Single neuron models: from Hodgkin-Huxley to AdEx

Spring semester 2022

Read the general instructions carefully before starting the mini-project.

Biological neurons come with a high number of various ion channels and their electrophisiological properties can be accurately modelled by the Hodgkin-Huxley (HH) equations; but extracting parameters for every channel is a substantial effort (e.g. see Channelpedia or ICGenealogy). Moreover, simulating networks of HH neurons is computationally expensive. Threshold neuron models such as the Adaptive Exponential Integrate and Fire (AdEx) are much simpler models that can capture most of the relevant membrane potential behaviours.

In this project, you will explore HH models with more than the 2 ion channels we have seen in the lecture and exercises. These additional channels allow for more complicated behaviour of the membrane potential, you will be asked to implement and comment on the various effects each channel has. Next, you will perform stimulation protocols on the biophysical HH models, as an experimentalist would do on real neurons, to extract the parameters of the simpler AdEx model.

0 Review of the models

We will start with single compartment HH neurons with different ionic currents:

$$C\frac{dV}{dt} = -g_l(V - E_l) - I_{Na} - I_K - I_M + I_{ext} \tag{1}$$

where $C = 1\mu F, g_L = 0.1mS, E_L = -70mV$ and I_{ext} is the external injected current. The specific parameters for the different ion channels are found in section 3.

The AdEx model is described by two coupled differential equations:

$$\begin{aligned} C\frac{dV}{dt} &= -g_l(V - E_l) + g_l\Delta_T e^{\frac{V-\theta_{rh}}{\Delta_T}} - w + I_{ext} \\ \tau_w\frac{dw}{dt} &= a(V - E_l) - w \end{aligned} \tag{2}$$

where θ_{rh} is called the rheobase voltage.

As we have seen in the lecture, this model is an exponential Leaky Integrate and Fire (eLIF) combined with an adaptation current w. Every time V reaches a threshold V_T the neuron spikes and the two variables are updated as such:

$$\begin{aligned} V &\to V_{Reset} \\ w &\to w + b \end{aligned} \tag{3}$$

1 Exploration of Hodgkin Huxley neurons

1.1 Getting started

As a starting point, take the implementation of the Hodgkin Huxley function from Neurodynex and modify it with the parameters of the channels given in section 3. Write a function for the *regular_spiking* HH model with only I_{Na} and I_K ionic currents and one for the *adaptive* HH model with currents I_{Na}, I_K, I_M.

In order to avoid initial transient at the beginning of the simulation, find the stable points of each variable by simulating the neuron with no input current. Some variables are slower than others: make sure to simulate for long enough. You can add these stable values as parameter initialization.

Tips: Make sure to add to the `StateMonitor` object the channel variables (i.e $m, n, ...$) and the ionic currents (I_{Na}, $I_K, ...$) so that you will be able to access them via e.g. `st_mon.I_Na`. Good plotting substantially helps in understanding your simulations, improve the `plot_data` function by: 1. Making it bigger, too many traces in a small figure are hard to read! 2. Adding subfigures: one for the additional channel parameter (p) and one or two for ionic currents.

1.2 Rebound spike?

This *regular_spiking* neuron doesn't have rebound spikes, show that this is true with some stimulation protocols and explain why by plotting the channel gating variables x_∞, τ_x vs. V for $x \in \{m, n, h\}$.

Tip: what changed with respect to the neuron of exercise 5?

1.3 Adaptation

- Stimulate the *adaptive* neuron with a $2.0\mu A$ current for $1500ms$ and plot the resulting voltage trace, gating variables and ionic currents. Describe the role of the new channel I_M. How does p change over time? What is its effect on the membrane potential?
- Write a function that extracts the spike timings from the voltage trace, use it to come up with a figure titled *Adaptive behaviour* that shows the adaptive behaviour of the neuron; explain and label what you put on the x and y axis of the plot.
- With the help of the figure you created above, modify the parameters of I_M, p_∞, τ_p to:
  - Slow down the adaptation rate, i.e. the neuron takes more time to reach a stable firing rate;
  - Decrease the stable firing rate without changing the adaptation rate;
  - Reverse the adaptation: stable firing rate lower than initial firing rate.

  Report both the *Adaptive behaviour* figure, the resulting voltage traces and the new parameter values for the three cases.

Tip: For the *adaptive behaviour* figure you should come up with a measure that allows you to read all the points discussed above

Warning: Copying the many equations of the ion channels is very prone to typos, in section 4 there are figures for stimulation protocols of both neurons, check if your code gives similar results. You can also take inspiration from this figure to modify the default one of neurodynex ;)

2 From HH to AdEx

In this exercise you will perform different stimulation experiments on the *adaptive* HH neuron to tune an AdEx model to match the behaviour of the biophysical HH model. The parameter extraction is partly inspired by the original AdEx paper [1]. You will use the *adaptive* neuron model throughout the whole exercise, consider the HH *adaptive* model as the ground truth data, as if it were the biological neuron that experimentalists do stimulations on.

2.1 Passive properties

Similar to the LIF exercise, come up with stimulation protocols to extract the passive membrane parameters C, g_l, E_l, τ_m, R. Describe your steps and report the figures of your stimulations.

2.2 Exponential Integrate and Fire

To get an intuition on how to extract the parameters θ_{rh} and Δ_T sketch the nonlinear membrane dynamics without adaptation current:

$$CdV/dt = f(V) = -g_l(V - E_l) + g_l\Delta_T e^{\frac{V-\theta_{rh}}{\Delta_T}} + I_{ext}$$

as function of V. What happens to the membrane dynamics if the minimum of this function is slightly larger than zero? Find a step current intensity that puts the *adaptive* neuron in this scenario, report what happens. Extract the voltage trace from the simulation and compute its discrete derivative, describe how you can extract the value of θ_{rh} from it.

Tip: Sketch f(V) vs V for different current values and reason about the dynamics of V when it is initialized to its resting state.

In the absence of external stimulation $f(V)$ has two zeros, the lower one at $\sim E_l$ and the higher one at V_S. To find V_S, stimulate the neuron with a very short current pulse of $1\mu s$ and find the current amplitude that reaches the maximal voltage without making the neuron spike. V_S is the maximal voltage reached without spiking. Report the stimulation amplitude found and describe why this protocol allows to find V_S.

In order to find Δ_T, it is sufficient to plug in V_S in the equation of $f(V)$:

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

The only unknown is Δ_T and the equation has two zeros, you can find them by using the `scipy.optimize.fsolve` tool and playing with the initial guess. Pick the lowest zero as Δ_T. Report the value found and plot the curve $f(V)$ for a reasonable membrane voltage range.

Tip: Be careful, the value of Δ_T is very sensitive to the value of VS, tune the current to find VS up to some decimal points.

2.3 Subthreshold adaptation

If the voltage dynamics are slow enough and are far from threshold we can neglect these terms:

$$\frac{dV}{dt} \approx 0, \frac{dw}{dt} \approx 0, e^{\frac{V-\theta_{rh}}{\Delta_T}} \approx 0,$$

write I_{ext} as a function of the remaining terms. Note that there is a linear dependence between I_{ext} and V, you can extract a from the $I - V$ curve of a neuron stimulated by a $10s$ current ramp from $0.0\mu A$ to $1.2\mu A$. Report the result of the stimulation, the $I - V$ curve and how you found a.

2.4 Remaining parameters

Now only three parameters are missing to have an AdEx model that replicates the *adaptive* neuron! To get an understanding of the remaining parameters b, τ_w, V_{Reset}, you will tune them by hand to match the spike train of a $2.0\mu A$ step current stimulation on the HH model; the one you already simulated in exercise 1.3. Simulate the AdEx neuron model with the parameters you extracted so far using the `adex_model.AdEx.simulate_AdEx_neuron` function, use an initial guess for b, τ_w and V_{Reset}. Compare the spike trains of the two models by overlaying their voltage traces, your goal is to tweak the remaining three AdEx parameters in order to match the spike timings of the *adaptive* neuron.

To help you tune the parameters use the *Adaptive behaviour* figure you created in exercise 1.3. Identify the key features of the adaptation behaviour and report how each of the three remaining parameters influences the adaptation behaviour (no need of mathematical arguments). Report the parameters found along with the voltage traces of HH and AdEx overlayed and the overlayed *Adaptive behaviour* figures.

Tips: Use a spike threshold of $30mV$. Do not try to match the subthresold voltage behaviour, we are only interested in the spike timings.

2.5 Testing on random input

Stimulate both models with a gaussian random current $I_{ext} \sim \mathcal{N}(\mu = 1\mu A, \sigma = 15\mu A)$ for $500ms$. Plot an overlay of the two voltage traces and mark the spikes of both models using the function of exercise 1.3. Stimulate again but for $2500ms$, comment on the accuracy of the model for the two cases.

Tips: You can use the function `numpy.random.randn` to generate gaussian random samples. To create a custom current stimulation check how any of the functions in neurodynex.tools.input_factory are implemented. Fix the numpy random seed for reproducibility.

3 Ionic currents equations

The neuron models are inspired from ref. [2].

3.1 I_{Na}

$$
\begin{aligned}
I_{Na} &= \overline{g_{Na}} m^3 h (V - E_{Na}) \\
dm/dt &= \alpha_m (1 - m) - \beta_m m \\
dh/dt &= \alpha_h (1 - h) - \beta_h h \\
\alpha_m &= -\frac{0.32(V + 47)}{exp(-0.25(V + 47)) - 1} \\
\beta_m &= \frac{0.28(V + 20)}{exp(0.2(V + 20)) - 1} \\
\alpha_h &= 0.128 exp(-(V + 43)/18) \\
\beta_h &= \frac{4}{exp(-0.2(V + 20)) + 1}
\end{aligned}
\tag{4}
$$

with $\overline{g_{Na}} = 50mS, E_{Na} = 50mV$.

3.2 I_K

$$
\begin{aligned}
I_K &= \overline{g_K} n^4 (V - E_K) \\
dn/dt &= \alpha_n (1-n) - \beta_n n \\
\alpha_n &= -\frac{0.032(V+45)}{exp(-0.2(V+45)) - 1} \\
\beta_n &= 0.5 exp(-(V+50)/40)
\end{aligned}
\tag{5}
$$

with $\overline{g_K} = 5mS, E_K = -90mV$.

3.3 I_M

$$
\begin{aligned}
I_M &= \overline{g_M} p (V - E_K) \\
dp/dt &= \frac{p_\infty - p}{\tau_p} \\
p_\infty &= \frac{1}{exp(-0.1(V+40)) + 1} \\
\tau_p &= \frac{2000}{3.3 exp((V+20)/20) + exp(-(V+20)/20)}
\end{aligned}
\tag{6}
$$

with $\overline{g_M} = 0.07mS$.

4 HH neurons behaviours

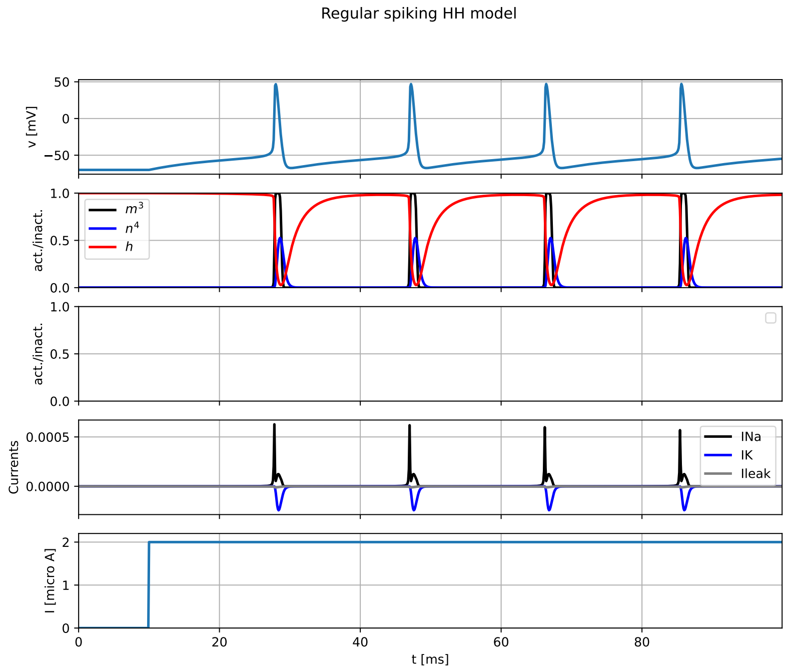

Figure 1: *Regular spiking* stimulation protocol of $2.0\mu A$ current from $10ms$ to $100ms$.

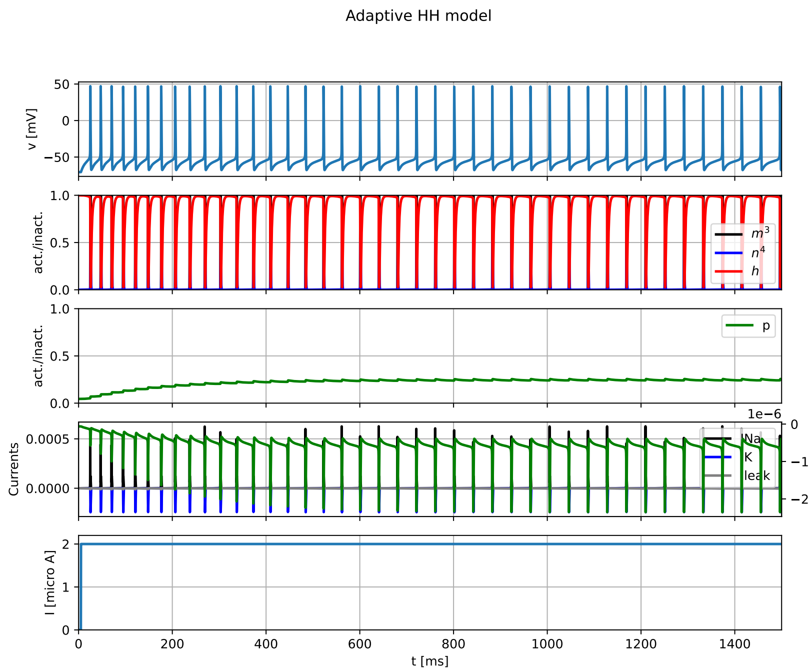

Figure 2: *Adaptive* stimulation protocol of $2.0\mu A$ current from $0ms$ to $1500ms$.

References

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

[2] Martin Pospischil, Maria Toledo-Rodriguez, Cyril Monier, Zuzanna Piwkowska, Thierry Bal, Yves Frégnac, Henry Markram, and Alain Destexhe. Minimal hodgkin–huxley type models for different classes of cortical and thalamic neurons. *Biological cybernetics*, 99(4):427–441, 2008.