Small conductance based network

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Introduction

In the nervous system, a synapse is a structure that permits a neuron (or nerve cell) to pass an electrical or chemical signal to another neuron . This structure that allows each neuron to communicate with others is vital to form groups of them with high complexity degree. In this report synapses and their dynamics are studied within a small 2-neuron network.

This qualitative study begins with the modelling of single synapse input and how it can stimulate a single neuron. Subsequently, the factors that affect the interaction in a two neural cell network are studied, such as synaptic conductance. Finally, the short term memory that can be created between these two cells is explored also referred as short term synaptic plasticity (STP).

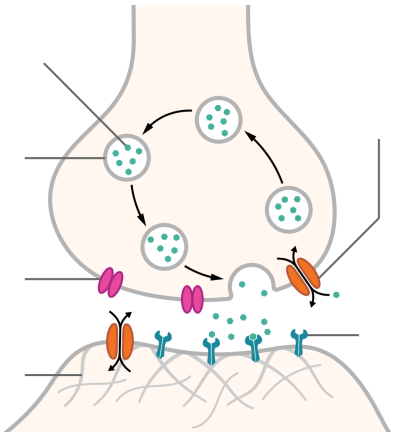

Figure 1: Schematic of synapse. Source: [1]

Spike trains and Poisson distribution

Neurons are thought to convey signals mainly if not exclusively through the information content of their spike trains. A spike train consists of the series of times at which the neuron has fired. It is possible to record spike trains from individual neurons using various electrophysiological methods in vivo and in vitro and such methods have generated a good number of datasets, which in turn have revealed many properties of the neural computation.

Spike train definition

Define $\rho(t)$, the neural response function to be a bunch of impulses, one for each action potential:

$$\rho(t) = \sum_{i=1}^{k} \delta(t - t_i)$$

where k is the total number of spikes in the spike train, and t_i are the times that each spike occurred. The unit impulse signal is defined as:

$$\delta(t) = \begin{cases} 1, & \text{if } t = 0 \\ 0, & \text{otherwise} \end{cases}$$

such that the integral of $\delta(t)$ is one:

$$\int_{-\infty}^{\infty} \delta(t) = 1$$

The instantaneous firing rate (of a neuron) can be defined as the expectation of the neural response function, averaged over an infinite number of repeats:

$$r(t) = \langle \rho(t) \rangle$$

The Homogeneous Poisson Process

The random process with a constant firing rate r is called a homogeneous Poisson process. Imagine that we are given a long interval $(0, T)$ and we place a single spike in that interval at random. Then we pick a sub-interval (t_1, t_2) of length $\triangle t = t_2 - t_1$. The probability that the spike occurred during the sub-interval occurred during the sub-interval equals $\triangle t / T$.

Now let's place k spikes in the $(0, T)$ interval and find the probability that n of them fall in the (t_1, t_2) sub-interval. The probability is given by this expression using the binomial formula:

$$P\{n \text{ spikes during } \triangle t\} = \frac{k!}{(k-n)!n!} p^n q^{k-n}$$

where $p = \triangle t / T$ and $q = 1 - p$. Subsequently, we increase k and T keeping the ratio $r = k/T$ constant. Since k is the total number of spikes and T is the total time, $r = k/T$ is the mean firing rate. If $k \to \infty$ it can be proven that the probability that n spikes are in an interval of length $\triangle t$ equals:

$$P\{n \text{ spikes during } \triangle t\} = e^{-r\triangle t} \frac{(r\triangle t)^n}{n!}$$

This is the formula for the Poisson probability density function. The spikes count for a homogeneous Poisson process, dropping the time-dependence is given by

$$\langle n \rangle = \int_{t_1}^{t_2} r \, dt = r\triangle t$$

for any interval of length $\triangle t = t_2 - t_1$. As expected, the average spikes count equals the mean firing rate times the duration.

Waiting time between spikes

How can we find the waiting time for the next spike to occur? This can be computed if we know the probability function for no spikes to occur within the interval $(t_o, t_o + \tau)$. Plugging $n = 0$ in the previous equation we get:

$$P\{\text{next spike occurs after } \tau\} = e^{r\tau}$$

The probability that a spike has already occured is 1 minus this result, i.e.,

$$P\{\text{next spike occurs after } \tau\} = 1 - e^{r\tau}$$

This is a cumulative distribution function for the probability of a spike occurring within the interval $(t_o, t_o + \tau)$. It is zero for $\tau = 0$ and increases monotonically to 1. The probability density function for the waiting time until the next spikes is the derivative of the previous cumulative distribution:

$$p(\tau) = \frac{d}{dt}(1 - e^{r\tau}) = r\, e^{-r\tau}$$

Then the Interspike Interval time (ISI from now on) for a homogeneious Poisson spike train is an exponential function. The mean duration between events is:

$$\langle n \rangle = \int_{\infty}^{0} \tau p(\tau)\, d\tau = 1/r$$

Generating Poisson trains

An approach to numerically generate a Poisson spike train is the following, based on the approximation of the probability of a spike occurring during a short time interval. For the homogeneous Poisson process, this expression can be rewritten removing the time dependence) as

$$P\{1 \text{ spike during } \delta t\} = r\delta t$$

This equation can be used to generate a Poisson spike train by first subdividing time into a bunch of short intervals, each of duration δt. Then generate a sequence of random numbers $x[i]$, uniformly distributed between 0 and 1. For each interval, if $x[i] \leq r\delta t$, generate a spike. Otherwise, no spike is generated. This procedure is appropiate only when δt is very small, i.e, only when $\delta t << 1$.

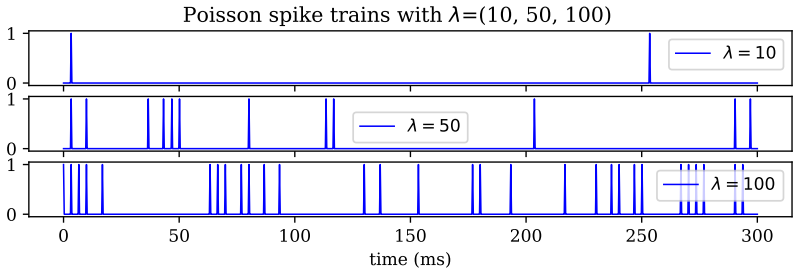

Figure 2: Generated spike train with varies value of λ

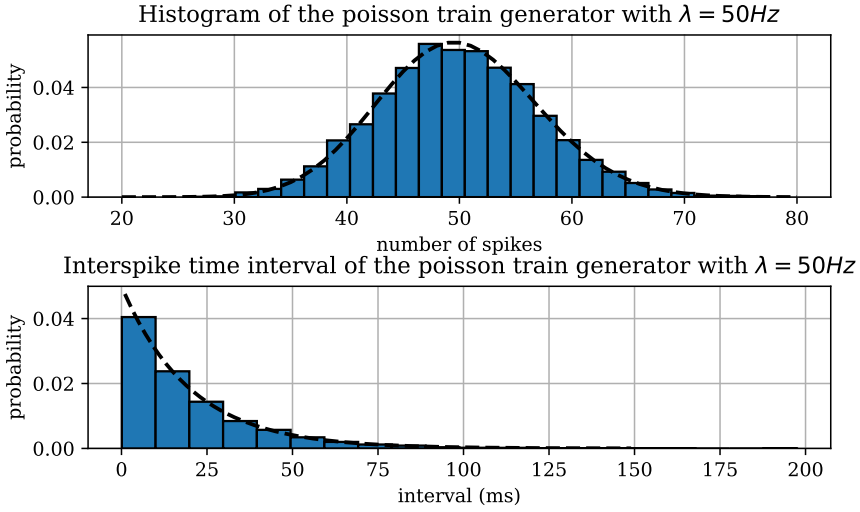

Figure 3: Histogram of number of spikes and ISI time with the theoretical distribution

Why the Poisson model?

The Poisson model has been adopted as the null hypothesis by much of the neuroscience community, given its general adequacy in describing spike data recorded in vivo. The properties which account for its success are:

- Independence of ISI intervals. If we write $I_S = \{\text{ISI}_1, \text{ISI}_2, ..., \text{ISI}_{N-1}\}$ then we can consider ISI_k as the realisation of a random variable μ_k. The independence property is then equivalent to μ_k and $\mu_{k'}$ being independent for all $k = k'$.

- $\mu_k \sim \mu$ for all k. The ISIs are independent draws of identically distributed random variables. From here on we relinquish this formality by saying that the ISIs are independent draws of the same random variable μ.

- $p_\mu(x) = \lambda e^{-\lambda x}$ or μ has exponential distribution. $1/\lambda$ is the mean ISI and λ is the intensity of the process. For spike trains we also call λ the mean firing rate.

Neuron model

Conductance based models are sets of equations like the Hodgkin Huxley model [2] — they represent neurons with the conductances of various ion channels and the capacitance of the cell membrane. Conductance based models are a simple but varied class of models. Unlike simpler models (such as integrate and fire model), conductance based models are capable of generating spikes. Some are also capable of resonating, oscillating, rebound spiking, bi-stability spiking, and so on.

The current flowing across the neuron membrane is described by these models as follows (these are the most common types of channels):

$$I = C\dot{V} + I_{Na} + I_{Ca} + I_K + I_{Cl}$$

And the dynamics of the models are generally described as the following:

$$C_m \frac{dV}{dt} = \sum_i g_i(V_i - V) + I_{external}$$

Our model

For this project we are using a two dimensional conductance based model neuron, that follows the structure we just explained. It models the persistent sodium channel $I_{Na,p}$ and the potassium channel I_K. Also we add an I_{app} parameter to study the neuron behaviour.

$$C\dot{V} = \overbrace{-g_L(V - E_L)}^{\text{leak}} - \overbrace{g_{Na} m_\infty(V)(V - E_{Na})}^{\text{instantaneous } I_{Na,p}} - \overbrace{g_K n(V - E_K)}^{I_K} + \overbrace{I_{app}}^{\text{external I}}$$
$$\tau_n \dot{n} = n_\infty(V) - n$$

with:

$$m_\infty(V) = 1/(1 + exp(-(V - V_{max,m})/k_m))$$
$$n_\infty(V) = 1/(1 + exp(-(V - V_{max,n})/k_n))$$

Let's analyze the system for three different I_{app} values, $I_{app} \in (0, 160, 300)$. In Figure 2 we see

a temporal simulation of the model in the three scenarios, each with three different V starting points, equilibrium, equilibrium + 25 and equilibrium + 50, to see the effect of a perturbation in the system.

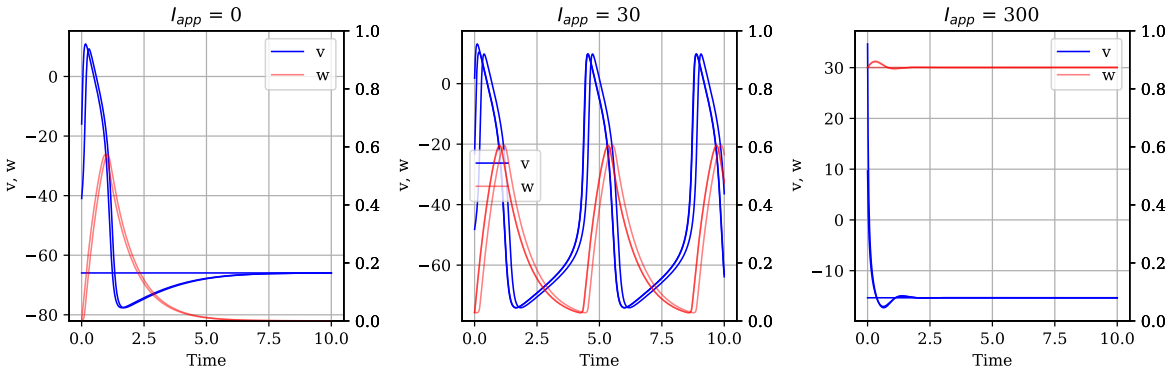

Figure 4: Temporal run with three scenarios

In the first scenario we observe how a big enough perturbation kicks the system out of stability, creates a voltage spike and comes back to equilibrium point, but if the perturbation is not big enough the system doesn't. In the second scenario, the perturbation does not affect the behaviour of the system, after a short transitory phase the system comes to the periodic oscillation. In the final scenario the perturbations don't affect the system neither, it always ends up at saturation point. The next diagram is a plot with the null-clines, the phase diagram and the equilibrium points:

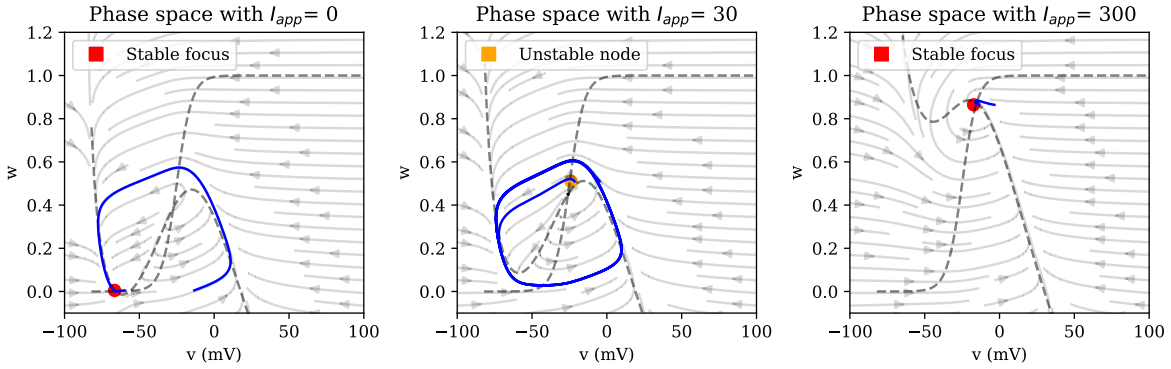

Figure 5: Phase plot with three scenarios

Post-synaptic potentials induced by a Poisson train

Like other currents we model the synaptic current as the product of a conductance times a voltage difference

$$I_{syn} = g_{syn}(t)(V - V_{syn})$$

Modelling the synaptic excitation

But in this case it depends on the presynaptic neuron (in this case train of spikes). We model the conductance as a sum of fixed functions which depend only on the times the presynaptic cell has spikes:

$$g_{syn}(t) = \overline{g} \sum_j \alpha(t-t_j) \cdot H(t - t_j)$$

Where $\overline{g}$ is a constant conductance and $\alpha(t)$ is a prescribed function of time, vanishing for $t < 0$ and positive for $t > 0$, it also has integral of 1. The times t_j are when the presynaptic cell has spiked. In our model:

$$\alpha(t) = 1/\tau_d^2 t e^{-t/\tau_d}$$

$$H(t) = \begin{cases} 1, & \text{if } t \geq 0 \\ 0, & \text{otherwise} \end{cases}$$

When we set up the Poisson train as the synaptic input we get the following result.

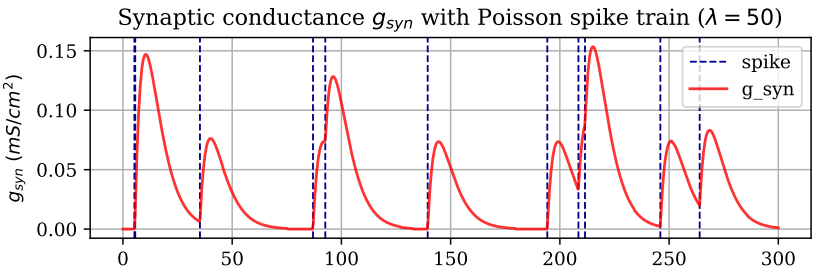

Figure 6: Temporal run of the $g_{syn}(t)$ function

Neuron response to synaptic excitation

Coming back to the current equation. The synaptic current is given by the conductance times the potential difference between the current cell voltage and the potential equilibrium of the synapse.

$$I_{syn} = g_{syn}(t)(V - E_{syn})$$

The potential equilibrium depends on whether the synapse is excitatory or inhibitory. In the first case the equilibrium voltage E_{syn} is set equal to 0 and as the resting potential is negative, the resulting synaptical current will be positive. If it is inhibitory, the equilibrium potential is set at a value below the resting potential of the neuron (around -80 mV), so the resulting synaptical is negative.

As we have seen in the previous section if the neuron potential is above a threshold it spikes, so it is just a matter of the synaptical current being strong enough to fire the neuron. See the next figure:

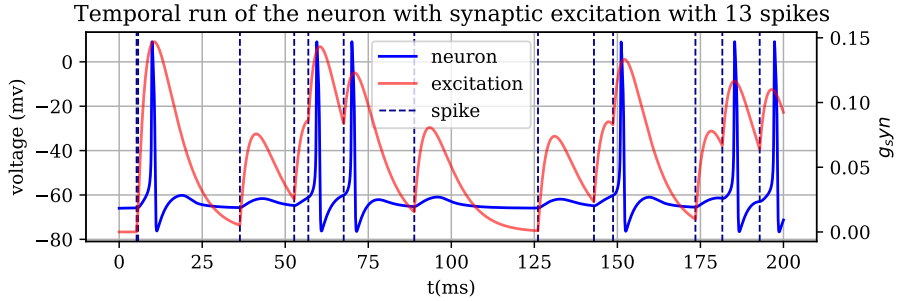

Figure 7: Neuron response to synaptical excitation

In this neuron model we set up the $\overline{g}$ to 1. With this value it needs to get at least two neural spikes in a short period of time to (make the neuron) spike. If a larger value of $\overline{g}$ is used it may spike with each input.

Next we study the frequency-intensity curve given by the network. We take a two-fold approach, first we compute the F-I curve with a constant I_{app} and the second approach is to integrate and average the I_{syn} current across time and see the frequency response of the neuron to the averaged I_{syn}.

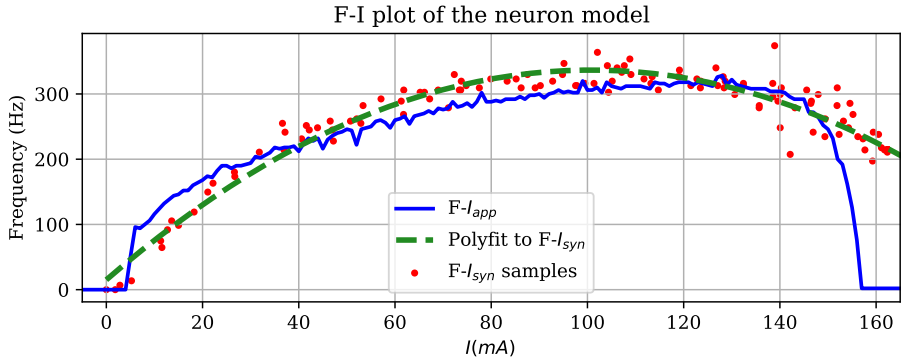

Figure 8: Neuron response to synaptical excitation

Two neuron model with graded synapses

So far we have studied the situation where a neuron is excited by an external (Poisson) spike train. In this section we study the behaviour of two neurons coupled using synaptic channels.

The neuron model is exactly the same as in the previous section, but with the synaptic current I_{syn} added:

$$C\dot{V}_i = I_i - g_L(V_i - E_L) - g_{Na}m_\infty(V_i)(V_i - E_{Na}) - g_K n_i(V_i - E_K)$$
$$\tau\dot{n}_i = n_\infty(V_i) - n_i$$

for $i = 1, 2$. The synaptic current is modelled by the fraction of synaptic channels open times the max conductance times the potential difference.

$$I_{syn} = -g_{syn,max}s_j(V_i - E_{syn})$$

And the dynamics of the fraction of open channels is modelled with the following differential equation:

$$\dot{s}_i = A_s f_{pre}(vi)(1 - s_i) - \beta_i s_i, \;\; i = 1, 2$$

With:

$$f_{pre} = 1/(1 + exp(-(v - v_t)/v_s))$$

In our experiments neuron 1 is going to be excited by the external Poisson train, then neuron 1 is going to excite neuron 2 and neuron 2 is going to inhibit neuron 1.This implies that $V1$ contains the term $-g_{inh,max}s_2(V_1 - E_{inh})$ and $V2$ contains the term $-g_{exc,max}s_1(V_1 - E_{exc})$

Some results

The first experiment with the model is the case where g_{exc} and g_{inh} is zero. The result is trivial, neuron 1 acts with the expected behaviour (the one commented on the previous section) and neuron 2 is at resting potential (-66 mV). c

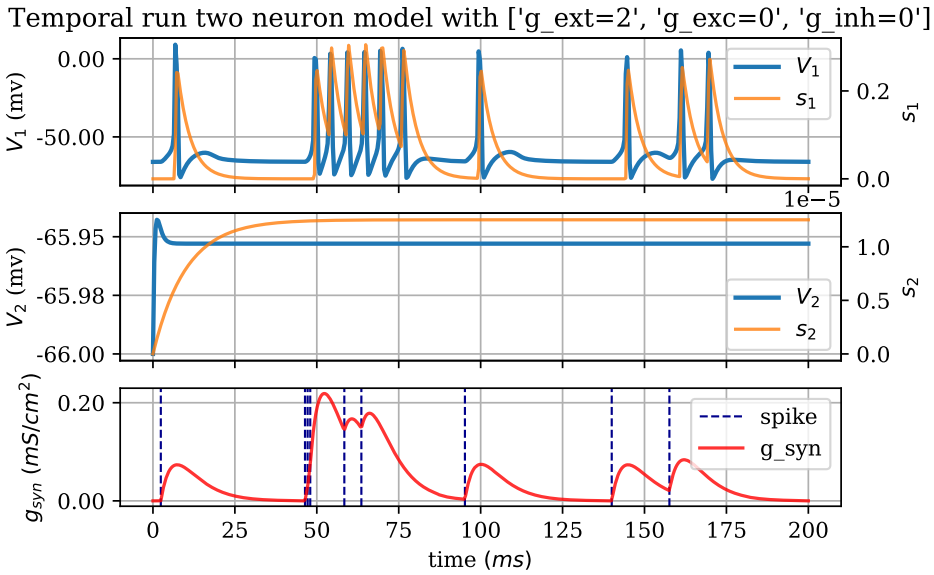

Figure 9: Neuron response with no synapse activity

The second experiment is when adding the excitatory synapse to neuron 2. Here we see neuron 2 responding to spikes generated by neuron 1. Depending on the value of g_{exc} chosen we see a completely direct, one on one response or some partial response, only firing when neuron 1 has a big number of spikes in a short time. See figures 10 for a representation of this behaviour.

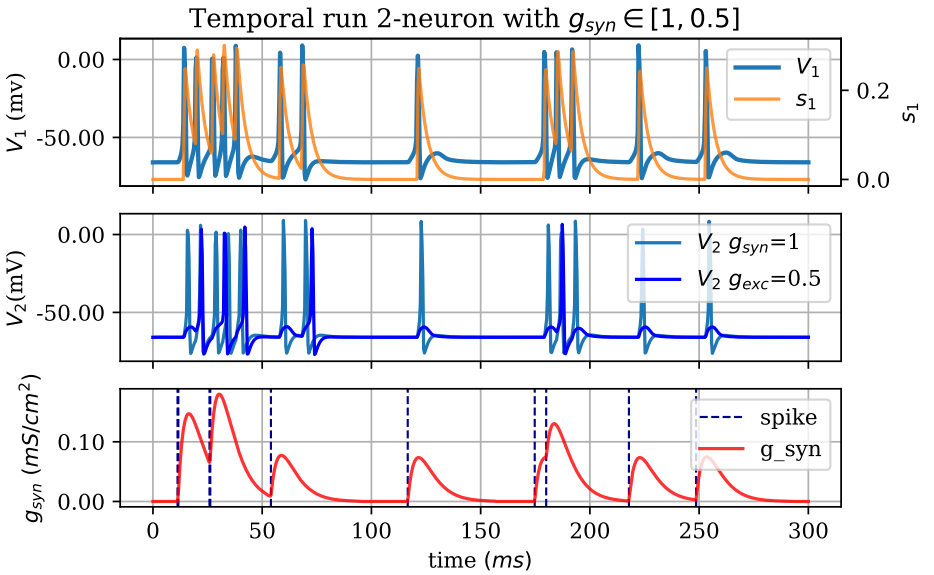

Figure 10: Plot showing synaptic excitation behaviour

From now on we are going to set the value of g_{exc} to 1 and assume a direct response from neuron 2 in future experiments.

In the next experiment we activate the inhibition synapse on neuron 1. The results are somewhat confusing at first sight, they will be later studied in depth. An option to get a clear sight on the impact of the inhibition on the cells is to add external excitation to neuron 2 with an external constant current and see what causes to neuron 1.

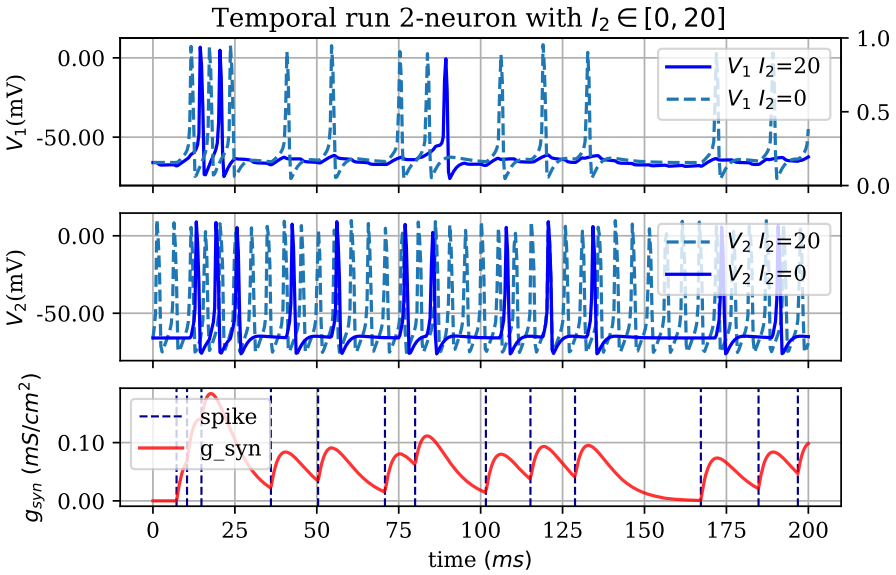

Figure 11: Plot showing the synaptic inhibition behaviour

The response of neuron 2 to a high I_{app} current is periodic high frequency spiking. This high energy signal gets reflected to neuron 1 by 'cancelling' some of the existing spikes.

Behaviour of the network

For this section we set g_{exc} to 1, so the dynamics we get is an identical response from neuron 1 and neuron 2, as the excitation is strong enough to make neuron 2 mimic neuron 1 and the inhibition from neuron 2 directly applies to neuron 1.

The goal is to understand how changing the g_{inh} impacts the model, we set g_{inh} to different values $g_{inh,maxs} \in [0, 1, 2]$ mS/cm^2 and study the response. As the response from neuron 1 and neuron 2 is the same we are going to obviate the voltage from the second neuron in favour of more spatial resolution.

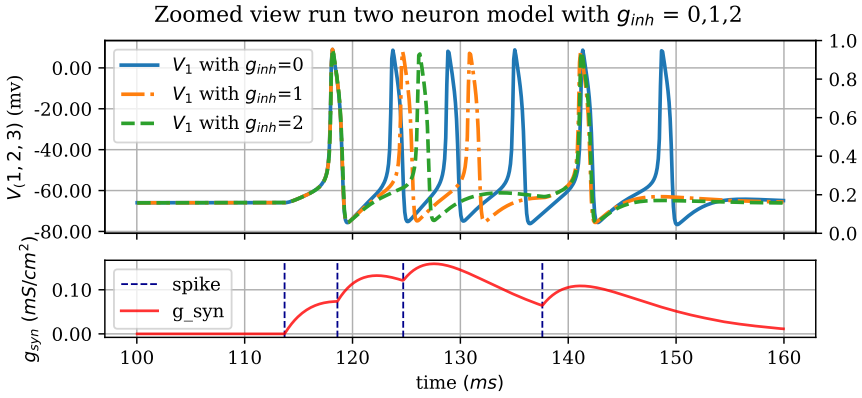

Figure 12: Neuron potentials with different g_{inh} values

We see that the higher the value of g_{inh} the more time there is between the spikes. This makes sense looking at the equations, the higher the inhibition, the lower the total current to it, thus it needs more time to get to the firing threshold. A direct consequence of this is that there are less spikes, as they take more time between spikes and we have the same excitation there is less effective frequency. From some experiments we have observed that the frequencies are

around 66 Hz, 43 Hz and 35 Hz respectively.

The next exercise was quite challenging. Here we change the time constants of excitatory and inhibitory synapses, $1/\beta_1$ and $1/\beta_2$ respectively, by multiplying them by a factor $\lambda \in [1, 0.5, 0.1]$. Just as a quick reminder, the time constants represent how fast the fraction of open channels decreases, coming back eventually to zero. So this means that with the addition of this λ we are doubling and multiplying by 10 the relaxation time of the synaptic channels. This already gives us some insight on the consequences of this.

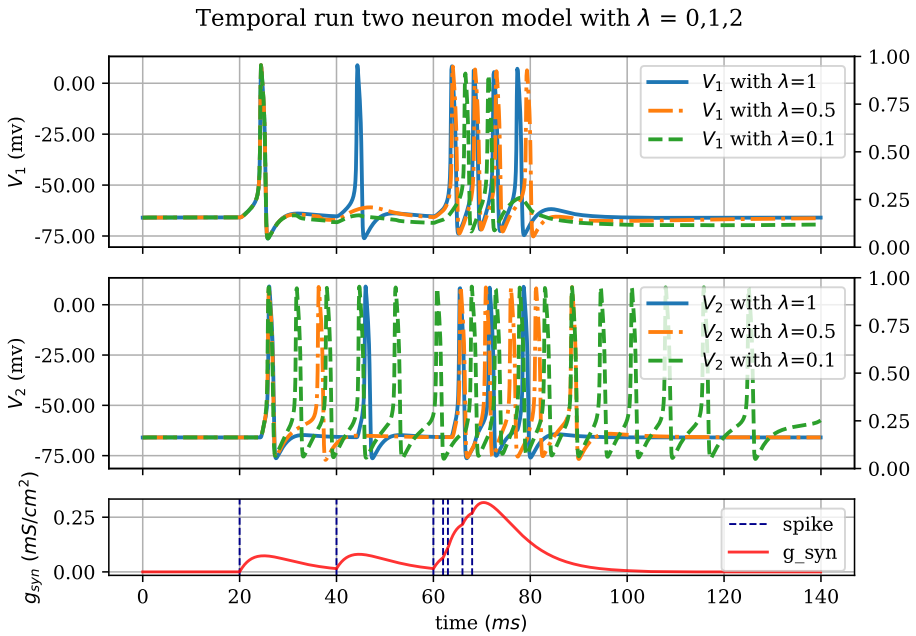

Figure 13: Neuronal potentials with different values of λ

In the plot we observe two different behaviours, for the first neuron the smaller the lambda value the fewer spikes we have. As the neuron 2 inhibits neuron 1 for longer periods is capable of 'deleting' spikes that otherwise would have appeared. The result is even more noticeable on neuron 2, here the lower the lambda value the more spikes we have. In this case what happens is that neuron 1 excites neuron 2 for more time, therefore neuron 2 fires more times. And thinking in second order effects, these extra spikes on neuron 2 inhibit even more neuron 1 that is why we have an even stronger inverse response.

Short Term Neuroplasticity

Short-term plasticity (STP) [3], also called dynamical synapses, refers to a phenomenon in which synaptic efficacy changes over time in a way that reflects the history of presynaptic activity. Two types of STP, with opposite effects on synaptic efficacy, have been observed in experiments. They are known as Short-Term Depression (STD) and Short-Term Facilitation (STF). STD occurs due to exhaustion of neurons during continuous spiking activity and affects the axon terminal of a pre-synaptic neuron, while STF is connected with high levels of calcium into the axon terminal after spike generation.

Dynamics of STP

More explicitly, the fraction of available neurotransmitters is denoted as x ($0 \leq x \leq 1$) and their release probability as u. After a synaptic spike, neurotrasmitting availability is clearly

decreased and u is increased. So after the spike their values are formed as,

$$u^+ = u^- + f(1 - v^-)$$
$$x^+ = x^-(1 - u^+)$$
$$s^+ = s^- + Au^+x^-$$

and their dynamics are formed as,

$$\tau_d \dot{x} = 1 - x$$
$$\tau_f \dot{u} = -u$$
$$\tau \dot{s} = -s$$

Here τ_i, for $i \in [d, f, s]$ is the recovery rate for each of these variables to its equilibrium. In the following plot there is a simulation of both types of STP:

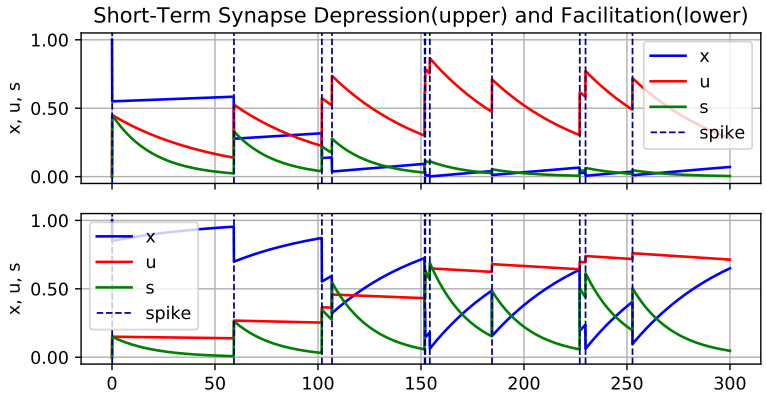

Figure l3: Simulation of two STP modelled synapses with STD and STF

STP on the 2-neuron network

In the next experiments we apply short term plasticity to the 2-neuron model and study it's behaviour.

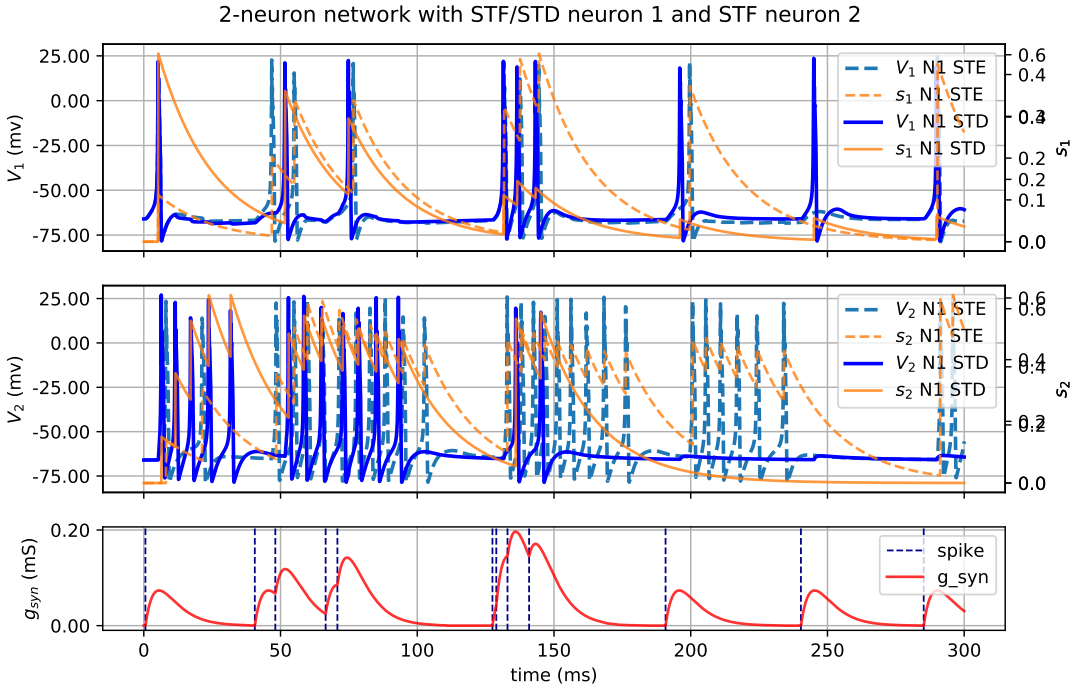

Figure 14: Simulation of the 2-neuron network with different STP

In the first experiment we set neuron 1 with STF/STD dominated STP, and neuron 2 with STF dominated STP. Neuron 1 is set up as an excitatory synapse to neuron 2, so the spikes in N1 are reflected in N2. Then depending on if we have STD or STP the s is higher or lower, this is reflected on the latter part of the plot where there are no spikes for N2 in the case of STD dominated STP N1. Apart from that neuron 2 inhibits neuron 1, so the less spikes there are on N2 the less inhibition will have N1, said in a simpler way, N1 will have more current thus more spikes.

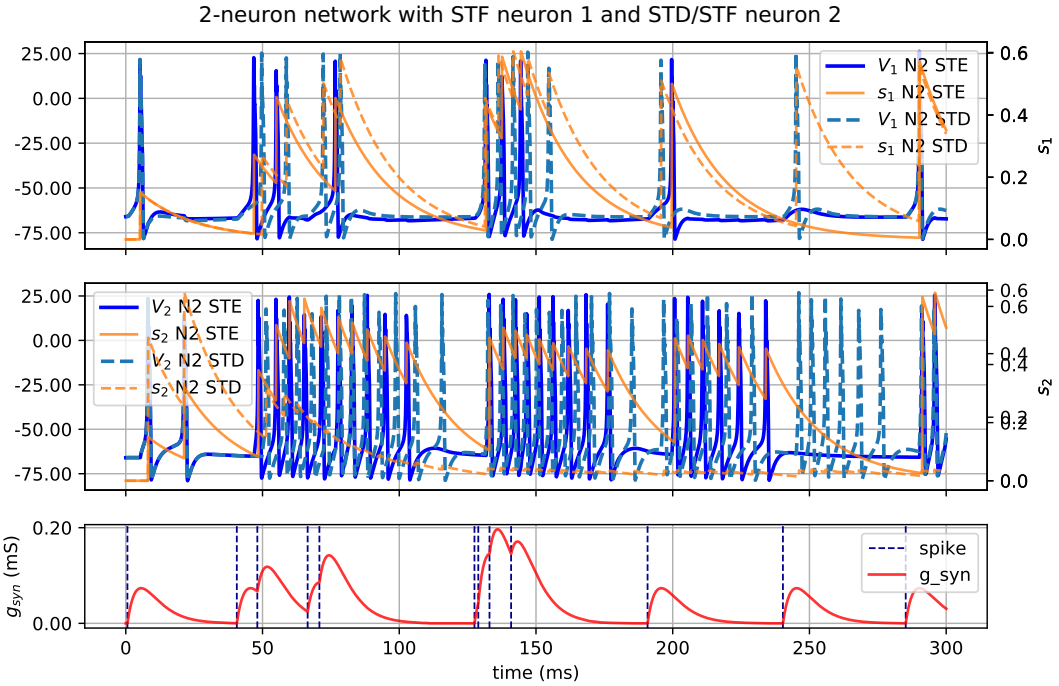

Figure 15: Simulation of the 2-neuron network with different STP

In the second experiment we set neuron 1 with STF dominated STP, and neuron 2 with STD/STF dominated STP. Due to the STF dominated neuron 1, neuron 2 receives a lot of excitation from neuron 1. Neuron 2 is connected to neuron 1 with an inhibitory synapse, the difference between having STD or STF (in neuron 2) means that we will have more or less inhibition in neuron 1. This is reflected in the fact that we have more spikes in neuron 1 in the case with N2 STD. As a direct consequence neuron 2 will also have more spikes due to the higher number of spikes in neuron 1.

A comment about implementations

All the plots from this document have been produced by the authors. They have been created by running numerical simulations with the Python programming language and its scientific programming libraries (Numpy and Scipy), and plotted using the Matplotlib library. All the code for the simulations and visualizations is accessible in the form of Jupyter notebooks in the linked public git repository.

References

[1] T. Splettstoesser, "Schematic of a synapse." `https://commons.wikimedia.org/wiki/File:SynapseSchematic_en.svg`, July 2015.

[2] A. L. Hodgkin and A. F. Huxley, "A quantitative description of membrane current and its application to conduction and excitation in nerve," *Physiology*, vol. 115, pp. 500–544, 1952.

[3] K. P. M Tsodyks and H. Markram, "Neural networks with dynamic synapses," *NLM-ME*, May 1998.