EPFL

Single neuron models: from Hodgkin-Huxley to AdEx

Biological modeling of neural networks
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1 Introduction

The Hodgkin-Huxley model well predicts the behaviour of the membrane potential of a neuron. Nevertheless, it can be extended to include other ion channel types, allowing then to account for more complicated phenomena, for instance the adaptation. Much simpler models have also been created, like the *Adaptive Exponential Integrate and Fire model* (AdEx). While it only considers a reduced number of parameters, it is able to accurately predict the trend of the membrane potential. The goal of this project is to start from the biophysical HH model, which accounts for the adaptation phenomenon, and use different stimulation protocols to extract the right parameters of a simpler AdEx model. In order to do so, some functions of the already implemented libraries `Brian2` and `Neurodynex` have been used as starting point.

2 Exploration of Hodgkin Huxley neurons

2.1 Getting started

First of all, we set up the HH neuron we want to stimulate, starting from the implementation of the standard HH neuron model present in the `Neurodynex` library. Since we want to account for adaptation, we need to modify this model by adding one more ion channel, so that we end up with two models: the standard one, described through the function `simulate_HH_neuron_regular()`, which has only Na and K ion channels, and the adaptive one, with the function `simulate_HH_neuron_adaptive()`, which in addition considers a slow non-inactivating K ion channel. The parameters have been set as in [2].

Each parameter should be initialized in order to avoid transients at the beginning of the stimulation. Both neurons have been stimulated with no input current for a long period of time in order to find the stable points of all the variables. We report below the initial values yielding stable behaviours for both models.

For the regular spiking neuron: $v_{m,0} = -70\ mV$, $m_0 = 0.00167$, $h_0 = 0.9996$, $n_0 = 0.0065$.

For the adaptive neuron: $v_{m,0} = -70.6074\ mV$, $m_0 = 0.00145$, $h_0 = 0.99972$, $n_0 = 0.00584$, $p_0 = 0.04475$.

2.2 Rebound spike

The rebound spike is a feature not shared by all neurons. It consists in the emission of a spike when a hyper-polarizing current is injected into the neuron. In our case, the regular spiking neuron that we are considering does not exhibit any rebound spike (see Figure 1).
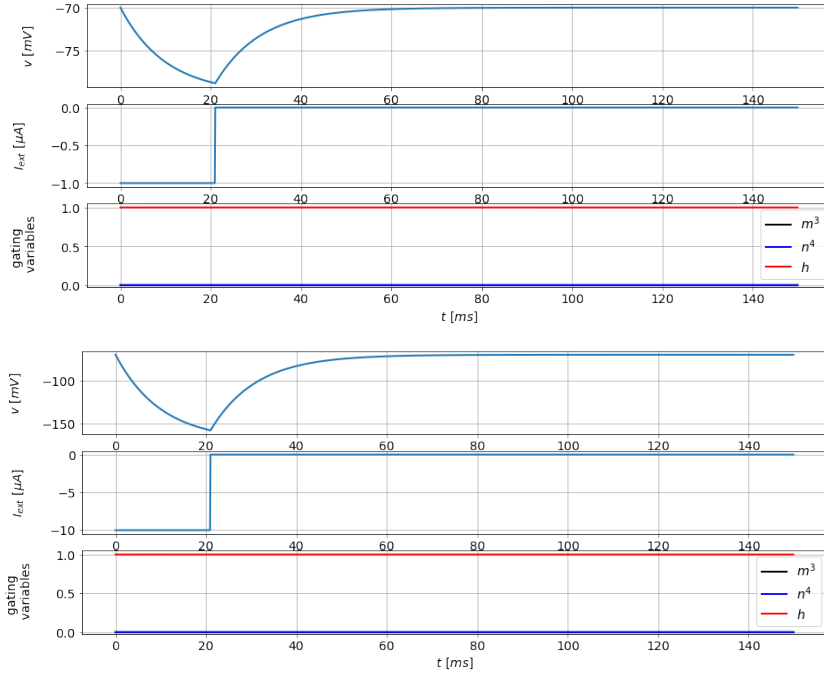

Figure 1: Membrane potential v_m, external current $I_{ext} = -1\mu A$ (above) and $I_{ext} = -10\mu A$ (below), and gating variables m^3, n^4, h. No rebound spike.

In Figure 2, we report the behaviour of the channel gating variables, their limit values, and their time scale. It is clear from these plots that they do not allow the neuron to fire if a large negative external current is injected. The values of the gating variables at infinity and their time constants are obtained by rearranging the equations in [2], until obtaining the expressions in (1).

$$\frac{dx}{dt} = \frac{x_\infty - x}{\tau_x} \qquad x_\infty = \frac{\alpha_x}{\alpha_x + \beta_x} \qquad \tau_x = \frac{1}{\alpha_x + \beta_x} \qquad x \in \{m, n, h\} \tag{1}$$
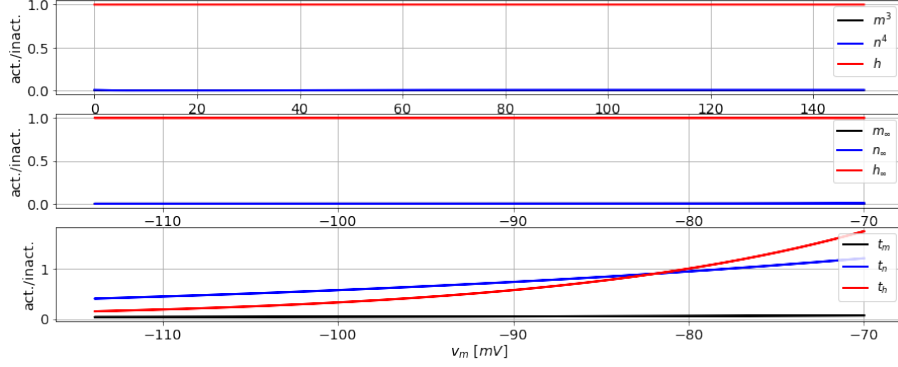

Figure 2: Regular neuron stimulated with $I_{ext} = -5\mu A$. Plot of the gating variables m^3, n^4, h, their limit values m_∞, n_∞, h_∞ and time constants τ_m, τ_n, τ_h. No rebound spike.

The hyper-polarizing current forces the membrane potential to become very negative. Under these conditions, the values of the gating variables at their limit m_∞, n_∞ and h_∞ remain constant. At the same time, the respective time constants τ_m, τ_n and τ_h are all very small and have the same order of magnitude. They can therefore be considered as fast variables: when not in a situation of rest, they instantaneously tend to their limit value. When the input current is released (i.e back to 0 A), the membrane potential is still very negative, so that the limit values of the gating variables are not modified, and the channels' apertures do not vary either. However, the change in the membrane potential does enforce a change of the gating variables. All together and at the same speed, they bring the potential to rest, preventing it from creating a spike through the opening/closure of only one channel before the others. The fact that all the gating variables are fast variables in this case is determinant. In a regular case, the smaller time scale of the m variable is what allows the spike emission.

In Exercise 5 a similar neuron has been studied. However the equations implemented were different than the ones used here. Consequently, the two neurons behave differently. Most notably, the neuron in Exercise 5 exhibited a rebound spike. In this case, when the hyper-polarizing current is injected, the membrane potential gets very close to the reversal potential of Potassium E_K, so that the Potassium current I_K is very small, while I_{Na} is very big and negative. In this situation, the time constants of the gating variables have different values: τ_m is very small, so that m can be considered a fast variable. On the contrary, τ_n and τ_h are big so that n and h are slow variables. Therefore, when the injected current is back to 0 A, m suddenly changes the aperture of the Sodium channel and the neuron fires, while the other variables slowly open and close the other channels.

2.3 Adaptation

We now focus on the adaptive neuron, trying to understand the role of the new ion channel I_M. In order to do so, a stimulation of this neuron is performed with a step current of 2.0 μA for 1500 ms. To be able to catch the differences between this neuron and the regular one, we stimulate also the latter in the same way, so that we can compare their behaviours.

As seen in Figure 3, the regular spiking neuron has a constant firing rate, meaning that the time period between two adjacent spikes is the same during the whole simulation. On the contrary, the adaptive neuron shows an increasing time interval between the emitted spikes. Its firing rate is thus decreasing with the time of the stimulation. This is caused by the presence of I_M which allows the neuron to 'adapt' to the stimulus. Looking at the plot of the time constant τ_p with respect to the voltage, it is clear that at the moment of the spike, τ_p is very small, implying a fast change of p. Right after the spike, τ_p becomes large, corresponding to a slow increase of I_M. Consequently, the increase of the membrane potential is lower than in the absence of I_M. The time needed before the emission of the next spike is thus larger, translating into a lower firing rate.
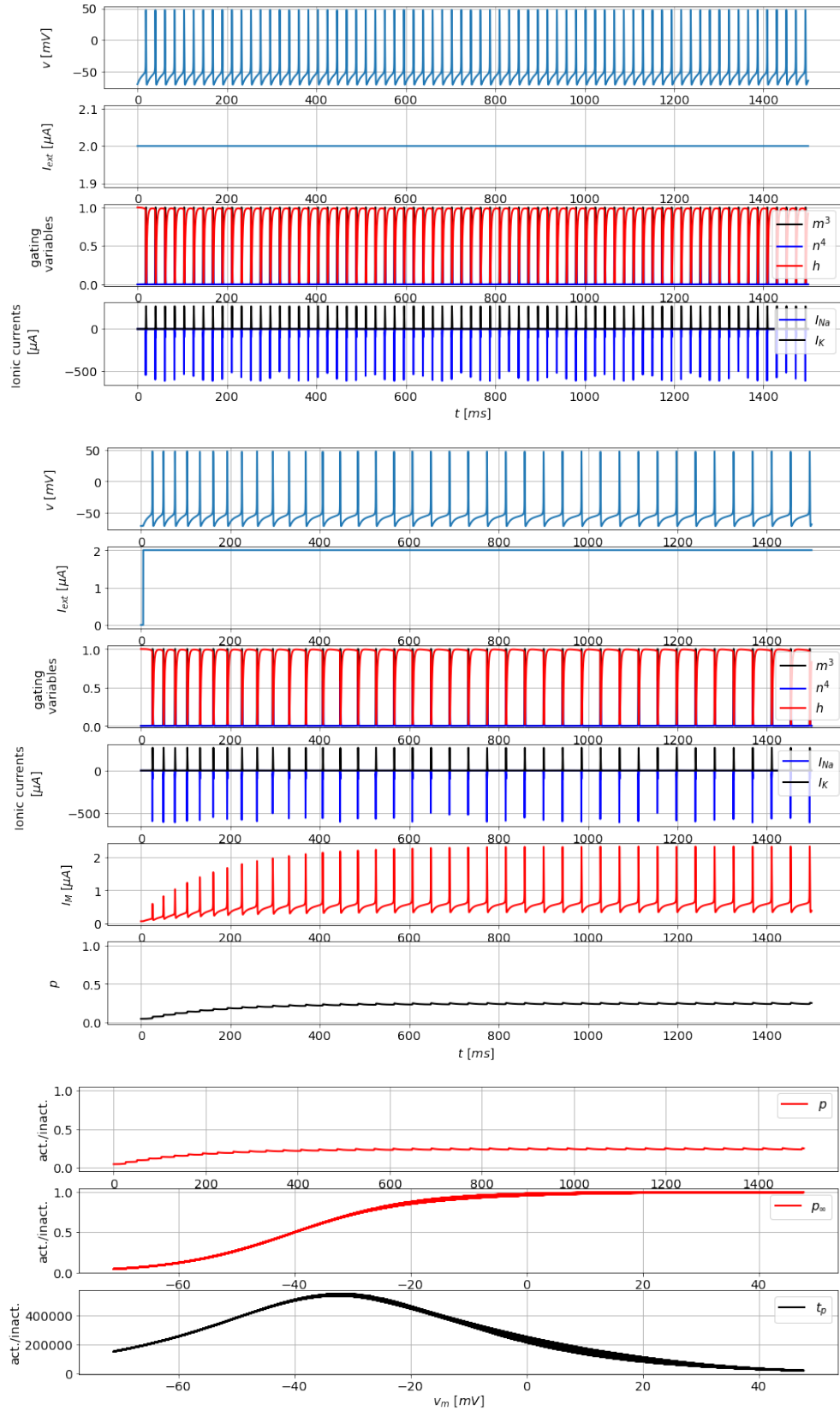
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Figure 3: Stimulation of the regular (above) and adaptive (below) neurons with a current $I_{ext} = 2\mu A$ and plot of the gating variables of the adaptive neuron.

In order to clearly show this particular behaviour of the adaptive neuron, a new figure called *Adaptive behaviour* is introduced (Figure 4). By extracting the spike timings from the plot of v_m of the adaptive neuron, it is possible to calculate the time interval between consecutive spikes as a function of time. Consequently the firing rate of the neuron can be found and plotted as a function of the simulation time.

When the external current is injected, the neuron starts emitting spikes with a 'high frequency', so that the firing rate suddenly goes from zero to an high value. Then the adaptation increases the time between consecutive spikes, so that they are emitted less often and the frequency is lower. We can indeed see that the curve is decreasing. If a threshold is fixed, it is also possible to find a specific value of the firing rate that can be considered stable, reached at a precise time during the simulation. This value is calculated by looking at the variation of the firing rate between two consecutive time steps. When the difference becomes lower or equal than the threshold, we consider that the stable firing rate has been reached.

Using this figure as reference, we can experiment with the parameters I_M, p_∞ and τ_p, and modify them to affect the behaviour of the neuron in different ways.

- Slow down the adaptation rate. This means that the neuron will take more time to reach a stable firing rate, i.e the decrease of the firing rate is slower. If the time constant of the variable p is bigger, p itself is a slower variable. As a consequence, the K channel opens/closes more slowly. Thus, I_M has a smaller impact and the firing rate takes more time to stabilize. The only parameter that has been changed in this case is thus τ_p. The following expression is obtained (the modification is shown in blue).

$$\tau_p = \frac{5000}{3.3 \exp((V + 20)/20) + \exp(-(V + 20)/20)} \tag{2}$$

- Decrease the stable firing rate without changing the adaptation rate. Starting again from the original model, we want to obtain a lower stable rate, but reached in the same amount of time as before. Two parameters need to be changed: p_∞ and τ_p. The first parameter allows p to tend to a higher value, which means it accounts for a larger aperture of the I_M channel. This then increases the impact of I_M on the membrane potential so that, by following the same explanation about the mechanism that governs I_M and the adaptive neuron given before, the firing rate decreases. However, this modification also leads to a decrease of the adaptation rate, i.e the stable firing rate is reached faster. In order to avoid this, we can modify the time constant of p. Indeed, decreasing it makes the process faster, compensating the effect of reaching a higher value of p_∞. More generally, if we want to reach a higher value in the same amount of time, the process needs to be faster.

$$p_\infty = \frac{1}{\exp(-0.1(V + 45)) + 1}$$
$$\tau_p = \frac{1500}{3.3 \exp((V + 20)/20) + \exp(-(V + 20)/20)} \tag{3}$$

- Reverse the adaptation. We want the stable firing rate to be higher than the initial firing rate. In order to do so, we add a negative sign to the equation of I_M. In this way this current goes in the opposite direction and brings the membrane potential always farther away from the resting potential E_K. Indeed it becomes larger. Consequently the spikes are generated in smaller time and the firing rate becomes higher.

$$I_M = -\overline{g_M}\, p\,(V - E_K) \tag{4}$$

3 From HH to AdEx

In this section, we focus on the extraction of the parameters needed to describe the reduced AdEx model from the adaptive neuron. We assume that the HH adaptive neuron studied so far is the biological neuron used in experiments, i.e the 'ground truth', and look at the plots as if they were the experimental data. This procedure is inspired by [1].

3.1 Passive properties

First of all, the passive membrane parameters C, g_l, E_l, τ_m, R, need to be extracted using different stimulation protocols.
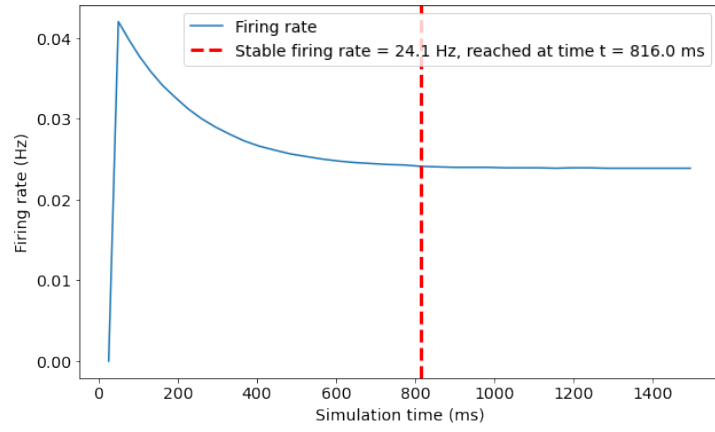
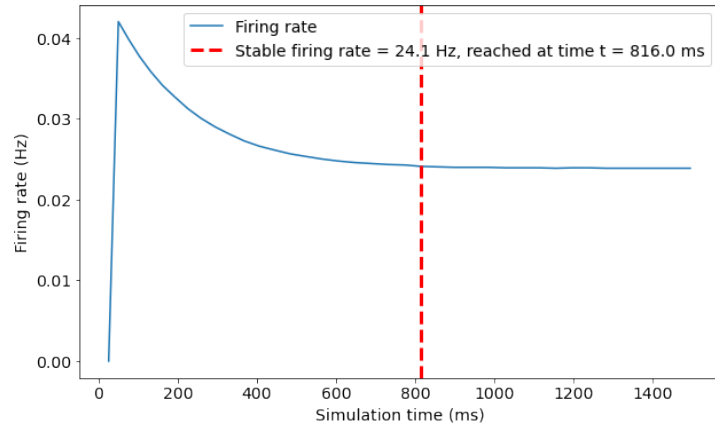Figure 4: Normal behaviour ($I_{ext} = 2\ \mu A$)

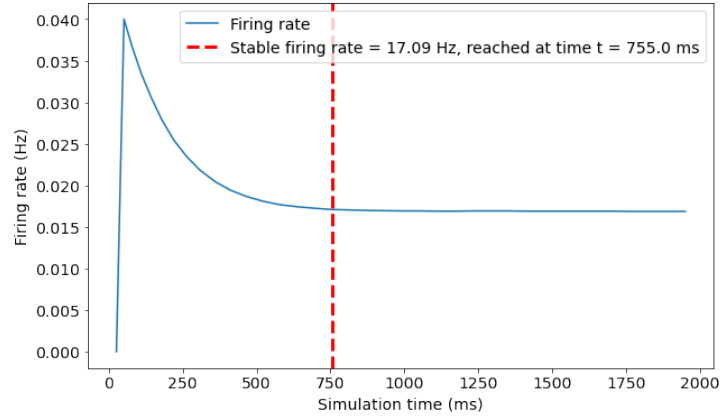Figure 5: Slower adaptation ($I_{ext} = 2\ \mu A$)

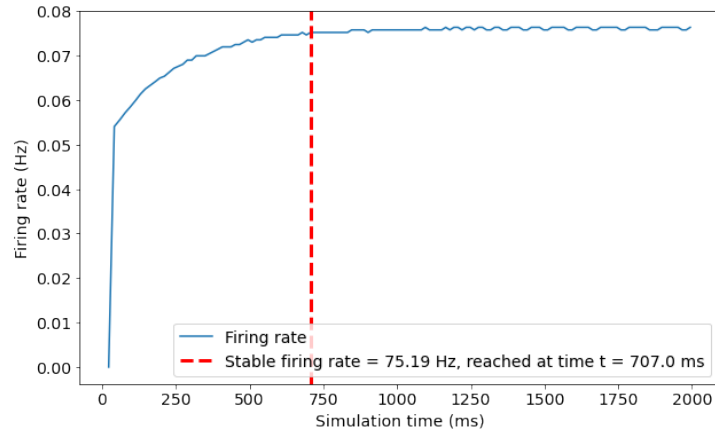Figure 6: Decreased stable firing rate ($I_{ext} = 2\ \mu A$)

Figure 7: Reversed adaptation ($I_{ext} = 2\ \mu A$)

- τ_m: it is the time constant of the neuron when modeled as a circuit. We need to inject a pulse current into the neuron of value 1 μA, so that it doesn't fire. As a consequence, we can see the exponential decay, typical of an RC circuit. Looking at the membrane potential, we can find the moment in time where the difference between the membrane potential and the resting potential reaches 1/3 of the difference between the maximum value of the membrane potential and the resting potential. Subtracting the spike timing from it (so the time when the potential is maximum), we get the value of τ_m.

$$\tau_m = 11.3 \ ms \tag{5}$$

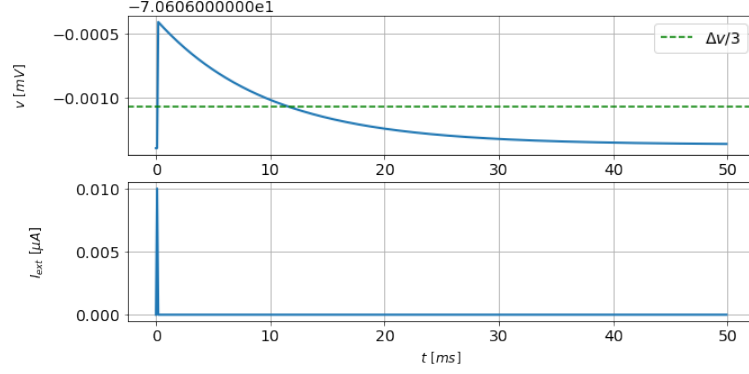Figure 8: Membrane potential of the adaptive neuron when it has been stimulated with a current of $I_{ext} = 1\mu A$. Where $\Delta v = v_{rest} - v_{max}$

- C: it is the capacity of the neuron when modeled as an RC circuit. It can be calculated using the same stimulation protocol as before and plugging in the equation:

$$\frac{1}{C} = \frac{v_{max} - v_{rest}}{I} = \frac{-70.60640451 \ mV + 70.6074 \ mV}{10 \ nA} \iff C = 1.004 \ \mu F \tag{6}$$

- R: it is the resistance of the membrane, when, once again, the neuron is modeled as an RC circuit. It can be calculated through the relation that links together the time constant τ_m, the capacity C and the resistance itself. From the previously found values:

$$\tau_m = RC \iff R = \frac{\tau_m}{C} = \frac{11.3 \ ms}{1.004 \ \mu F} = 11248.9 \ \Omega \tag{7}$$

- g_l: it is the conductance of the leak channel. It can be calculated from the relation between resistance and conductance. In this case the resistance R calculated before corresponds to the resistance of the leak channel, so that the following result is found, through the data already collected.

$$g_l = \frac{1}{R} = \frac{1}{11248.9 \ \Omega} = 88.89 \ \mu s \tag{8}$$

- E_l: it is the reversal potential of the leak channel. If we assume that the currents I_{Na}, I_K, I_M are zero then the derivative of the potential is zero when $V = E_l$, meaning that the neuron is at rest.

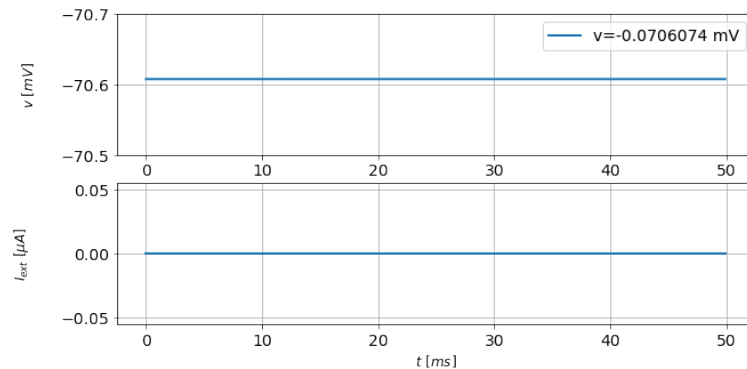$$E_l = v_{rest} = -70.6074 \ mV \tag{9}$$

Figure 9: Membrane potential of the adaptive neuron when it is at rest, $I_{ext} = 0\mu A$.

3.2 Exponential Integrate and Fire

We now want to extract the parameters θ_{rh} and Δ_T present in the AdEx model, from the HH adaptive neuron. In order to do so, we sketch the function $f(V)$ which describes the non-linear membrane dynamics without adaptation current and set $I_{ext} = 0$ A.

$$C\frac{dV}{dt} = f(V) = -g_l\,(V - E_l) + g_l\Delta_T e^{\frac{V - \theta_{rh}}{\Delta_T}} \tag{10}$$

From this equation, we see that this function corresponds to the first derivative of the membrane potential V with respect to time. It therefore describes how the potential changes in time and it is a function of V itself. We note that the value of I_{ext} shifts the function upwards or downwards, depending on its sign. We sketch in Figure 10 its form for a zero external input current.
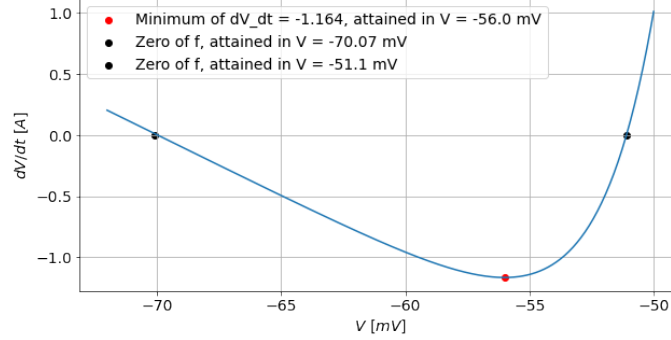

Figure 10: Function $f(V)$ (10), with the membrane potential in the range between v_{rest} and the threshold. The external current has been set to 0 μA.

The different values of I_{ext} give rise to three different situations.

1. If I_{ext} is positive and large enough, $f(V)$ is always positive, and so is $\frac{dV}{dt}$. Therefore, the membrane potential will continuously grow. From the form of f's profile, the increase will be very fast at first, then steadily decrease to a lower value, before going up again.

2. If I_{ext} is positive and has the exact value to allow $f(V)$ to have only one zero, the membrane potential will reach a value for which its derivative in time is 0, so that it will stop changing.

3. Finally, if I_{ext} is negative, or not big enough to shift the minimum of f on the x-axis, $f(V)$ has two zeros. One of them (the lowest one) is a stable fixed point of V, while the other is unstable. The membrane potential will stop changing its value after reaching the first zero.

From this analysis, we can deduce that if the minimum of this function is only slightly larger than zero, the dynamics of V are like in the first situation, but it reaches a very slow rate of change when its derivative is minimal. When the membrane potential starts evolving from its resting value, it first increases rapidly, then continues increasing but with an always lower speed, until it almost reaches a constant value. Then, the rate of change gets steadily higher, until the potential reaches the firing threshold. In this case, the neuron enters a regime of repetitive firing.

We now want to bring our adaptive neuron in this situation: we have to find a step current I_{ext} yielding similar dynamics for the membrane potential, using our previously defined `simulate_HH_neuron_adaptive()` function. Setting $I_{ext} = 2\mu A$ gives a membrane potential pattern as in Figure 11, which is exactly what we were looking for.

We now want to find the value of θ_{rh}. By taking the first derivative of $f(V)$ with respect to V, we see that the minimum of the function is in θ_{rh}.

$$\frac{df(V)}{dV} = -g_l + g_l\,\Delta_T\,\frac{1}{\Delta_T}\,e^{\frac{V - \theta_{rh}}{\Delta_T}} = -g_l + g_l\,e^{\frac{V - \theta_{rh}}{\Delta_T}} = 0 \Longleftrightarrow V = \theta_{rh} \tag{11}$$

From the above-conducted analysis, we therefore have to find the value of the membrane potential for which its derivative is minimal. In order to numerically do so, we compute the derivative of the membrane potential using the Forward Finite Differences scheme. It is shown in Figure 12. The minimum of the function is attained for $V = -56$ mV, which means that we can set $\theta_{rh} = -56$ mV.
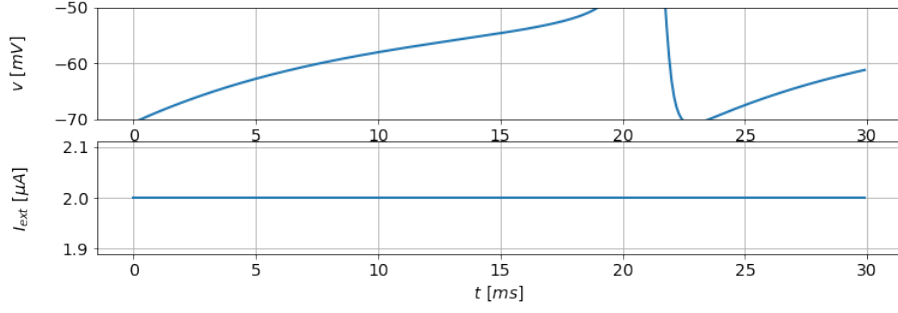
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Figure 11: Stimulation of the adaptive neuron with $I_{ext} = 2\mu A$. Plot of membrane potential and external current as a function of time t $[ms]$
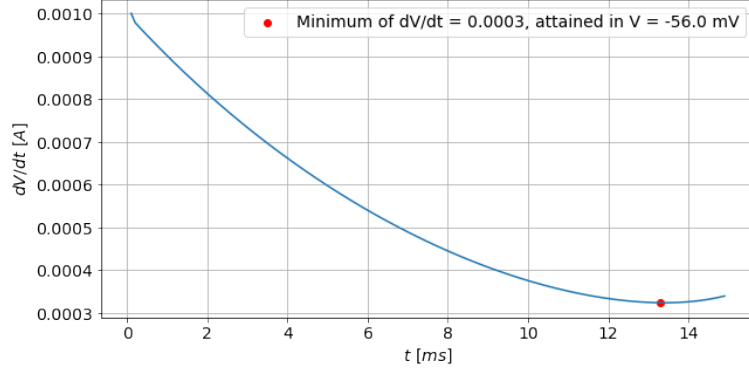

Figure 12: First derivative of the membrane potential shown in Figure 11 between the resting potential and the threshold. It is calculated through Forward Finite Differences.

The function $f(V)$ has two zeros, one at E_l and the other one at V_S. In order to find the value of V_S, a precise stimulation protocol is required. V_S is the maximum voltage reached by the membrane potential without emitting a spike. Indeed, it is the unstable zero of $f(V)$, and this implies that when we are in the vicinity of that point, different behaviours can occur: the neuron can either spike or go back to the resting state without firing. If we are on its left side, the dynamics make the potential go down to the resting state without emitting a spike. On the other hand, if the input current is large enough to bring the membrane potential on the right side of the unstable point, the potential keeps increasing until the neuron fires. Thus, we stimulated the neuron with short current pulses of 1 μs and different amplitudes. We found that the higher value of I_{ext} that doesn't make the neuron fire is $I_{ext} = 197.011$ μA and the higher value reached by the membrane potential is $V_S = -51.0075$ mV.

Finally, we want to estimate the value of the parameter Δ_T. In order to do so, we plug the values of θ_{rh} and V_S inside the expression of $f(V)$ and solve for $f(V_S) = 0$.

$$f(V_S) = 0 \iff -g_l(V_S - E_l) + g_l\Delta_T e^{\frac{V_S - \theta_{rh}}{\Delta_T}} = 0 \tag{12}$$

The only unknown in this equation is Δ_T, and it can take two values, corresponding to the two roots of 12. We found them by using the tool `scipy.optimize.fsolve()` function. The solutions are shown as functions of the initial guess in Figure 13.

From this, we can use the value of the smallest root as an estimate of Δ_T, and thus set it to 2.3570250 mV.

Figure 10 is actually the right behaviour of $\frac{dV}{dt}$, using the values found above for Δ_T, θ_{rh} and g_l.

3.3   Subthreshold adaptation

We now focus on the estimation of the parameter a in the AdEx model. When the voltage dynamics are slow enough and far from the threshold, the terms $\frac{dV}{dt}$, $\frac{dw}{dt}$, $e^{\frac{V - \theta_{rh}}{\Delta_T}}$ are almost zero, so that they can be neglected. Consequently, the equations simplify into the following.

$$I_{ext} = (a + g_l)(V - E_l) \tag{13}$$

From this equation, a direct linear dependence between the external current and the voltage can be seen, so that by stimulating the neuron with a ramp current of 10 s (which goes from 0 μA to 1.2 μA), it is possible to extract the parameter a. Indeed the I_{ext} versus V curve is a very straight line, so that a can be easily expressed as in (14).

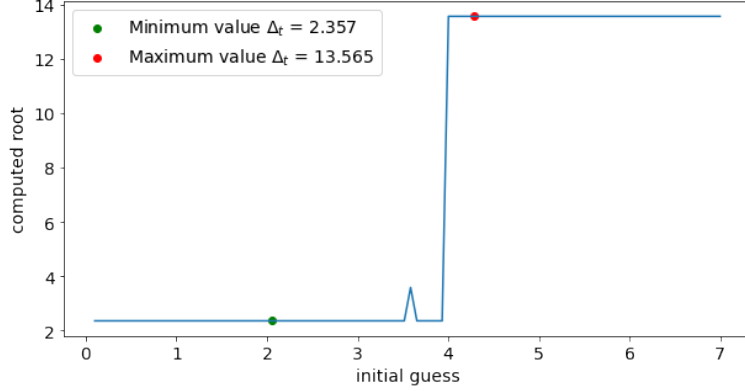$$a = \frac{I_{ext}(10s) - I_{ext}(0s)}{V(10s) - V(0s)} - g_l = 15.733 \ \mu S \tag{14}$$

Figure 13: Best solution of Equation (12) found through the tool `scipy.optimize.fsolve`, as a function of the initial guess.

3.4 Remaining parameters

Only the last three parameters remain to be estimated: b, τ_w, V_{reset}. We can tune them by hand in order to match as best as we can the spike timings of the HH adaptive neuron. Here, we are only interested in the prediction of the spike trains through the AdEx model, and not in the subthreshold voltage behaviour. Therefore we set, as suggested, a firing threshold of 30 mV and stimulate both the HH adaptive neuron and the AdEx neuron with a step current of 2 μA for 1500 ms.

Looking at the *Adaptive behaviour* figure created before, we can get an intuition of the role of these parameters inside the model.

- b defines the jump that the current w makes every time a spike is emitted. Consequently, it affects the time needed by the neuron to reach the stable firing rate. If b is large, then the adaptation is fast. Adaptation being a complex process, this parameter also affects the value of the final stable firing rate of the process.

- τ_w is the time constant of the adaptation current w. It then governs the speed of the dynamics of w. In particular, if the time constant is large, the adaptation current needs more time to act on the membrane potential, so that the adaptation process is slow and the stable firing rate reached is also low.

- V_{reset} is the value of the membrane potential after the emission of a spike. It affects the time that the neuron needs to recover after a spike. In particular its influence is evident in the first emitted spikes, when the adaptation current is not acting completely on the neuron. If the modulus of V_{reset} is small, the first spikes are emitted very fast and the firing rate at the beginning of the stimulation is very high.

In order to understand if the spike timings predicted by the AdEx neuron are accurate, we need to compare them with the ones produced by the adaptive neuron. The best values we have found for the remaining parameters are the followings. The relative overlapped firing rates and voltage traces for the two models are shown in Figure 14.

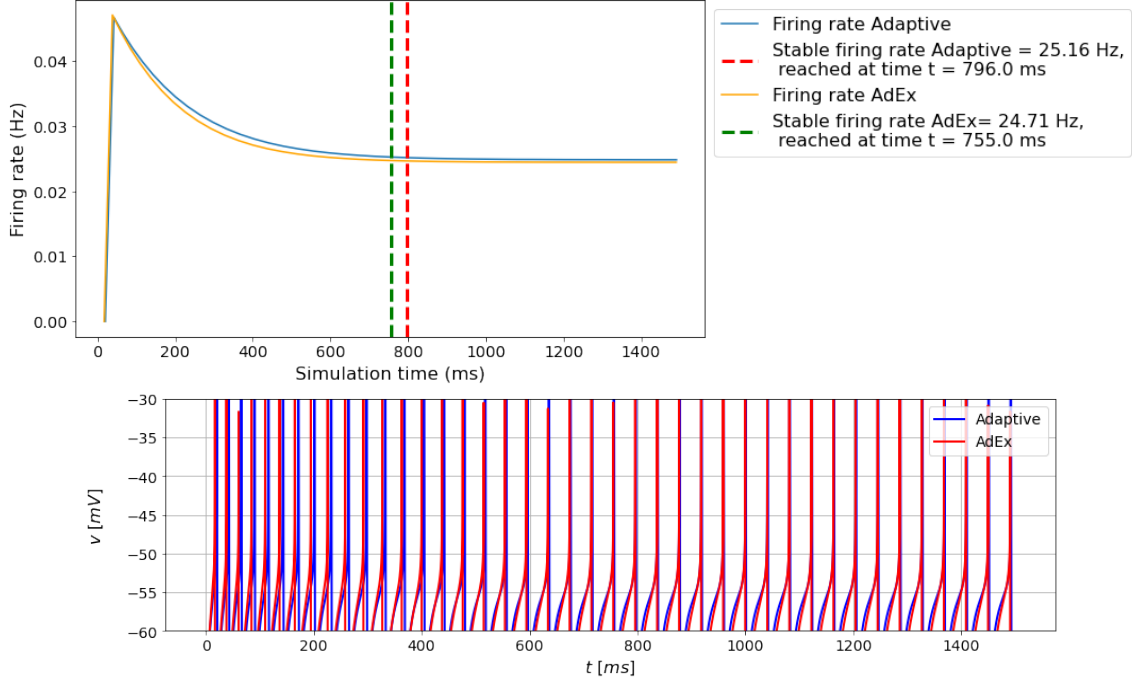$$V_{reset} = -77.45 \ mV \quad b = 0.06775 \ \mu A \quad \tau_m = 281.32 \ ms \tag{15}$$

Figure 14: Overlap of *Adaptive behaviour* figures and voltage traces of AdEx model with parameters as in (15) and HH adaptive neuron model.

3.5 Testing on random input

As a final test of the accuracy of the model, we stimulate it with a Gaussian random current I_{ext} with mean $\mu = 1\ \mu A$ and standard deviation $\sigma = 15\ \mu A$ for a duration of $500\ ms$ and $2500\ ms$. We then compare its behaviour to the adaptive HH model's with the same stimulation. The random Gaussian input currents are generated through the `numpy.random.randn()` function.

First we inject a $500\ ms$ current. The results are shown in Figure 15. As we can see, both the firing rate and voltage traces follow the same trends for both models, even though some spikes are missed by the AdEx model around $t = 200\ ms$, which then results in a lower firing rate. Since we are using a random noisy Gaussian input current, this is a good sign that the two models are in fact different implementations of the same phenomenon.

The same experiment is repeated with a Gaussian random current with a duration of $2500\ ms$. See Figure 16. Once again, the trends are quite similar, up to imprecision errors in the computation of the firing rate. This validates the correctness of our implementation of the AdEx model, as an alternative to the HH adaptive model.

4 Conclusions

In this project, we started from the basic implementation of the Hodgkin-Huxley neuron model to study spike emissions. Then, we expanded this model with an additional current to take into account the adaptation phenomenon. We studied the parameters of this model and described the various situations that they govern. From there, we moved on to the Adaptive Exponential Integrate and Fire model, a simpler tool expressed as a combination of two equations on the membrane potential and an adaptation current. We compared this model to the adaptive HH and derived its parameters in order to match their behaviours. Finally, we assessed its correctness by running simulations involving random noisy currents and comparing the results with the adaptive HH.

While the results are definitely satisfactory, a few improvements could be made, mainly regarding the accuracy of the spike predictions. For instance, the way the firing rate computation is implemented could be made more precise, and the current assessment of its stability is a bit subjective. Nevertheless, we believe that this does not impact the correctness of this work, and its goal, which was to compare two adaptation neuron models, has successfully been attained.
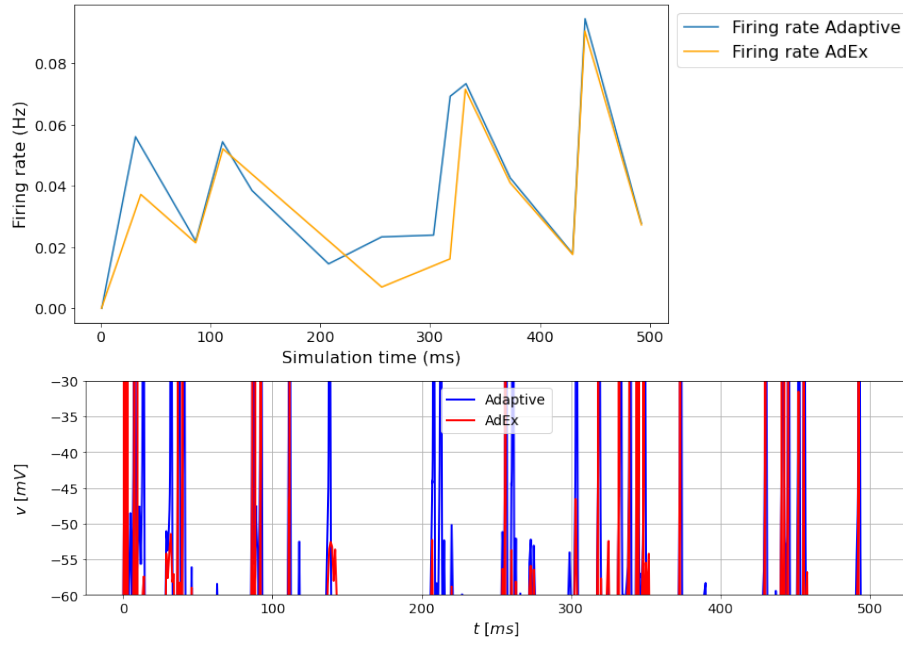
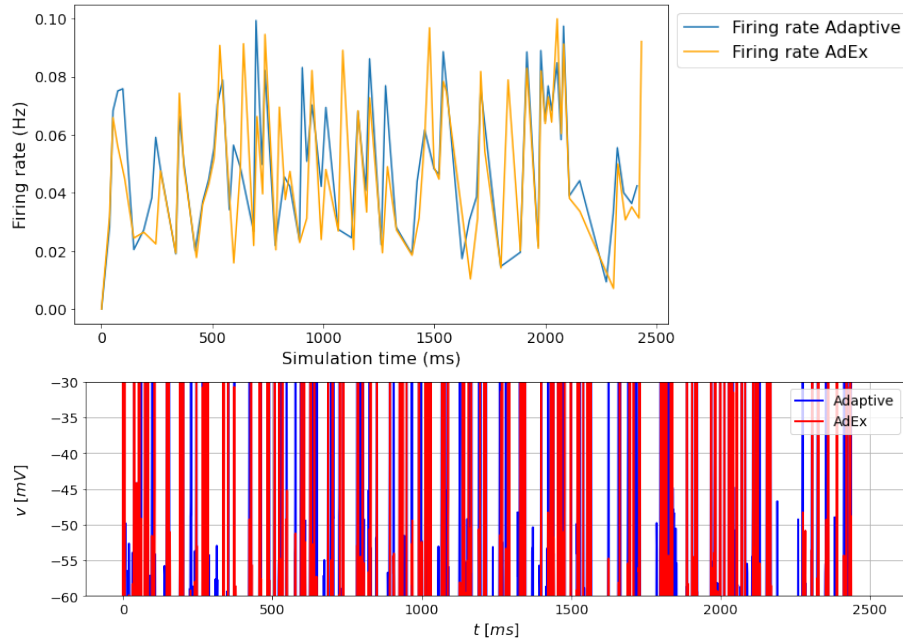Figure 15: Firing rate (above) and spike timings (below) for a stimulation with a random Gaussian current of 500 ms.

Figure 16: Firing rate (above) and spike timings (below) for a stimulation with a random Gaussian current of 2500 ms.

References

[1] R.Brette and W.Gerstner. *Adaptive exponential integrate-and-fire model as an effective description of neuronal activity*, Journal of neurophysiology, 94(5):3637–3642, 2005.

[2] M.Pospischil, M.Toledo-Rodriguez, C.Monier, Z.Piwkowska, T.Bal, Y.Frégnac, H.Markram, A.Destexhe, *Minimal hodgkin–huxley type models for different classes of cortical and thalamic neurons*, Biological cybernetics, 99(4):427–441, 2008.