M2 Biology **22/10/18**

TD3: Models of Neurons III

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`https://github.com/Elieoriol/2021_UlmM2_ThNeuro/tree/master/TD3`

In the first tutorial, we have developed the most basic model of a spiking neuron: the LIF neuron. In the second one, we have underlined the inability of this model to account for a fundamental property of real neurons that is post-spiking refractoriness, and have developed possible theoretical mechanisms to address this problem. We have also introduced the QIF model, richer in behavior than the LIF one.

In this tutorial we will be interested in the modeling of two more features of biological neurons: adaptation and shunting inhibition.

1 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.

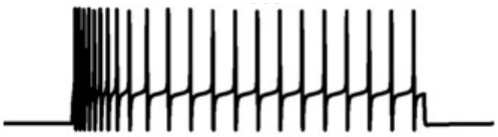

Figure 1: Example of firing rate adaptation in response to an injected current.

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:

$$\tau_m \frac{\mathrm{d}V}{\mathrm{d}t} = -V - W + I \tag{1}$$

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:

$$\tau_w \frac{\mathrm{d}W}{\mathrm{d}t} = -W \tag{2}$$

1.1 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 (1) 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:

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

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

6. Show that W_0 is given by:

$$W_0 = \frac{W_R}{1 - \exp(-T/\tau_w)}. \tag{3}$$

   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:

$$T = \tau_m \cdot \log\left(\frac{I - W_R\tau_w/T}{I - V_{th} - W_R\tau_w/T}\right). \tag{4}$$

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:

$$r(I) \sim aI \tag{5}$$

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.

2 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.

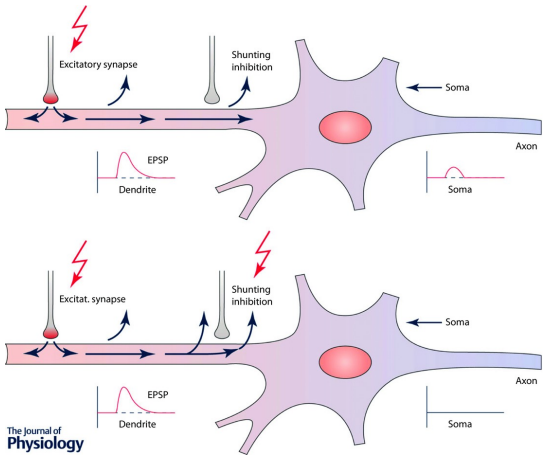

Figure 2: Shunting inhibition.

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:

$$C_m \frac{\mathrm{d}V}{\mathrm{d}t} = -g_L(V - V_L) - g_E(t)(V - V_E) - g_I(t)(V - V_I) \tag{6}$$

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 (6) 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 (6) can be rewritten as:
   $$\tau_{eff}(t) \frac{\mathrm{d}V}{\mathrm{d}t} = -V + V_{eff}(t) \tag{7}$$
   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:
   $$\tau_{eff}(t) = \frac{\tau_m}{1 + \tilde{g}_I(t) + \tilde{g}_E(t)} \qquad V_{eff}(t) = \frac{\tilde{g}_E(t)}{1 + \tilde{g}_I(t) + \tilde{g}_E(t)} V_E$$

2.1 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 $t = \tau_E$,

$$\tilde{g}_E(t) = \begin{cases} 0 & t < 0 \\ g_E & t \in [0, \tau_E] \\ 0 & t > \tau_E \end{cases} \tag{8}$$

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, (7) 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.

2.2 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 $t = \tau_I$,

$$\tilde{g}_I(t) = \begin{cases} 0 & t < 0 \\ g_I & t \in [0, \tau_I] \\ 0 & t > \tau_I \end{cases} \tag{9}$$

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.

2.3 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.