constant τ_c. Equation 1 describes that:

$$\tau_c \dot{C}(t) + C(t) = R_1 I(t) \tag{1}$$

The amount of increase in Ca^{2+} concentration in response to a single spike is controlled by R_1/τ_c.

As discussed earlier, the release of the transmitters depends on (1) the presence of the spikes which leads to (2) the inflow of calcium ions into the cell, which leads to (3) the binding of the vesicles to the terminal. Such a process can be modeled as a simple multiplication of those factors, which can be interpreted as three **necessary conditions** for the release, in Equation 2, the released neurotransmitter, $\mathbf{N}(t)$ at time t is proportional to available vesicles, $\mathbf{V}(t)$, the difference of Ca^{2+} intracellular concentration from resting condition baseline, $\mathbf{C}(t)$ and the arrival of action potential spike train, $\mathbf{I}(t)$, with the constant, α.

$$N(t) = \alpha V(t) C(t) I(t) \tag{2}$$

The last process is the fusion of vesicles into the membrane and the release of neurotransmitters and providing new vesicles. Assuming that initially there are V_0 vesicles available in the cell body, vesicles are used, as the neurotransmitters are released. When the cell is not releasing, vesicles are produced to reach the initial number. A time constant τ_v, controls how fast vesicles are reproduced. and the consumed vesicles per release is controlled by R_2/τ_v:

$$\tau_v \dot{V}(t) + V(t) - V_0 = -R_2 N(t) \tag{3}$$

3 Parameters

In this section, biologically plausible parameters from the literature are discussed.

Cells at rest have a Ca^{2+} concentration of 100 nM (nano-molar concentration) but are activated when this level rises to roughly 1000 nM [2], So it is plausible in Equation 1 to assume $R_1/\tau_c \approx 9 \times 10^5$ nM. The time constant τ_c for the decay of calcium concentration is dependent on various cell types and the location in the cell [3]. Figure 2 shows the response of voltage-gated calcium channels with these parameters.

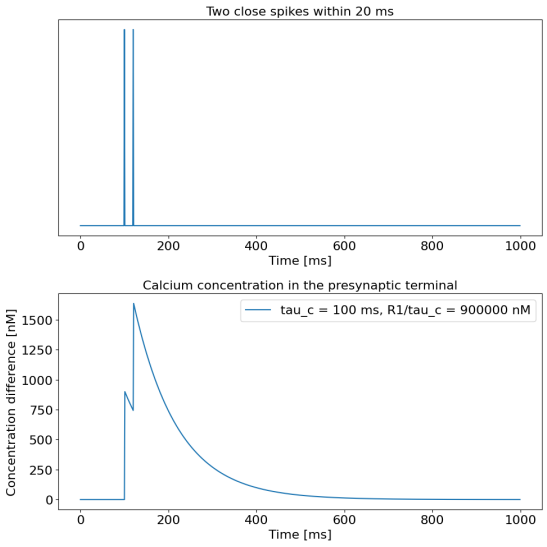

Figure 2: Changes in the calcium concentration in response to two consecutive spikes

It is normally thought that, following release, neurotransmitters in the cleft reach a peak concentration that is in the millimolar ($10^6 nM$) range and decay rapidly[4], although, in the scope of this report, we are not concerned with the neurotransmitter concentration in the cleft, we can use this fact to adjust the parameter α in Equation 2. It is stated that around 130 vesicles can be released per synaptic bottom[5], we can conclude that after an incoming spike and exited $Ca2+$ concentration of 1000 nM and availability of 130 vesicles to reach the 500 mM concentration of neurotransmitter, $\alpha \approx 5000$. We will assume neurotransmitters trapped in a blister have a concentration of 0.2 mM, Therefore we can set the vesicle consumption rate, $R_2/\tau_v \approx 5 \times 10^{-6}$.

By specifying the parameters R_1/τ_c and R_2/τ_v, we can study the model behavior in response to different input and time constants. Figure 3 shows the synaptic transmission in response to the same input as figure 2 and instance release.

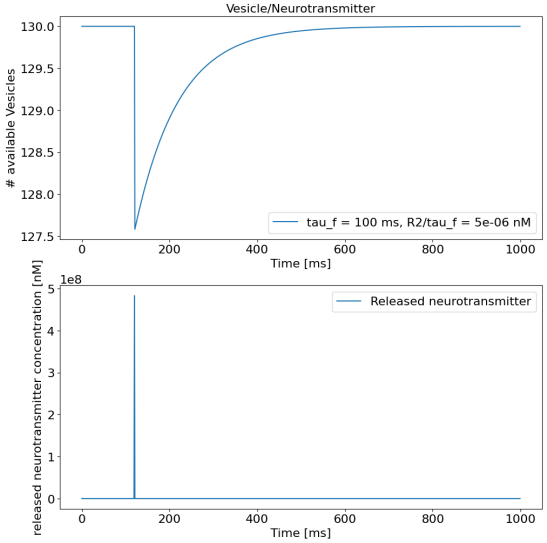

Figure 3: **Top** consumption of initial vesicles for the release and producing (or reuptake) **Bottom** Neurotransmitter release peaking at 500 mM

4 Results

4.1 Facilitation

Neural facilitation, also known as paired-pulse facilitation (PPF), is a phenomenon in which postsynaptic potentials evoked by an impulse are increased when that impulse closely follows a prior impulse. PPF is thus a form of short-term synaptic plasticity. The mechanisms underlying neural facilitation are exclusively presynaptic; broadly speaking, PPF arises due to increased presynaptic Ca2+ concentration leading to a greater release of neurotransmitter [6]. The current model indeed captures this phenomenon, two illustrate that we add a third impulse to the same spike input that we had in Figure 1, once with the same interval of 20 ms and once with the 80 ms, as shown in 4.

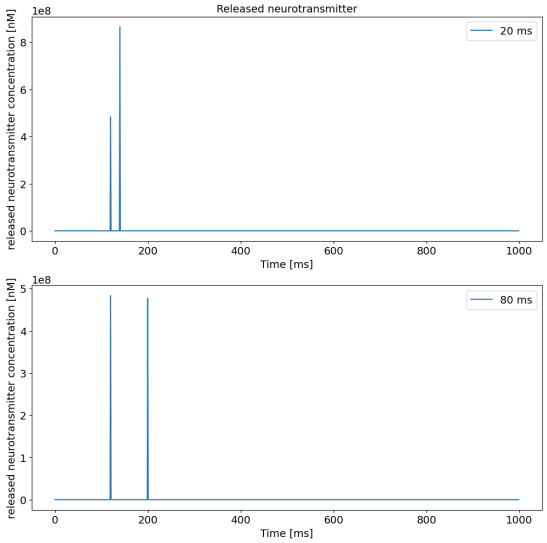

Figure 4: A third impulse with the interval **Top** 20 ms and **bottom** 80 ms, when the third impulse is close enough the released neurotransmitter is greater and hence postsynaptic potentials increases

4.2 Time Constants and Adaptation

It is worth mentioning the interpretation of the time constants; Higher values of τ_c indicate that it takes longer for Ca^{2+} to decay to the resting state concentration after a jump in response to an incoming spike. Higher values of τ_v correspond to slower production (reuse) of vesicles in the cell after a release, since the release is a product of both Ca^{2+} and V, τ_v and τ_c have the opposite effect on the release of neurotransmitters. To study the effect of the two time constants, τ_v and τ_c, the input is set to a constant rate of 50 Hz and each time constant varies between 10, 100, and 1000 ms. Figure 5 shows the released neurotransmitter for different time constants. The magnitude of transmitter spikes is increasing due to higher τ_c (top panels to bottom panels) and lower τ_v (right panels to left panels).

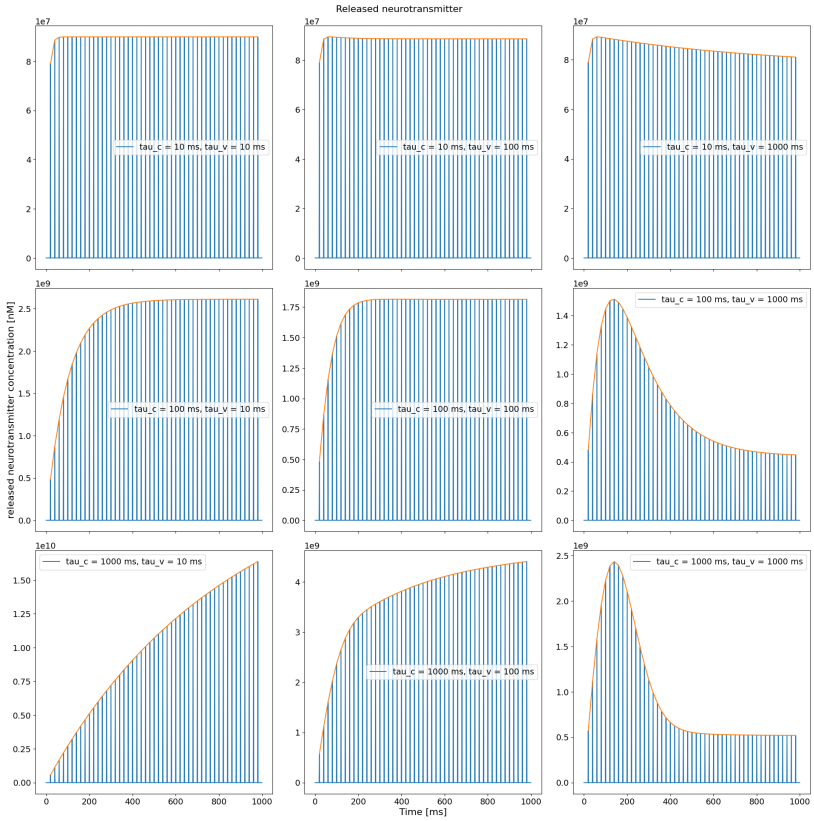

Figure 5: The released neurotransmitter in different time constants, for all the configurations, **Facilitation** in the beginning and for some configurations, **adaptation** to the same input through the time can be observed

Since the input is a spike train of 50 Hz and the values of available vesicles and calcium fluctuate with the frequency of input; to address the observed adaptation, the upper and lower envelope of the $V(t)$ and $C(t)$ for better visualizations are plotted in 6.

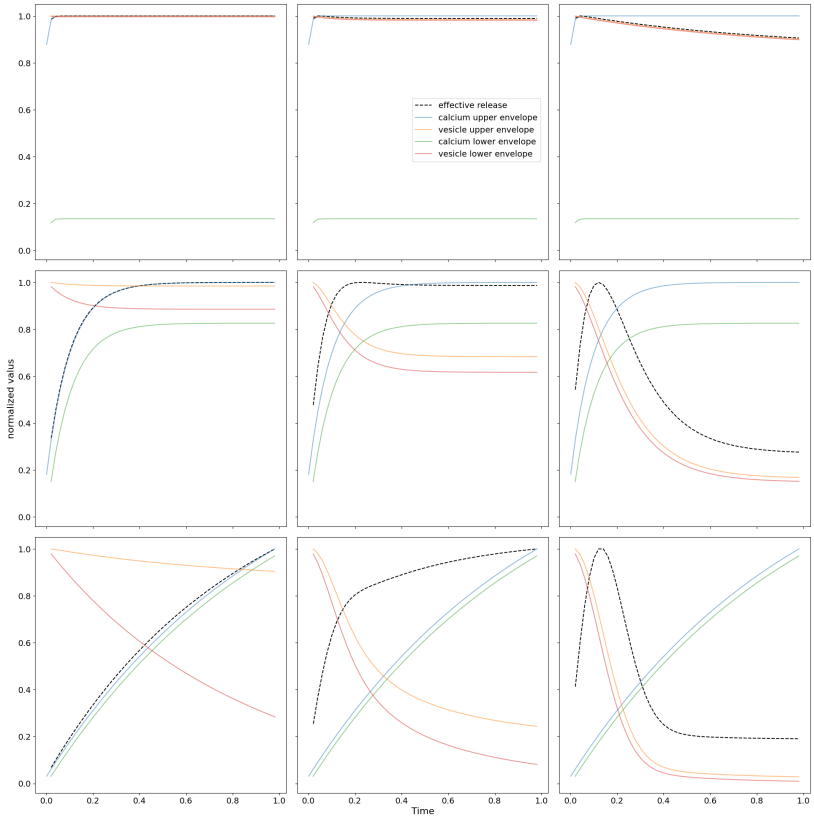

Figure 6: Normalized values,Adaptation happens when the vesicles pool is almost used completely and it is not able to produce vesicles fast enough in response to the increased influx of the calcium

As described by Equation 2, the release times match the input spikes, $I(t)$, and since it is the input to the equation

1, the jumps in Ca^{2+} influx also matches with the incoming spikes, same for vesicles pool through neurotransmitter being the input of the equation 3, we only need to consider the upper envelope of the two signal V and C and multiply them (as in equation 2) to get the effective values for release-the dashed line in figure 6- have the same scheme as the released neurotransmitter in figure 5. We can write the equation 3 as :

$$\tau_v \dot{V}(t) + V(t) - V_0 = -RV(t)C(t)I(t) \tag{4}$$

Higher values of τ_c increase the accumulated Ca^{2+} and the input to the equation 4 increases, higher τ_v induce a longer time of reaching the initial V_0 number of vesicles and that explains the depleted vesicles pool in the bottom and middle right panels in figure 6.

4.3 Released Neurotransmitter as postsynaptic Rate Modulator

Dependent on the receptor on the postsynaptic membrane, the released neurotransmitter from the presynaptic neuron, can inhibit or excite the postsynaptic neuron firing rate [7]. Consider the postsynaptic firing follows a Poisson process with the rate $\lambda(t)$ and mean rate r. The normalized effective release plotted in 6,$ER(t)$ scaled by r, in the case of the excitatory synapse, and $1 - ER(T)$, scaled by r, in the case of the inhibitory synapse, is equal to the rate $\lambda(t)$. In figure 7, the postsynaptic activity of an inhibitory and an excitatory neuron for a presynaptic neuron with the time constants and the effective release in the bottom right panel of figure 6 ($\tau_c = 1s$ and $\tau_v = 1s$) is plotted.

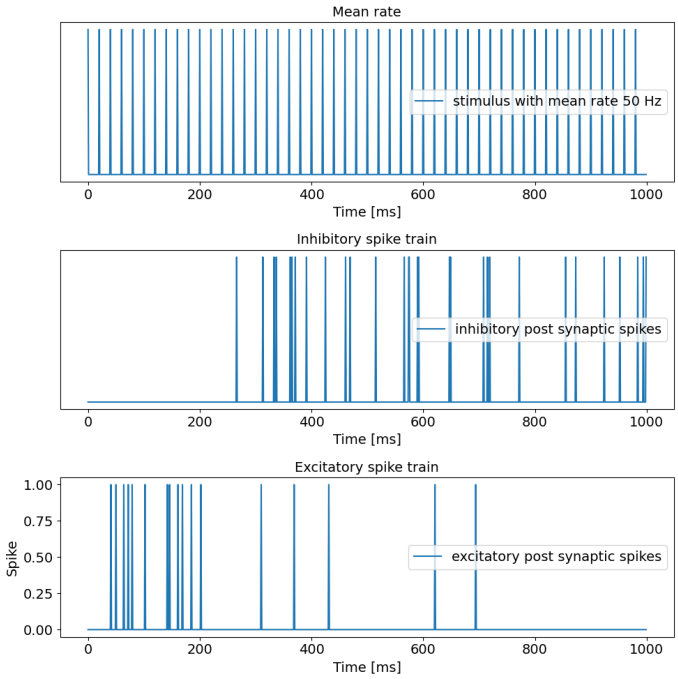

Figure 7: postsynaptic activity, The synapse showed adaptation in neurotransmitter release, postsynaptic firing shows excitation and inhibition within first few 100 ms

5 Discussion

As many biological neuron models, use a dynamical system to describe how voltage potential across the cell membrane evolves [8], we also propose a dynamical system with **multiplicative interaction** nonlinearity 2, which can be seen as a state-dependent model for neurotransmitter release (states being available vesicles in vesicle pool, calcium ion concentration, and spikes input). Although it was tried to utilize suitable parameters such as the time constants and initials vesicles for the model, the mentioned parameters are not exclusive to a single neuron type, given the variety of the neurons in the nervous system. Some of the limitations of the model are:(1) Despite The available vessels being integer numbers, the model treats them as float numbers; (2) The model does not differentiate between production, reuptake, and fuse of vesicles and assumes a constant rate for it, (3) There has been more than 100 types of neurotransmitter identified [9], but we only modeled two abstract concepts of inhibitory and excitatory neurotransmitter and postsynaptic receptors; (4) Refractory period for the action potential is a known property of neurons, but we didn't model a refractory period for the released neurotransmitters. To summarize, in this short project we showed the capability of this model to capture the simple mechanism of release of neurotransmitters by how the voltage-gated calcium ion channels can increase the intracellular Ca_{2+} concentration by the arrival of the action potential, and how vesicles in the cell containing the neurotransmitters are modulated.

The implemented code for the figures and model is available here. [1]

[1] Github

References

[1] Michael S. Gazzaniga et al. *Cognitive neuroscience: The biology of the mind*. W.W. Norton & Company, 2019.

[2] Michael J. Berridge, Peter Lipp, and Martin D. Bootman. "The versatility and universality of calcium signalling". In: *Nature Reviews Molecular Cell Biology* 1.1 (Oct. 2000), pp. 11–21. ISSN: 1471-0080. DOI: 10.1038/35036035. URL: http://dx.doi.org/10.1038/35036035.

[3] Farhan Ali and Alex C. Kwan. "Interpreting in vivo calcium signals from neuronal cell bodies, axons, and dendrites: a review". In: *Neurophotonics* 7.01 (July 2019), p. 1. ISSN: 2329-423X. DOI: 10.1117/1.nph.7.1.011402. URL: http://dx.doi.org/10.1117/1.NPh.7.1.011402.

[4] Annalisa Scimemi and Marco Beato. "Determining the Neurotransmitter Concentration Profile at Active Synapses". In: *Molecular Neurobiology* 40.3 (Oct. 2009), pp. 289–306. ISSN: 1559-1182. DOI: 10.1007/s12035-009-8087-7. URL: http://dx.doi.org/10.1007/s12035-009-8087-7.

[5] Kaori Ikeda and John M. Bekkers. "Counting the number of releasable synaptic vesicles in a presynaptic terminal". In: *Proceedings of the National Academy of Sciences* 106.8 (Feb. 2009), pp. 2945–2950. ISSN: 1091-6490. DOI: 10.1073/pnas.0811017106. URL: http://dx.doi.org/10.1073/pnas.0811017106.

[6] Robert S. Zucker and Wade G. Regehr. "Short-Term Synaptic Plasticity". In: *Annual Review of Physiology* 64.1 (Mar. 2002), pp. 355–405. ISSN: 1545-1585. DOI: 10.1146/annurev.physiol.64.092501.114547. URL: http://dx.doi.org/10.1146/annurev.physiol.64.092501.114547.

[7] Alan Peters and Sanford L. Palay. "The morphology of synapses". In: *Journal of Neurocytology* 25.1 (Jan. 1996), pp. 687–700. ISSN: 1573-7381. DOI: 10.1007/bf02284835. URL: http://dx.doi.org/10.1007/BF02284835.

[8] Wulfram Gerstner and Werner M. Kistler. *Spiking Neuron Models: Single Neurons, Populations, Plasticity*. Cambridge University Press, Aug. 2002. ISBN: 9780511815706. DOI: 10.1017/cbo9780511815706. URL: http://dx.doi.org/10.1017/CBO9780511815706.

[9] Javier Cuevas. "Neurotransmitters and Their Life Cycle". In: *Reference Module in Biomedical Sciences*. Elsevier, 2019. DOI: 10.1016/b978-0-12-801238-3.11318-2. URL: http://dx.doi.org/10.1016/B978-0-12-801238-3.11318-2.