

TD1: Models of Neurons I

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TD material is available at:

https://github.com/Elieoriol/2122_UlmM2_ThNeuro/tree/master/TD1

The goal of this series of problems is to investigate various dynamical properties of the simplest type of single neuron models: point neurons. In these models, a neuron's complex morphology is simplified to a single point, characterised by its membrane potential V , which is the difference in potential between inside/outside the neuron.

In the following we will consider the parameters:

C_m	g_l	E_l	V_{th}	V_{reset}
100 pF	10 nS	-70 mV	-50 mV	-80 mV

1 LIF neurons

1.1 Preliminary maths

Consider the following differential equation for a variable x evolving with the time t :

$$\tau \frac{dx}{dt} = -x(t) + c(t) \quad (1)$$

where the initial condition is given by $x(t=0) = x_0$.

1. Compute the time evolution of $x(t)$ when $c(t)$ is constant, equal to c_0 .

With $c(t) = c_0$, one can easily verify that $u(t) = x(t) - c_0$ is solution to the linear first order differential equation $\tau \frac{du}{dt} = -u(t)$. Its solution has to be remembered:

$$u(t) = A \cdot e^{-t/\tau}$$

with A a constant to be determined using the initial conditions at $t=0$. We finally find $x(t) = c_0 + (x_0 - c_0) \cdot e^{-t/\tau}$.

2. **Bonus: General case** For an arbitrary function $c(t)$, verify that a general solution to the differential equation is given by:

$$x(t) = e^{-\frac{t}{\tau}} \left[x_0 + \frac{1}{\tau} \int_0^t c(t') e^{\frac{t'}{\tau}} dt' \right]. \quad (2)$$

You can either plug the final expression in Eq. 1, or start from the guess $x(t) = X(t) e^{-\frac{t}{\tau}}$ and find a consistent expression for $X(t)$ (method of variation of constants).

1.2 Leaky neuron

Neuron membranes are permeable to ions, therefore differences in ion concentration and in electric potential between the interior and the exterior of the neuron result in a flow of ions across the membrane (through dedicated channels), according to:

$$I = -g_l(V_m - E_l) \quad (3)$$

where g_l is the leak conductance and the leak potential E_l is the value of the membrane potential V_m for which there is no current across the membrane. This current results in the accumulation of charge Q close to the membrane of the neuron that acts as a capacitor, itself resulting in a membrane potential:

$$Q = C_m V_m \quad (4)$$

where C_m is the membrane capacitance.

3. Knowing the current I corresponds to the variation in time of charge Q in the neuron, obtain a differential equation governing the time course of the membrane potential V_m . Solve this equation for a given initial V_0 . A characteristic relaxation time τ_m of the membrane should be introduced.

I is defined as the flow of charge $\frac{dQ}{dt}$. Therefore we have from 3 and 4:

$$C_m \frac{dV_m}{dt} = -g_l(V_m - E_l)$$

Applying the results from the preliminary maths:

$$V_m(t) = E_l + (V_0 - E_l) \exp(-t/\tau_m)$$

with $\tau_m = C_m/g_l$.

4. Depending on its initial value V_0 , how does the membrane potential V_m behave in time?

V_0 either increases or decreases to E_l if it is initially lower or greater than E_l .

1.3 Leaky Integrate-and-Fire model

The LIF model is a good starting point for simulating neurons. It reproduces some qualitative features of the membrane potential dynamics, and introduces a framework on which we can build more realistic models.

The LIF model is a differential equation for the membrane potential of a neuron with a capacitance and a leak term combined with an additional tweak: when the membrane potential reaches a particular value, called the threshold, a spike is emitted and the membrane potential is returned to a reset value.

The dynamical equation for the membrane potential is:

$$C_m \frac{dV_m}{dt} = g_l(E_l - V_m) + I_{app} \quad (5)$$

$$\text{if } V_m > V_{th} \text{ , then } V_m = V_{reset} \quad (6)$$

with I_{app} a constant applied current.

As we can observe on the simulations, there are different regimes depending on the injected current.

5. Can you find the condition on which the neuron is able to spike starting from a potential $V_0 < V_{th}$? Deduce the threshold current for which this condition is verified. Plot the corresponding bifurcation diagram in the 1D I_{app} space.

A spike can be emitted only if the membrane potential can reach the threshold V_{th} . Let's first consider there is no reset mechanism. Then the solution of the differential equation is the same as before, replacing E_l by $E_l + I_{app}/g_l$:

$$V_m(t) = E_l + I_{app}/g_l + (V_0 - E_l - I_{app}/g_l) \exp(-t/\tau_m)$$

The steady-state solution is defined as the solution for which the system does not evolve in time anymore. It is the infinite time limit of V_m . Here it is given by $V_m^{ss} = E_l + I_{app}/g_l$. This can be directly obtained from the differential equation, setting $\frac{dV_m}{dt} = 0$.

If the steady-state solution is above V_{th} , it means the membrane potential will evolve from V_0 to V_m^{ss} and cross V_{th} such that the neuron emits a spike. The spiking condition therefore is:

$$E_l + I_{app}/g_l > V_{th}$$

The corresponding threshold current is:

$$I_{th} = g_l(V_{th} - E_l)$$

With our parameters we obtain $I_{th} = 200$ pA.

1.4 Euler Method

Any real function f of a variable t that is infinitely differentiable can be written as a Taylor expansion in $t + \Delta t$:

$$f(t + \Delta t) = f(t) + \sum_{n=0}^{\infty} \frac{f^{(n)}(t)}{n!} (\Delta t)^n$$

with $f^{(n)}(t)$ the n^{th} derivative of $f(t)$. For Δt small enough, up to first order:

$$f(t + \Delta t) = f(t) + f'(t) \Delta t + \mathcal{O}(\Delta t^2) \quad (7)$$

6. Using this formula, can you elaborate a method to simulate the differential equation of the membrane potential obtained in question 1? And for the LIF model?

The formula above with only the first order term gives a numerical scheme for the simulation: we get the evolution of f by steps of Δt , adding at each step to the current value of f its derivative $f'(t)$ times the time step Δt . For the LIF neuron we just need to manually set the voltage to its reset value whenever the threshold is reached.

7. **num** This numerical scheme is called the Euler method. Implement it in Python to get the evolution of V_m without the reset mechanism and compare with your solution obtained at question 3 for different values of I_{app} . Now add the reset mechanism, what do you observe?

Without the reset mechanism, the evolution of V_m should correspond to the equation obtained in question 3. With the reset mechanism, the evolution should still correspond until V_m reaches V_{th} . The process then repeats indefinitely and allows us to define a firing rate as the inverse of the inter-spike interval, that is the time between two consecutive spikes.

Note: All the equations above were dependent on the time variable t . The same ideas can be transferred to functions of space coordinates x, y, \dots or any other type of variable.

Parenthesis: stiff equations A stiff equation is a differential equation for which certain numerical methods for solving the equation are numerically unstable, unless the step size is taken to be extremely small. With the Euler method, even simple linear equations can be stiff, such as:

$$f'(t) = -15f(t) \quad f(0) = 1 \quad (8)$$

8. What is the analytical solution of this equation?

$$f(t) = \exp(-15t)$$

9. **num** What will be the problem with the Euler method? Can you numerically verify it?

The problem is that if the step is too big we can have oscillations and divergence in the numerical resolution (see Jupyter notebook).

There is a theorem (not to be remembered) for linear equations of the form $f'(t) = -kf(t)$ with $k \in \mathbb{R}$ stating that the numerical simulation is stable for $|1 - k\Delta t| \leq 1$. In our case with $k = 15$ this corresponds to $\Delta t \in [0; 2/15]$.

The Euler method is not widely used because of its potential instability. However, in common biological equations and with a small enough step size, this method is often sufficient. It also has the advantage of working even if noise is added. In the case you need to simulate a deterministic equation and the Euler method does not work, you can look to more advanced methods like the Runge-Kutta one.

1.5 Firing rate as a function of current (f-I curve)

When the applied current is held fixed, the time for the neuron membrane potential to increase from its reset value to the threshold can be calculated.

10. **num** Compute the inter-spike interval T_{ISI} as well as the firing rate f of the neuron. Numerically compute the firing rate for different values of I_{app} and compare.

We consider that the initial value of the membrane potential is the reset potential. Under these conditions, the solution to the differential equation can be written:

$$V_m(t) = V_m^{ss} + (V_{reset} - V_m^{ss}) \exp(-t/\tau_m)$$

The next spike is produced when $V_m(t) = V_{th}$. This equation can be rearranged as:

$$\exp(-T_{ISI}/\tau_m) = \frac{V_m^{ss} - V_{th}}{V_m^{ss} - V_{reset}}$$

If we impose the requirement $V_m^{ss} > V_{th}$ (otherwise there is no solution), we obtain:

$$T_{ISI} = -\tau_m \log \left(\frac{V_m^{ss} - V_{th}}{V_m^{ss} - V_{reset}} \right) = -\tau_m \log \left(\frac{E_l + \frac{I_{app}}{g_l} - V_{th}}{E_l + \frac{I_{app}}{g_l} - V_{reset}} \right)$$

and the firing rate

$$f = \frac{1}{T_{ISI}}$$

11. Study the limits of this formula depending on I_{app} . Can you highlight a limit of the LIF model?

A first observation is that $\lim_{I \rightarrow \infty} f = \infty$ which does not seem very biological; action potentials are not points in time but last for a few milliseconds, and they moreover induce a refractory period in the neuron. Another observation is that for large values of I_{app} one can show that the firing rate becomes linear in I_{app} .

1.6 Response to an oscillating input current

We now inject of a small oscillating current $I_{app}(t) = 2I_0 \cos(\omega t)$ which we can also write as $I_{app}(t) = I_0 [e^{i\omega t} + e^{-i\omega t}]$. The membrane potential integrates this current, therefore when it reaches its steady state, it oscillates at the same frequency with a certain time lag given by a phase ϕ . We can therefore write the steady-state membrane potential as:

$$V_m(t) = E_l + A [e^{i(\phi+\omega t)} + e^{-i(\phi+\omega t)}] = E_l + 2A \cos(\omega t + \phi) \quad (9)$$

12. Show that:

$$A \exp(i\phi) = \frac{I_0}{g_l + i C_m \omega} \quad (10)$$

This question can be answered in a more or less elegant manner:

- Directly using (2), one finds:

$$V_m(t) = E_l + \left(V_0 - \frac{I_0}{1 + \tau_m^2 \omega^2} \right) e^{-t/\tau_m} + \frac{I_0}{g_l} \left[\frac{e^{i\omega t}}{1 + i\omega \tau_m} + \frac{e^{-i\omega t}}{1 - i\omega \tau_m} \right]$$

Then at steady-state, taking the $t \rightarrow \infty$ limit, one finds (10) from the identification of the previous result with (9).

- Using (9) as an ansatz in the differential equation, terms in $e^{i\omega t}$ and in $e^{-i\omega t}$ can be respectively identified between both sides of the equation as equal Fourier representations.

13. Compute the amplitude A and phase ϕ of the response. Provide an explanation of the limiting behaviours at low ($\omega \ll g_l/C_m$) and high frequency ($\omega \gg g_l/C_m$). Does the membrane response show a peak at a particular non-zero frequency?

A complex number z can be written either in a Cartesian $z = x + iy$ or polar $z = |z| e^{i\phi_z}$ representation. From Cartesian to polar coordinates, its module and phase are given by:

$$|z| = \sqrt{x^2 + y^2} \quad \phi_z = \arctan(y/x) + 1_{\{x < 0\}} \cdot \text{sgn}(y) \cdot \pi$$

In our case, we write $A \exp(i\phi) = \frac{I_0}{g_l^2 + C_m^2 \omega^2} \cdot (g_l - i C_m \omega)$ such that:

$$A = \frac{I_0/g_l}{\sqrt{1 + \tau_m^2 \omega^2}} \quad \phi = -\arctan(\tau_m \omega)$$

A and ϕ respectively correspond to the amplitude and the phase shift (or time delay) of the response of V_m to the sinusoidal current. Indeed, reinjecting in (9):

$$V_m(t) = E_l + 2 \frac{I_0/g_l}{\sqrt{1 + \tau_m^2 \omega^2}} \cos[\omega t - \arctan(\tau_m \omega)]$$

At low frequency, the membrane response can perfectly follow the sinusoidal input such that the amplitude tends to its maximum $A = I_0/g_l$ and the phase tends to 0. If ω is small enough we have $\arctan(\tau_m \omega) \approx \tau_m \omega$ such that:

$$V_m(t) \approx E_l + 2I_0/g_l \cos[\omega(t - \tau_m)]$$

We see that the difference in phase just corresponds to the time for the membrane to relax (with the characteristic time scale τ_m).

At high frequency, the input oscillates too quickly for the membrane to have the time to integrate the signal (τ_m). In that case, A decreases to 0 with ω and the phase to $-\pi/2$:

$$V_m(t) \approx E_l + 2 \frac{I_0}{C_m \omega} \cos[\omega t - \pi/2]$$

The membrane potential acts as such as a first-order low-pass filter. There is no peak in the membrane frequency as can be seen with higher order integrators.

Note: Instead of writing $2 \cos(\omega t) = e^{i\omega t} + e^{-i\omega t}$ we could have written $\cos(\omega t) = \Re(e^{i\omega t})$. That way, we could have used a complex oscillating current $I_{app}(t) = I_0 \cdot e^{i\omega t}$ (which has no physical meaning) and take the real part of the equations.