M2 Biology **30/09/21**

TD2: Models of Neurons II

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TD material is available at:

`https://github.com/Elieoriol/2122_UlmM2_ThNeuro/tree/master/TD2`

In the first tutorial, we have developed the most basic model of a spiking neuron: the LIF neuron. In this tutorial, we will underline the inability of this model to account for a fundamental property of real neurons that is post-spiking refractoriness. We will also be interested in the modeling of two more features of biological neurons: adaptation and shunting inhibition. Finally, we will introduce the QIF model, richer in behavior than the LIF one.

1 Refractory period

Additional rules can be added to account for other observed features of real spikes, also called action potentials. One of the observed features is a refractory period; immediately after a spike the neuron cannot produce another spike for a short period of time called the refractory period. The refractory period can be included in models of neurons in a number of ways.

1.1 Forced voltage clamp

The voltage is fixed at its reset value following a spike for the duration of the refractory period τ_{ref}.

1. What is the maximal firing rate f with this method?

   The maximal firing rate is obtained when the neuron fires immediately after the refractory period. Thus:

   $$max\ f = \frac{1}{\tau_{ref}} \tag{1}$$

   A disadvantage of this method is that as the firing rate of the neuron increases, the neuron spends a greater proportion of its time in the refractory period with the membrane potential at its low reset value. Therefore, the mean membrane potential decreases with increased input in such a model, in contrast to the behavior of real neurons.

1.2 Refractory conductance

A solution closer to biology is to add a large conductance g_K at spike time, producing an outward hyperpolarizing current. In real neurons, such a late current can most often be related to potassium channels.

2. Explain why a large conductance can replace the LIF reset mechanism. Propose a differential equation for g_K to enable the neuron to spike again after the refractory period. Does this model solve the previous problem?

A large conductance is associated to a small relaxation time. If a large conductance associated to a low reversal potential is induced when the membrane potential reaches its threshold value, it will be forced to decrease strongly. This way it can be brought back close to its reset value and remain there as long a required. We now need a second ingredient defining the time the system will stay in the refractory period. For our neuron to spike we needed g_K to be null. A way to make it spike again after a given time is to make g_K decay to 0 with a relaxation time corresponding to the refractory period τ_{ref}. Finally:

$$\frac{\mathrm{d}g_K}{\mathrm{d}t} = -g_K/\tau_{ref} \qquad \textit{after a spike, } g_K \to g_K + \Delta g$$

Now the potassium current produced by this refractory conductance yields an additional term to the membrane potential equation $g_K(t)\,(E_K - V_m(t))$.

The time spent at the reset value depends on the strength of other currents entering the neuron; the stronger the other inputs, the more quickly they overcome the decaying refractory current. As such the mean membrane potential increases with increased input.

Note: This is a first step towards the Hodgkin-Huxley model of spiking neurons. The difference resides in that instead of roughly adding a decaying conductance at spike time, this conductance is made non-linearly voltage-dependent: when the membrane potential reaches high values, this conductance becomes large and brings the potential down.

1.3 Raised threshold

A third alternative could be to consider that the neuron does not really go into a refractory period but instead becomes less prone to spiking by raising its threshold.

3. By analogy with the previous method, can you think of a way to implement a raised threshold method?

   Following a spike the voltage threshold can be raised and allowed to decay back to its baseline constant:

$$\frac{\mathrm{d}V_{th}(t)}{\mathrm{d}t} = -\frac{V_{th}^{(0)} - V_{th}(t)}{\tau_{ref}} \qquad \textit{after a spike, } V_{th} \to V_{th} + \Delta V_{th}$$

   This method has the advantage that the refractory period is not absolute: the greater the input, the sooner the membrane potential will reach the decaying threshold.

4. **num** Implement numerically the three previous methods.

2 Firing rate adaptation

A well-known property of neurons is adaptation. For instance, driven by an injected current, a decrease in time of the firing rate of a neuron to a steady-state value can be observed.

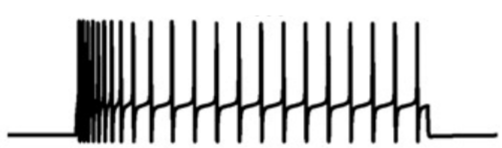

Figure 1: Example of firing rate adaptation in response to an injected current.

We are going to model this phenomenon by considering the effect of ion channels which open whenever a neuron fires a spike and let in negative current, such that:

$$\tau_m \frac{\mathrm{d}V}{\mathrm{d}t} = -V - W + I \tag{2}$$

where, after each spike occurring at V_{th}, W is increased by W_R and V is reset to 0. Between spikes, W decays back to zero with time constant τ_w:

$$\tau_w \frac{\mathrm{d}W}{\mathrm{d}t} = -W \tag{3}$$

2.1 First approximation

We first make the approximation that W is constant between spikes. A constant current $I_{syn} > V_{th}$ is injected into the neuron.

1. Discuss qualitatively what happens after the first spike.

   After the first spike, W increases by W_R, shifting the steady-state $V^S = I_{syn} - W$ by $-W_R$, making it closer to V_{th}.

2. At which value of W does the model stop spiking? Show that the total number of spikes emitted is roughly $(I_{syn} - V_{th})/W_R$.

   After several spikes, the steady-state may end up below V_{th}, in which case the neuron stops spiking. This happens for $W > I_{syn} - V_{th}$. Starting from $W = 0$, $W = kW_R$ after k spikes and reaches this limit for $k \sim (I_{syn} - V_{th})/W_R$.

3. Compute the duration of an interspike interval (ISI) as a function of W in that interval.

   In an interval, W is constant and (2) is a first-order linear equation. Denoting $U = V + W - I$, we have $\tau_m \frac{\mathrm{d}U}{\mathrm{d}t} = -U$. The ISI $T(W)$ is defined by:

   $$\int_{U(0)=W-I}^{U(T)=V_{th}+W-I} \frac{\mathrm{d}U}{U} = -T/\tau_m$$

   We finally find:

   $$T = \tau_m \cdot \log\left[\frac{I - W}{I - W - V_{th}}\right]$$

2.2 General firing rate

It is no longer possible to ignore the decay of W if the ISI becomes comparable to the time constant of the decay τ_w.

4. Can you explain why? Is it possible for the neuron to stop spiking?

   In that case the decay of W during the interval becomes significant and W cannot be considered constant anymore. This necessarily happens at some point because as we have seen previously, the neuron necessarily stops spiking if W is considered constant (corresponding to an infinite ISI); this approximation cannot hold all along.

We therefore consider that the system has reached its equilibrium firing rate and fires spikes with a period T.

5. Compute the time course of W between two successive spikes, assuming that immediately after the first of the two spikes $W(t=0) = W_0$.

   Solving (3), we immediately find $W(t) = W_0 \cdot e^{-t/\tau_w}$.

6. Show that W_0 is given by:

$$W_0 = \frac{W_R}{1 - \exp(-T/\tau_w)}. \tag{4}$$

   At equilibrium, W decays from W_0 until a spike is emitted at $t = T$. W_R is added to W and the condition of stationarity then writes:

$$W(t = T^-) + W_R = W_0$$

   Having $W(t = T^-) = W_0 \cdot e^{-T/\tau_w}$, we find the desired result.

7. We assume that $T \ll \tau_w$, such that W can be approximated by its average value during the whole interspike interval. Show that the period T of spike emission is given by:

$$T = \tau_m \cdot \log\left(\frac{I - W_R\tau_w/T}{I - V_{th} - W_R\tau_w/T}\right). \tag{5}$$

   If $T \ll \tau_w$, then W does not vary much and we approximate it by its average value, given by:

$$\langle W\rangle_{ISI} = \frac{1}{T}\int_0^T W(t)\,\mathrm{d}t = \frac{W_0}{T}\int_0^T e^{-t/\tau_w}\,\mathrm{d}t = \frac{\tau_w}{T}\cdot W_0(1 - e^{-t/\tau_w}) = \frac{\tau_w}{T}W_R$$

   Using our answer to question 3, we find the above expression for T.

8. Show that, as the injected current increases, the neuron firing rate $r(I)$ behaves as:

$$r(I) \sim aI \tag{6}$$

   with $a = [\tau_w W_R + \tau_m V_{th}]^{-1}$.

   The expression of T can be rewritten:

$$T = -\tau_m \cdot \log\left(1 - \frac{V_{th}}{I - W_R\tau_w/T}\right)$$

   For high currents:

$$T \approx \frac{\tau_m V_{th}}{I - W_R\tau_w/T} \qquad \Rightarrow \qquad I\cdot T \approx \tau_m V_{th} + \tau_w W_R$$

   The firing rate is given by $1/T$.

9. How does this compare to an integrate-and-fire neuron without firing rate adaptation?

   Without firing rate adaptation, we can do the calculations again or directly set $W_R = 0$ in the previous developments. We thus have $r(I) \sim \frac{I}{\tau_m V_{th}}$. Adaptation corresponds to the reduction of the firing rate by a term proportional to the gain W_R of the inhibitory current times its decay constant τ_w. The higher the gain and the larger the decay constant, the stronger adaptation is, effectively reducing the firing rate.

3 Non linear models

Linear models cannot reproduce all the behaviors of biological neurons. We propose to study a nonlinear model of neurons and show how it can display a richer repertoire of behaviors.

The model we consider is the *quadratic integrate and fire* (QIF) model:

$$\begin{aligned} &\frac{\mathrm{d}V}{\mathrm{d}t} = V^2 + b \\ &\text{if } V > V_{peak} \text{ , then } V \to V_{reset} \end{aligned} \tag{7}$$

We consider here the potential V and the quantity b to be adimensional (through normalization for instance). b can be a function of time (a varying current), but we consider it constant for the moment.

1. Would you describe V_{peak} as a threshold?

   V_{peak} is not exactly a threshold, it corresponds to the peak value of the spike (not the threshold value at which it is initiated).

3.1 $b > 0$

2. Describe the behavior of the neuron in this case.

   If $b > 0$, then the derivative of V is always strictly positive. This means we will observe periodic oscillations of the neuron. We can compute their period:

$$\begin{aligned} &\frac{\mathrm{d}V}{b + V^2} = \mathrm{d}t \\ \implies &\int_{V_{reset}}^{V_{peak}} \frac{\mathrm{d}V}{b + V^2} = T \\ \implies &\frac{1}{b} \int_{V_{reset}}^{V_{peak}} \frac{\mathrm{d}V}{1 + \left(V/\sqrt{b}\right)^2} = T \end{aligned}$$

With the change of variable $y = V/\sqrt{b}$:

$$\begin{aligned} T &= \frac{1}{\sqrt{b}} \int_{\sqrt{b}V_{reset}}^{\sqrt{b}V_{peak}} \frac{\mathrm{d}y}{1 + y^2} \\ &= \frac{1}{\sqrt{b}} \left[\arctan\left(V_{peak}\sqrt{b}\right) - \arctan\left(V_{reset}\sqrt{b}\right)\right] \\ &= \frac{1}{\sqrt{b}} \arctan\left[\frac{V_{peak} - V_{reset}}{1/\sqrt{b} + V_{peak}V_{reset}\sqrt{b}}\right] < \frac{\pi}{\sqrt{b}} \end{aligned}$$

The last line results from the identity $\arctan(x) - \arctan(y) = \arctan\left[\frac{x-y}{1+xy}\right]$.

In between, starting from a potential V_0 and reaching a potential $V(t)$ at time t, the last relation can be inverted to get the evolution of the membrane potential:

$$V(t) = \sqrt{b} \cdot \tan\left(\sqrt{b}(t + t_0)\right)$$

with $t_0 = \frac{1}{\sqrt{b}} \arctan\left(V_0/\sqrt{b}\right)$.

3.2 $b < 0$

3. Can you characterize the steady states of the neuron? Plot the graph of these steady states against b.

Canceling the time derivative in (7), when $b < 0$ we have two steady states $V_s^{\pm} = \pm\sqrt{|b|}$. Plotting on a graph against b, they describe a parabola.

To study their stability, we can add a small first-order perturbation to each of these values $V = \pm\sqrt{|b|} + \delta^{\pm}$ (linear stability analysis):

$$\frac{\mathrm{d}\delta^{\pm}}{\mathrm{d}t} \approx \pm 2\sqrt{|b|}\ \delta^{\pm}$$

We see that a small perturbation to the $+\sqrt{|b|}$ solution gets amplified whereas one to the $-\sqrt{|b|}$ solution decays to 0: the primer is unstable, the latter is stable.

A totally equivalent but quicker way to get the stability of the steady states is the following:

- *Get the steady state equation, obtained by canceling the derivative in the model equation: $V^2 + b = 0$*
- *Compute the derivative of the left hand side according to the variable you are looking at, here V: $2\,V$*
- *Look at its sign evaluated at the steady states; a positive/negative sign respectively correspond to an unstable/stable steady state: $2\,V_s^{\pm} = \pm 2\sqrt{|b|}$, such that V_s^{+} is unstable and V_s^{-} is stable*

4. Depending on V_{reset} and $b < 0$, what are the different behaviors of the neuron regarding excitation?

We count 3 possible behaviors, as V_{reset} can either be:

- *Strictly lower than $\sqrt{|b|}$: after a reset, the neuron is brought to the stable solution. It is however excitable. A short pulse of current, if strong enough, can drive it above the unstable point and make it spike.*
- *Equal to $\sqrt{|b|}$: after a reset, the neuron in on the unstable point. A tiny current can either drive it to spiking or to stability.*
- *Above $\sqrt{|b|}$: after a reset, the neuron keeps on spiking. However, it can start and remain on the stable point; a strong enough pulse of current would then bring it to oscillatory spiking. As such, the neuron is said to be bistable.*

3.3 Bifurcation diagram

5. Plot the bifurcation diagram of the system, in the V_{reset} and b space.

Regardless of the value of V_{reset}, we have a bifurcation at $b = 0$, which gives a straight vertical line. We have another line for $V_{reset} = \sqrt{-b}$ because it corresponds to a change of behavior, as described in the previous question.

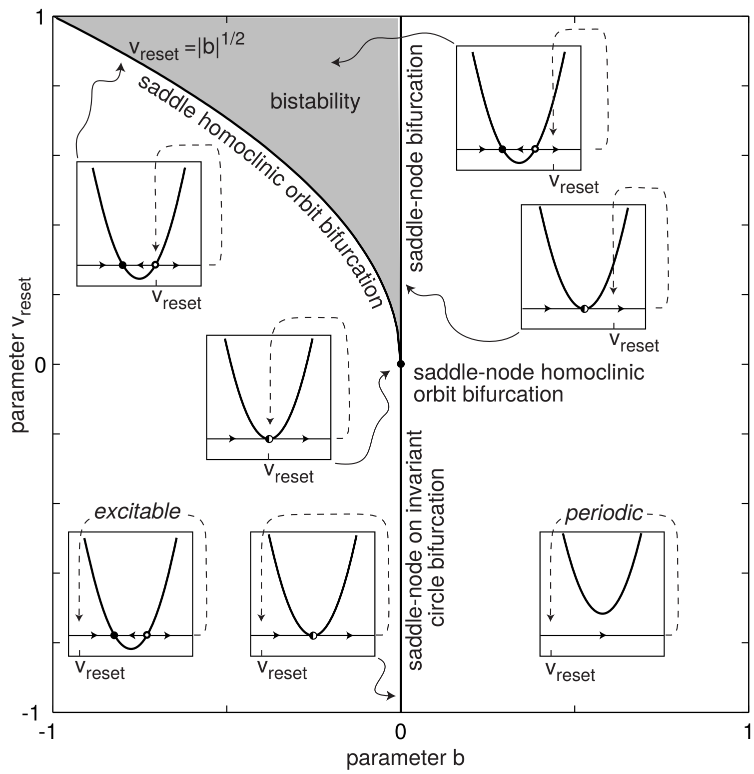

Figure 2: Bifurcation diagram of the QIF model. The insets show the parabola corresponding to the steady-state solutions of (7). V evolves on the horizontal line which moves up and down depending on b. Reproduction from Izhikevich, *Dynamical Systems in Neuroscience.*

6. We consider $V_{reset} > \sqrt{|b|}$. Can you compute the period of the oscillations? We note that the solution of the differential equation in this case is:

$$V(t) = \sqrt{|b|}\,\frac{1+\exp\left(2\sqrt{|b|}(t+t_0)\right)}{1-\exp\left(2\sqrt{|b|}(t+t_0)\right)}$$

with $t_0 = \frac{1}{2\sqrt{|b|}} \log\left(\frac{V_{reset}-\sqrt{|b|}}{V_{reset}+\sqrt{|b|}}\right)$.

Using the previous formula to get the period T to go from $V = V_{reset}$ to $V = V_{peak}$, we find:

$$T = \frac{1}{2\sqrt{|b|}}\left[\log\left(\frac{V_{peak}-\sqrt{|b|}}{V_{peak}+\sqrt{|b|}}\right) - \log\left(\frac{V_{reset}-\sqrt{|b|}}{V_{reset}+\sqrt{|b|}}\right)\right] \tag{8}$$

3.4 Analogy with "theta neurons"

The theta model is described by the following equation:

$$\frac{\mathrm{d}\theta}{\mathrm{d}t} = 1-\cos\theta(t) + [1+\cos\theta(t)]\cdot I(t) \tag{9}$$

We consider that a spike is emitted when θ reaches the value π.

7. Show that for $I < 0$ there are two equilibria for the system, a stable and an unstable one. Show that if θ is not initially equal to the unstable equilibrium, it converges to the stable equilibrium.

   Canceling the derivative in the above equation, we get the steady state equation:

$$\cos\theta = \frac{1+I}{1-I} \tag{10}$$

   If $I < 0$ this equation has two solutions. We obtain the stability by looking at its derivative $-\sin\theta$.

8. In the case $I > 0$, show that there is no equilibrium. Conclude that the trajectories are periodic orbits with regular spiking.

   If $I > 0$, $1 + I(t) > I(t) - 1$, hence the steady state equation has no solution. Because it is positive, we observe periodic orbits.

9. Can you see a link with the quadratic model? What happens when $I = 0$?

   We remark that the change of variable $v = \tan\theta$ transforms the quadratic integrate and fire ODE into the theta neuron equation. At $I = 0$ we have a bifurcation from 2 to 0 equilibrium points.

4 Conductance-based synapses and shunting inhibition

Another interesting phenomenon is shunting inhibition. Experimentally, one can observe that the effects of inhibition and excitation do not necessarily sum in a linear fashion, such that inhibition can "shunt" the effect of excitation. This effect particularly applies with excitatory synapses spanning the dendritic tree and inhibitory synapses closer to the soma.

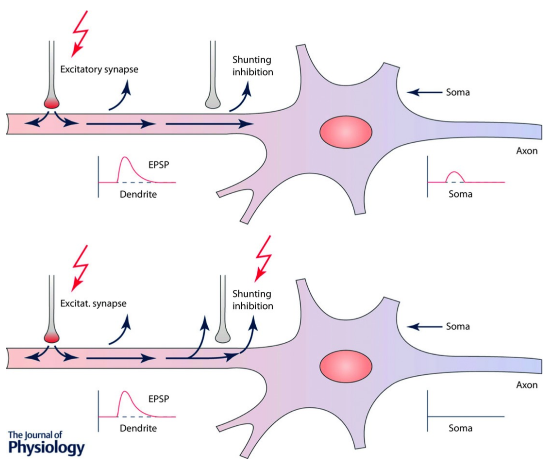

Figure 3: Shunting inhibition.

We consider a neuron well below the threshold for action potential initiation. The neuron is described by its membrane potential $V(t)$ that obeys the equation:

$$C_m \frac{\mathrm{d}V}{\mathrm{d}t} = -g_L(V - V_L) - g_E(t)(V - V_E) - g_I(t)(V - V_I) \tag{11}$$

with:

- C_m the membrane capacitance

- g_L the leak conductance and V_L the resting membrane potential
- $g_E(t)$, $g_I(t)$ the time-dependent excitatory/inhibitory synaptic conductances
- V_E, V_I the excitatory/inhibitory reversal potentials

In real neurons, $V_L \sim -70$mV, $V_I \sim -70$mV or lower, $V_E \sim 0$ mV. For the sake of simplicity we set here the resting potential to be $V_L = 0$mV, and we set $V_I = V_L$.

We consider the situation in which the voltage is $V = 0$ at $t = 0$, and investigate the effects of various combinations of excitatory and inhibitory conductances on the voltage response.

1. Rewrite (11) in terms of the membrane time constant $\tau_m = C_m/g_L$, rescaled conductances $\tilde{g}_E(t) = g_E(t)/g_L$, $\tilde{g}_I(t) = g_I(t)/g_L$, and V_E.

   With $V_L = 0mV$ and $V_I = V_L$, we divide each side by g_L to obtain:

   $$\tau_m \frac{\mathrm{d}V}{\mathrm{d}t} = -\left[1 + \tilde{g}_I(t) + \tilde{g}_E(t)\right] V + \tilde{g}_E(t) V_E$$

2. Show that (11) can be rewritten as:

   $$\tau_{eff}(t) \frac{\mathrm{d}V}{\mathrm{d}t} = -V + V_{eff}(t) \tag{12}$$

   where $\tau_{eff}(t)$ and $V_{eff}(t)$ are functions of τ_m, $\tilde{g}_E(t)$, $\tilde{g}_I(t)$, and V_E.

   Dividing each side by $1 + \tilde{g}_I(t) + \tilde{g}_E(t)$, we obtain the desired equation with:

   $$\tau_{eff}(t) = \frac{\tau_m}{1 + \tilde{g}_I(t) + \tilde{g}_E(t)} \qquad V_{eff}(t) = \frac{\tilde{g}_E(t)}{1 + \tilde{g}_I(t) + \tilde{g}_E(t)} V_E$$

4.1 Excitation only

We consider a situation in which there is no inhibition. The (rescaled) excitatory conductance opens abruptly at $t = 0$, and closes abruptly at $t = \tau_E$,

$$\tilde{g}_E(t) = \begin{cases} 0 & t < 0 \\ g_E & t \in [0, \tau_E] \\ 0 & t > \tau_E \end{cases} \tag{13}$$

3. Compute the response of the voltage (EPSP, excitatory post-synaptic potential) in both intervals $t \in [0, \tau_E]$ and $t > \tau_E$. Sketch qualitatively the shape of the EPSP.

   In both intervals, (12) can be written as a first-order linear equation with constant parameters. We can solve separately on each of these intervals, the solution being:

   $$V(t) = V_{eff} + C \cdot e^{-t/\tau_{eff}}$$

   - *$t \in [0, \tau_E]$: we have $\tau_{eff} = \frac{\tau_m}{1+g_E}$, $V_{eff} = \frac{g_E}{1+g_E} V_E$ and the initial condition $V(t = 0) = 0$, such that:*

     $$V(t) = \frac{g_E}{1 + g_E} \left[1 - e^{-(1+g_E)\,t/\tau_m}\right] V_E$$

   - *$t > \tau_E$: we have $\tau_{eff} = \tau_m$, $V_{eff} = 0$ and the continuity condition $V(t = \tau_E^+) = V(t = \tau_E^-)$, such that:*

     $$V(t) = V(\tau_E^-)\, e^{-(t-\tau_E)/\tau_m}$$

Therefore, V increases to its peak amplitude from $t = 0$ to $t = \tau_E$ and drops back to 0 for $t > \tau_E$ after the excitatory conductance closes.

4. What is the amplitude of the peak of the EPSP? Discuss qualitatively how it depends on g_E, V_E and the ratio of time constants τ_E/τ_m.

   The peak of the EPSP is at $t = \tau_E$:

$$V(\tau_E) = \frac{g_E}{1+g_E}\left[1 - e^{-(1+g_E)\,\tau_E/\tau_m}\right] V_E$$

   It linearly increases with the excitatory reversal potential V_E. Its maximum possible value is $\frac{g_E}{1+g_E}V_E$, and the higher the ratio τ_E/τ_m, the smaller the exponential term is and the closer the peak of the EPSP is to its maximum value. The dependence on g_E is more complicated. At small values of g_E, the prefactor term is roughly linear in g_E, $\frac{g_E}{1+g_E} \sim g_E$ and the exponential term almost does not depend on it. For high values, $\frac{g_E}{1+g_E} \sim 1$ and the exponential term decreases such that we tend to $V(\tau_E) \sim V_E$.

   In other words, a very high excitatory conductance and a longer opening time τ_E compared to the membrane relaxation time τ_m force the neuron to reach its reversal potential V_E.

4.2 Inhibition only

We consider the reverse situation in which there is no excitation, and the (rescaled) inhibitory conductance opens abruptly at $t = 0$, and closes abruptly at $t = \tau_I$,

$$\tilde{g}_I(t) = \begin{cases} 0 & t < 0 \\ g_I & t \in [0, \tau_I] \\ 0 & t > \tau_I \end{cases} \tag{14}$$

5. Compute the response of the voltage (IPSP, excitatory post-synaptic potential). What does it look like?

   In this case we always have $V_{eff} = 0$. Starting from $V = 0$, the membrane potential remains there.

4.3 Both

We now consider the situation in which there is a tonic inhibitory conductance, $g_I(t) = g_I$. The excitatory conductance again opens abruptly at $t = 0$ and closes abruptly at $t = \tau_E$.

6. Repeat the steps of section 1. Compare what happens with and without inhibition. Does the system sum linearly excitatory and inhibitory inputs?

   - *$t \in [0, \tau_E]$: we have $\tau_{eff} = \frac{\tau_m}{1+g_I+g_E}$, $V_{eff} = \frac{g_E}{1+g_I+g_E}V_E$ and the initial condition $V(t=0) = 0$, such that:*

$$V(t) = \frac{g_E}{1+g_I+g_E}\left[1 - e^{-(1+g_I+g_E)\,t/\tau_m}\right] V_E$$

   - *$t > \tau_E$: we have $\tau_{eff} = \frac{\tau_m}{1+g_I}$, $V_{eff} = 0$ and the continuity condition $V(t = \tau_E^+) = V(t = \tau_E^-)$, such that:*

$$V(t) = V(\tau_E^-)\, e^{-(1+g_I)(t-\tau_E)/\tau_m}$$

   The peak of the EPSP now is:

$$V(\tau_E) = \frac{g_E}{1+g_I+g_E}\left[1 - e^{-(1+g_I+g_E)\,\tau_E/\tau_m}\right] V_E$$

Compared to the case in which there is no inhibition, the inhibitory conductance reduces the peak amplitude but also reduces the time constant of the EPSP, such that the system converges faster but to a smaller amplitude value. Interestingly, its effect is not linear on the amplitude but divisive.

If the excitatory conductance is very high compared to the inhibitory one, the effect of inhibition can be neglected. However, we generally have in biological neurons $g_I, g_E \gg g_L$ *and* $g_I > g_E$*. Then* $\frac{g_E}{1+g_I+g_E} \sim \frac{1}{1+g_I/g_E}$*. If* $g_I = a \cdot g_E$*, then the peak amplitude of the EPSP is bounded by* $\frac{1}{1+a}$*. In a neuron, inhibitory inputs can therefore drastically reduce the magnitude of excitatory effects, not linearly as one would expect but multiplicatively.*