## THEORETICAL NEUROSCIENCE
## TD1: MODELS OF NEURONS I

All TD materials will be made available at https://github.com/helene-todd/TheoNeuro2425.

The goal of these first three tutorials is to understand the dynamics of a simple 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 this tutorial, we will introduce the leaky integrate-and-fire model. In order to understand the different dynamics of this model, we will learn how to explicitly solve linear ODEs and implement them numerically.

# 1 Mathematical tools for ordinary differential equations (ODEs)

## 1.1 Analytical solution of linear ODEs

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

$$\frac{dx(t)}{dt} = ax(t) + b(t), \tag{1}$$

with initial condition

$$x(t_0) = x_0. \tag{2}$$

1. **Homogeneous case** $b(t) = 0$.

   Show that equation (1) admits a solution given by

   $$x(t) = x_0 \exp\left(\int_{t_0}^{t} a\,ds\right) = x_0 \exp(at - at_0). \tag{3}$$

   **Bonus:** show that this solution is unique.

   Existence:

   1. $x(t_0) = x_0 \exp(at_0 - at_0) = x_0$ : $x$ verifies the initial condition (2).

   2. $\dfrac{dx(t)}{dt} = ax_0 \exp(at - at_0) = ax(t)$ : $x$ is a solution to equation (1)

   Uniqueness:

   Let $x$ be a solution to equation (1) with initial condition (2). Note that $x$ is necessarily $C^1$ (continuous, differentiable with continuous derivative). We define

   $$y(t) = x(t) \exp\left(-\int_{t_0}^{t} a\,ds\right).$$

Then $y$ is $C^1$, and

$$y'(t) = x'(t) \exp\left(-\int_{t_0}^{t} ads\right) - x(t)a \exp\left(-\int_{t_0}^{t} ads\right) = 0.$$

This means that $y$ is constant and equal to $y(t_0) = x(t_0) = x_0$. Therefore

$$x(t) = y(t) \exp\left(\int_{t_0}^{t} ads\right) = x_0 \exp\left(\int_{t_0}^{t} ads\right).$$

2. **Non-homogeneous autonomous case** $b(t) = b$.

Using the solution to the homogeneous case, find a solution to equation (1).

Suppose $x$ is solution to equation (1) with initial condition 2. One can notice that

$$\bar{x}(t) = ax(t) + b$$

verifies the following homogeneous differential equation

$$\bar{x}'(t) = a\bar{x}(t).$$

Therefore, we have from (3) that

$$\bar{x}(t) = \bar{x}_0 \exp(at - at_0),$$

with

$$\bar{x}(t_0) = \bar{x}_0 = ax(t_0) + b = ax_0 + b.$$

We can now find the expression of $x(t)$

$$\bar{x}(t) = (ax_0 + b) \exp(at - at_0) = ax(t) + b$$

$$\Leftrightarrow ax(t) = (ax_0 + b) \exp(at - at_0) - b$$

$$\Leftrightarrow x(t) = \left(x_0 + \frac{b}{a}\right) \exp(at - at_0) - \frac{b}{a}.$$

One can easily verify that $x$ satisfies equation (1) with initial condition (2).

Note: one could also have used the more general variation of constants method.

3. **Bonus [general case]: Non-homogeneous non-autonomous case** $b(t)$.

Using the variation of constants method, show that the solution to equation (1) with initial condition (2) is

$$x(t) = \left(\int_{t_0}^{t} b(s) \exp(-as + at_0)ds + x_0\right) \exp(at - at_0). \tag{4}$$

*Hint*: suppose the solution to equation (1) is of the form

$$x(t) = K(t) \exp(at - at_0), \tag{5}$$

and substitute into equation (1).

Suppose that the solution is of the form

$$x(t) = K(t) \exp(at - at_0).$$

Then

$$x(t) = K'(t) \exp(at - at_0) + K(t) a \exp(at - at_0)$$
$$= ax(t) + b(t).$$

From the above equation, we have that

$$b(t) = K'(t) \exp(at - at_0)$$

$$\Leftrightarrow K'(t) = b(t) \exp(-at + at_0)$$

$$\Leftrightarrow K(t) = \int_{t_0}^{t} b(s) \exp(-as + at_0) ds + K(t_0).$$

Using initial condition (2), we deduce $K(t_0)$

$$x(t_0) = x_0 = K(t_0) \exp(at_0 - at_0) = K(t_0).$$

Therefore, the full solution to equation (1) is

$$x(t) = K(t) \exp(at - at_0) = \left( \int_{t_0}^{t} b(s) \exp(-as + at_0) ds + x_0 \right) \exp(at - at_0).$$

## 1.2 Numerical approximation of ODEs: Euler method

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

$$f(t + \Delta t) = f(t) + \sum_{n=0}^{+\infty} \frac{f^{(n)}(t)}{n!} (\Delta t)^n, \tag{6}$$

with $f^{(n)}(t)$ the $n^{th}$ derivative of $f(t)$. For $\Delta t$ small enough, the first order Taylor expansion is

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

4. Using equation (7), elaborate an algorithm that simulates a differential equation.

This algorithm computes the value of $x(T)$, where $x(0) = 0$ and $T = 2$ for example.

$dt \leftarrow 0.01$
$x_0 \leftarrow 0$
$N \leftarrow 2/dt$
**for** $k \leftarrow 1, \cdots, N$ **do**
    $x \leftarrow x_0 + dt * ODE(x_0)$
    $x_0 \leftarrow x$
**end for**
**return** $x$

# 2 Leaky integrate-and-fire (LIF) neurons

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 |

## 2.1 Modelling the leak term

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

$$I = -g_l(V_m - E_l), \tag{8}$$

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

$$Q = C_m V_m, \tag{9}$$

where $C_m$ is the membrane capacitance.

5. 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 condition $V(t = 0) = V_0$ . A characteristic relaxation time $\tau_m$ of the membrane should be introduced.

> $I$ is defined as the flow of change $\frac{dQ}{dt}$, therefore we have from equations (8) and (9)
>
> $$C_m \frac{dV_m}{dt} = -g_l(V_m - E_l) \Leftrightarrow \frac{dV_m}{dt} = -\frac{V_m}{\tau_m} + \frac{E_l}{\tau_m}, \text{ with } \tau_m := \frac{C_m}{g_l}.$$
>
> We have from question 2 of 1.1 that the solution is
>
> $$V_m(t) = E_l + (V_0 - E_l) \exp(-t/\tau_m).$$

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

> $V_m$ either increases or decreases to the fixed value $E_l$ depending on whether $V_0$ is initially lower or greater than $E_l$.

## 2.2 The full 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.

This model is described as 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

$$C_m \frac{dV_m(t)}{dt} = g_l(E_l - V_m(t)) + I_{app}, \text{ if } V_m > V_{th} \text{ then } V_m = V_{reset}, \tag{10}$$

with $I_{app}$ a constant applied current.

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

7. 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.

> A spike can be emitted only if the membrane potential can reach the threshold $V_{th}$.
>
> Let us 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 either reaches a constant value (equilibrium) or is bounded as $t$ reaches infinity.
>
> From the above solution, as $t$ tends to infinity, we directly obtain the steady-state
>
> $$V_m^{ss} = E_l + I_{app}/g_l.$$
>
> Note: one could also have solved $dV_m/dt = 0$ to find the steady-state $V_m^{ss}$. Indeed, in the case of autonomous ODEs, $dV_m/dt = 0$ means the system does not evolve in time anymore. One then has to make sure that the solution (called the equilibria) is stable (see next tutorials).
>
> If the steady-state solution is above $V_{th}$, it means that 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 is therefore
> $$E_l + I_{app}/g_l > V_{th}.$$
> The corresponding threshold current is therefore
>
> $$I_{th} = g_l(V_{th} - E_l),$$
>
> which is, with the parameters given in the table, $I_{th} = 200pA$.

## 2.3 Firing rate as a function of current ($fI$ 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.

8. From the previous question, deduce the inter-spike interval $T_{ISI}(I)$ as well as the firing rate $f(I)$ of the neuron as a function of the input current.

> We consider that the initial value of the membrane potential is the reset potential, i.e. $V(t_0 = 0) = V_{reset}$. Under these conditions, the solution to the differential equation is
>
> $$V_m(t) = V_m^{ss} + (V_{reset} - V_m^{ss}) \exp(-t/\tau_m).$$
>
> A spike occurs at time $T_{ISI}$ when $V_m(t) = V_{th}$, therefore
>
> $$\exp(-T_{ISI}/\tau_m) = \frac{V_m^{ss} - V_{th}}{V_m^{ss} - V_{reset}}.$$
>
> Imposing that $V_m^{ss} > V_{th}$ (otherwise there is no solution), we obtain
>
> $$T_{ISI} = -\tau_m \log\left( \frac{V_m^{ss} - V_{th}}{V_m^{ss} - V_{reset}} \right) = -\tau_m \log\left( \frac{E_l + I_{app}/g_l - V_{th}}{E_l + I_{app}/g_l - V_{reset}} \right)$$
>
> and the firing rate is
>
> $$f = \frac{1}{T_{ISI}}.$$

## 2.4  Response to oscillating input current

We now inject a small oscillating current

$$I_{app}(t) = 2I_0 \cos(\omega t) = I_0(e^{i\omega t} + e^{-i\omega t}). \tag{11}$$

The membrane potential integrates this current, therefore when it reaches its steady-state solution, it oscillates at the same frequency with a certain time lag given by a phase $\phi$. We can therefore write the membrane potential as

$$V_m(t) = E_l + 2A\cos(\omega t + \phi) = E_l + A(e^{i(\phi+\omega t)} + e^{-i(\phi+\omega t)}). \tag{12}$$

9. The goal is now to identify the time lag given by a phase $\phi$. Show that

$$Ae^{i\phi} = \frac{I_0}{g_l + iC_m\omega}. \tag{13}$$

> Note:  non-autonomous differential equations usually do not have constant steady-state solutions as their coefficients are functions of time (see expression (4)). Instead, their steady-state solutions (if they exist) are bounded in time.
>
> There are two methods that can be used to solve this question.
>
> 1. Substitute the solution (12) in the differential equation (10). We have
>
> $$V_m'(t) = A(i\omega e^{i\phi+i\omega t} - i\omega e^{-i\phi-i\omega t}) = e^{i\omega t}Ai\omega e^{i\phi} - e^{-i\omega t}Ai\omega e^{-i\phi}$$

and

$$V_m'(t) = -\frac{g_l V_m(t)}{C_m} + \frac{g_l E_l}{C_m} + \frac{I_0}{C_m}(e^{i\omega t} + e^{-i\omega t})$$

$$= -\frac{g_l E_l}{C_m} - \frac{g_l}{C_m}A(e^{i(\phi+\omega t)} + e^{-i(\phi+\omega t)}) + \frac{g_l E_l}{C_m} + \frac{I_0}{C_m}(e^{i\omega t} + e^{-i\omega t})$$

$$= e^{i\omega t}\left(\frac{-g_l A e^{i\phi} + I_0}{C_m}\right) + e^{-i\omega t}\left(\frac{-g_l A e^{-i\phi} + I_0}{C_m}\right).$$

Identifying between both expressions, for example the terms in $e^{i\omega t}$, we obtain

$$\frac{-g_l A e^{i\phi} + I_0}{C_m} = Ai\omega e^{i\phi} \Leftrightarrow A e^{i\phi}(g_l + iC_m\omega) = I_0 \Leftrightarrow A e^{i\phi} = \frac{I_0}{g_l + iC_m\omega}.$$

2. Use the explicit solution (4) and compare with (12). The explicit solution is

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

At steady-state, i.e. taking the $t \to \infty$ limit, one finds (13) from the identification with (12).

10. Compute the amplitude $A$ and phase $\phi$ of the response. Provide an explanation of the limit behaviours at low ($\omega \ll g_l/C_m$) and high frequencies ($\omega \gg g_l/C_m$). Justify that the membrane behaves as a low-pass filter.

Note: a complex number $z \in \mathbb{C} \simeq \mathbb{R}^2$ can be written in either Cartesian coordinates, i.e. $z = x + iy$, $x$ and $y \in \mathbb{R}$, either in polar coordinates, i.e. $z = |z|e^{i\phi_z}$, $\phi_z \in [0, 2\pi]$.
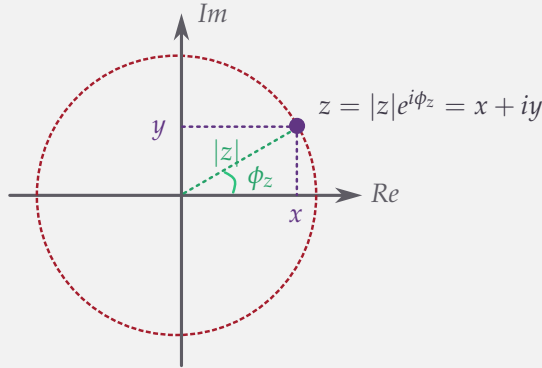


These two expressions are equivalent through the relationship

$$z = x + iy = r\cos(\phi_z) + ir\sin(\phi_z) = re^{i\phi_z},$$

with $r = \sqrt{x^2 + y^2} = |z|$ and $\phi_z = \tan\left(\frac{y}{x} + \mathbb{1}_{\{x<0\}}\text{sign}(y)\pi\right)$.

The goal is now to disentangle in (13) the expressions for $A$ and $\phi$. We begin by removing the complex terms from the denominator in (13)

$$A e^{i\phi} = \frac{I_0(g_l - iC_m\omega)}{g_l^2 + C_m^2\omega^2}.$$

Finding the amplitude $A$ means computing $|Ae^{i\phi}| = |A| = A$, i.e.

$$A = \left| \frac{I_0(g_l - iC_m\omega)}{g_l^2 + C_m^2\omega^2} \right| = \frac{I_0\sqrt{g_l^2 + C_m^2\omega^2}}{g_l^2 + C_m^2\omega^2} = \frac{I_0}{\sqrt{g_l^2 + C_m^2\omega^2}} = \frac{I_0/g_l}{\sqrt{1 + \tau_m^2\omega^2}}.$$

Now that we have the expression of $A$, one can now deduce $\phi$ either directly by identification to the $x$ and $y$ terms in $A$ either by solving

$$Ae^{i\phi} = \frac{I_0(g_l - iC_m\omega)}{g_l^2 + C_m^2\omega^2} \Leftrightarrow e^{i\phi} = \frac{g_l - iC_m\omega}{\sqrt{g_l^2 + C_m^2\omega^2}}$$

$$\Leftrightarrow \cos(\phi) + i\sin(\phi) = \frac{g_l}{\sqrt{g_l^2 + C_m^2\omega^2}} - i\frac{C_m\omega}{\sqrt{g_l^2 + C_m^2\omega^2}}.$$

And therefore

$$\phi = \arctan\left(-\frac{C_m\omega}{g_l}\right) = -\arctan\left(\frac{C_m\omega}{g_l}\right) = -\arctan(\tau_m\omega).$$

$A$ and $\phi$ respectively correspond to the amplitude and the phase shift of the response $V_m$ to the sinusoidal current - indeed, re-injecting into (12) we obtain

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

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 $\omega$ is small enough we have $\arctan(\tau_m\omega) \approx \tau_m\omega$ such that

$$V_m(t) \approx E_l + 2\frac{I_0}{g_l}\cos(\omega(t - \tau_m)).$$

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

At high frequency, the input oscillates too quickly for the membrane to have the time to integrate the signal. In this case, $A$ decreases to 0 with $\omega$ 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 frequency as can be seen with higher order integrators.