TD 1 – Models of Neurons I

Practical Information

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TD Material
https://github.com/esther-poniatowski/2223_UlmM2_ThNeuro

Goals of the TD

This first series of TDs aims to study models describing the **electrical behavior** of **single neurons**.
In particular, this first TD focuses on the simplest model of the Leaky Integrate and Fire neuron.

SUMMARY

Part 1 Revision of mathematical and numerical tools for differential equations.
Part 2 Introduction of the simplest model of neuron.
Part 3 Study of several regimes of the model.

1 Mathematical tools for Differential Equations

1.1 Definitions and Goals

First order differential equations

A first order differential equation is an expression which specifies the **derivative** of an unknown function at any (time) point. This derivative is itself a function (of time), which can be interpreted as the pace at which the unknown function evolves at any time point.

Generally, the derivative of the unknown function y at any time t can be expressed as a function f of its instantaneous value $y(t)$ and additional time dependencies :

$$\frac{\mathrm{d}y}{\mathrm{d}t} = f(y(t), t) \tag{1}$$

Often, a differential equation is accompanied with an **initial condition** $y(t = 0) = y_0$, which constraints the value of the unknown function y at a particular time point.

Note : In many applications in physics, equations are dependent on the time variable t. The same ideas can be transferred to functions of spatial coordinates (usually denoted x), or any other type of variable.

Linear first order differential equations

The linear first order differential equations are a subclass of simple differential equations. Their derivative only depends **linearly** on the instantaneous value of the function and an **independent term** :

$$\tau \frac{\mathrm{d}y}{\mathrm{d}t} = -y(t) + c(t) \tag{2}$$

where τ is a positive time constant which rescales the formula (for homogeneity).

Note : Here, the equation rewrites under the form $\frac{\mathrm{d}y}{\mathrm{d}t} = ay(t) + b(t)$ with a a constant coefficient. It is also possible to encounter linear first order differential equation with variable coefficient $a(t)$.

The **study of differential equations** mainly consists of :

- Finding the solutions (unknown function(s) y), i.e. the set of functions whose derivative corresponds to the expression given by the differential equation at any time.
- Studying the properties of the solutions.

⚠ Many differential equations admit solutions which *cannot* be expressed by *explicit formulas* (i.e. compositions of standard functions). In practice, it is nonetheless possible to compute *approximate* solutions by using numerical tools. However, many properties of their solutions can be determined even without computing them exactly.

1.2 Analytical solutions of linear first order differential equations

This part studies the problem defined by :

- A differential equation : $\forall t \geq 0,\ \tau \frac{\mathrm{d}y}{\mathrm{d}t} = -y(t) + c(t)$ (2).
- An initial condition : $y(t=0) = y_0$.

① *Independent term only*
For a differential equation containing only an independent term $c(t)$ in (2), justify that the analytical expression for the unknown function $y(t)$ is obtained by integrating from the initial condition y_0 up to an arbitrary time point t :

$$y(t) = y_0 + \frac{1}{\tau} \int_0^t c(t)\, \mathrm{d}t \tag{3}$$

Provide a graphical interpretation of this result.

② *No independent term*
For a differential equation containing only the linear term $-y(t)$ in (2), find a solution $y(t)$ which satisfies it.

③ *Constant independent term*
For the particular case in which the independent therm is constant, $c(t) = c_0$, compute the solution $y(t)$. Provide a graphical representation of the solution.

④ *Arbitrary independent term (Bonus)*
For an arbitrary function $c(t)$, verify that a general solution to the differential equation is given by :

$$y(t) = e^{-\frac{t}{\tau}} \left[y_0 + \frac{1}{\tau} \int_0^t c(s)\, e^{\frac{s}{\tau}}\, \mathrm{d}s \right]. \tag{4}$$

1.3 Numerical approximation with Euler Method

Multistep methods for numerical approximation

When a solution y cannot be expressed with explicit analytical expressions (especially when variables cannot be separated), several algorithms can be used to build a *numerical approximation* $\tilde{y}$ on a given time interval $[0, t_{max}]$.

Multistep numerical methods proceed as follows :

- The time interval $[0, t_{max}]$ is discretized in N intermediate points $0 < t_1 < ... < t_N = t_{max}$, regularly spaced by a small interval Δ :
$$t_{k+1} = t_k + \Delta,\ \forall k \in [\![0, N]\!].$$
- At the initial time point, the value is set exactly : $\tilde{y}_0 = y_0$.
- At each intermediate point, an approximated value of the function y is computed by *iteration* from the value at the previous time point, such that : $\tilde{y}_1 \approx y(t_1),\ ...,\ \tilde{y}_k \approx y(t_k),\ ...,\ \tilde{y}_N \approx y(t_N)$.

In particular, linear multistep methods use a linear combination of $\tilde{y}_k$ and $f(t_k, \tilde{y}_k)$ to calculate the next value $\tilde{y}_{k+1}$ (different methods exist).

- Between two intermediate points, the approximated values of the function are linked with a segment.

Euler's method, also named the **tangent method**, is one of the most commonly used multistep methods.

⑤ Write the Taylor expansion of $g(t + \Delta)$ for a real function g of a variable t which is infinitely differentiable.

By truncating the Taylor expansion to the first order in Δ, deduce the Euler method's recursive expression for $\tilde{y}_{k+1}$ as a function on the previous time point $\tilde{y}_k$. Provide a graphical interpretation.

⑥ **num** Implement an algorithm in Python for approximating the solution of a differential equation defined by an arbitrary function f, up to a maximal time t_{max}, and a with time step Δ.
Execute this algorithm with the differential equation (2) and $c(t) = 0$.

Instability of the approximation

A numerical method for approximation method can be **unstable** with respects to certain differential equations. This is the case when the accumulation of estimation errors leads the approximated solution to diverge from the exact solution (unless the step size is taken to be extremely small compared to the smoothness of the solution).

This phenomenon can occur with Euler's method, even with simple linear equations such as :

$$y'(t) = -ky(t) \qquad y(0) = 1 \tag{5}$$

where $k > 0$ is a large number.

Note : In common biological equations and with sufficiently narrow time steps, Euler's method is often sufficient. It also has the advantage of being flexible enough to add noise. However, when Euler's method fails, it can be replaced by more advanced methods such as Runge-Kutta's method.

⑦ Give the analytical solution of equation (5) and shows that it tends towards 0 as time goes by.

⑧ Write an immediate recurrence to express the approximated solution $\tilde{y}_n$ as a function of y_0, Δ and k. Find a condition over the time step Δ for this approximation to behave like the exact solution.

⑨ **num** Illustrate the problem of the Euler method numerically with the Python algorithm from question ⑥.

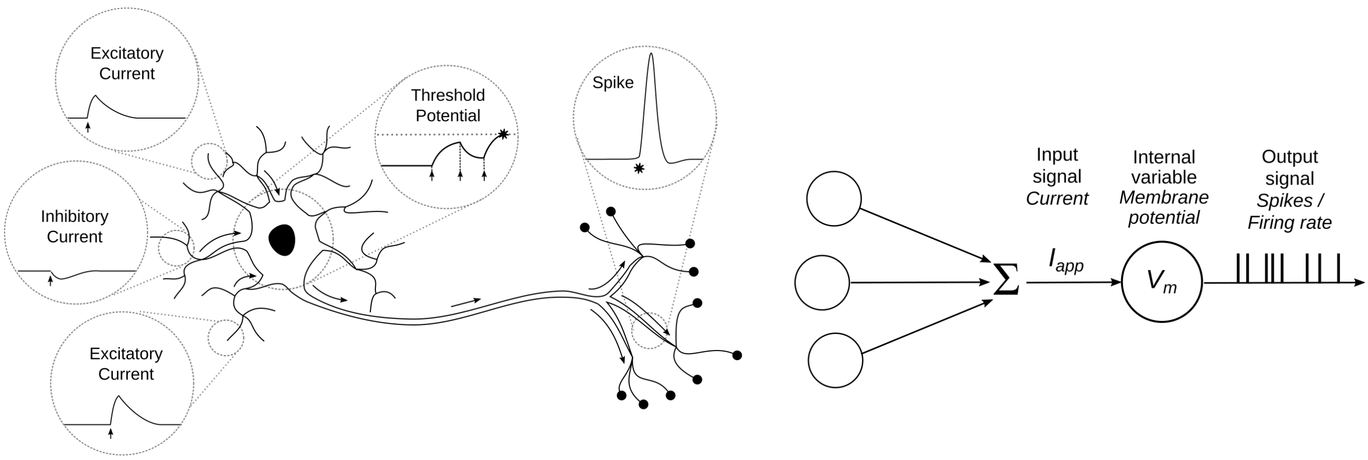
2 Models of Point Neurons

Describing the behavior of a neuron

A neurons is a specific type of cell, characterized by its **electrical excitability**. Its electrical behavior underlies the ability of the neuron to **transmit signals**.

Different models aim to describe the electrical behavior of a neuron. They usually reduce the description to a few key phenomena and variables which can be recorded experimentally :

- The state of the neuron is characterized by its **membrane potential** V, which corresponds to the difference in electrical potentials between the inside and the outside of the neuron. Indeed, the membrane of the neuron is able to maintain a difference of charges between both sides, but also to evolve by letting charges flow between the inside and the outside (through specific ion channels).
- The neuron receives **electrical currents** I resulting from its interactions with neighboring neurons. Those *input* currents are flows of charges, which contribute to modify the membrane potential of the neuron, with either an excitatory or an inhibitory effect.
- The membrane potential integrates those input currents up to a **threshold** (specific value of the membrane potential V_{th}). At this point, another phenomena takes place (opening of new ion channels), such that the membrane potential reacts by **spiking**, i.e. producing a brief and strong electrical discharge. The *output signal* sent by the neuron is encoded in its firing rate f, i.e. the frequency at which spikes occur.



Models of Point Neurons

In the simplest models, the neuron is reduced to a **single point**, characterized by a homogeneous membrane potential.

The goal of those models is to express the **temporal evolution of the membrane potential** $V(t)$ in response to a known input current.

To do so, models adopt the following approach :
- They assimilate the neuron to an **electrical circuit**.
- They express the law of variation of the membrane potential by a **differential equation** whose variable is the membrane potential.

Basic model of a neuron as an electrical circuit

① The **membrane** is assimilated to a **capacitor**.

Indeed, neuronal membranes are able to maintain an asymmetric distribution of electrical charges (ions) between the extracellular and intracellular sides. This asymmetry generates a *difference of potentials* between the exterior and the interior of the neuron (those potentials can be interpreted as the attraction that each media exerts on charges).

A capacitor is an electronic device adapted to model this property, since it stores electrical energy by accumulating electric charges on two closely spaced surfaces isolated from each other.

The potential resulting from the asymmetric distribution of charges between both sides is directly proportional to the charge itself (*equation of the capacitor*) :

$$Q(t) = C_m V_m(t) \tag{6}$$

with :
- $V_m(t) = E_i(t) - E_o(t)$: Membrane potential, defined as the difference between the internal and external potentials (convention : external media as the reference). ⚠This is the *instantaneous* potential at a given time.
- $Q(t)$: Difference of charge across the membrane.
- C_m : Membrane capacitance, constant which characterizes the capability of the membrane to accumulate electric charges.

② The **electrical (ionic) currents** flowing through the membrane are assimilated to a set **generator + resistor**.

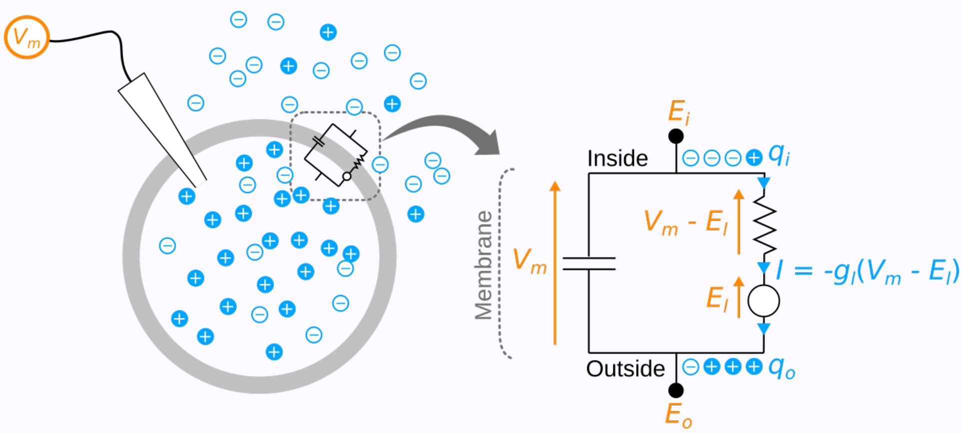
Indeed, the ionic currents through the membrane depend on two phenomena :

- The difference of (fixed) *concentrations* of ions between the interior and the exterior of the neuron favors their *diffusion* towards the compartment in which they are less concentrated. This effect is modelled by the *generator* of current, since this electrical device imposes a constant driving force.
- Additionally, the difference of *electrical potentials* between the interior and the exterior of the neuron attracts the ions towards the compartment which exhibits the opposite (or less similar) polarity. This effect is modeled by the *resistor*, since the electrical current through this this device is directly proportional to the difference between the potentials at its terminals.

Thus, the current flowing through the membrane at any time is governed by the following law (*Ohm's law)* :

$$I(t) = -g_l(V_m(t) - E_l) \tag{7}$$

with :
- $I(t)$: Current flowing across the membrane at a given time.
- E_l : Equilibrium potential. This constant is the value of the membrane potential at which no more *net* current is driven across the membrane. In this situation, the flow of ions induced by the difference of potentials compensates the diffusion of ions imposed by the (fixed) concentrations of those ions between both sides.
- g_l : Leak conductance of the membrane. This constant characterises the ease with which ionic currents flow through the membrane, imposed by the channels inserted within it.



Note : Any flow of ions modifies the distribution of charges between both sides of the membrane. It has large effects on electrical potentials, but only negligible effects on their concentrations, which are thus assumed to be fixed.

3 Three types of behaviors

In this part, the basic model of the point neuron is investigated through three particular cases :
- The **passive** behavior of the neuron, in absence of any external input current.
- The response to a **fixed** input current.
- The response to a **oscillating** input current.

Parameters of the models used in this TD

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

3.1 Leaky Neuron

(10) Remind the relation between the current $I(t)$ and the instantaneous variation of charges $Q(t)$ in the neuron.

(11) Deduce a differential equation governing the variation of the membrane potential $V_m(t)$ at any time.

(12) Solve this equation for an initial condition $V(t = 0) = V_r$. Introduce a characteristic relaxation time τ_m and give its expression. Interpret the physical meaning of this constant for the dynamics.

(13) Graph distinct behaviors depending on the initial value V_r relative to the equilibrium potential E_l.

3.2 Leaky Integrate-and-Fire model (LIF)

Leaky Integrate-and-Fire model

The Leaky Integrate-and-Fire model extends the previous model to simulate the **spiking behavior**.

Two elements are added compared to the previous electrical circuit :

- An **input electrical current** is applied to the neuron, modeled by an additional term $I_{app}(t)$ in the differential equation. It represents the global 'apparent' current, which corresponds to the sum of all the individual signals received from neighboring neurons (not specified explicitly).
- When the membrane potential reaches a **threshold** value V_{th}, a spike is emitted and the membrane potential instantaneously returns to its **reset** value V_r.

Thus, the dynamical equation for the membrane potential becomes :

$$C_m \frac{\mathrm{d}V_m}{\mathrm{d}t} = -g_l(V_m - E_l) + I_{app} \tag{8}$$

$$\text{if } V_m > V_{th} \text{ , then } V_m = V_r \tag{9}$$

with :
- I_{app} : 'Apparent' current applied to the neuron (which can be constant or variable in time).
- V_{th} : Threshold membrane potential at which a spike is triggered.
- V_r : Reset potential at which the membrane potential returns after a spike.

Note : Different regimes can be observed with this model, which thereby accounts for some qualitative features of the membrane potential dynamics. It introduces the basic framework on which more realistic models can be elaborated.

In this part, the input current I_{app} is considered to be constant in time. It is thus a parameter of the model. The neuron starts at a reset potential $V_r < V_{th}$.

14 *Threshold current for spiking*
Establish a link between the parameters I_{app} and V_r for the neuron being able to spike.
Deduce the threshold current I_{th} for which this condition is verified.

15 Graph the behavior of the membrane potential in time in response to a step of input current, in two cases : $I_{app} < I_{th}$ and $I_{app} > I_{th}$.

16 **num** Implement this new model with the reset mechanism in Python to get the evolution of V_m. Simulate different neuron's behaviors by choosing appropriate values of I_{app}.

17 *f-I curve (firing rate as a function of current)*
Compute the inter-spike interval $T_{ISI}(I)$ as well as the firing rate $f(I)$ as a function of the input current.

18 *Study of the function $f(I)$*

- Determine the range of values of I for which the function is defined.
- Compute the limits depending on I.
- Show that the function is asymptotically equivalent to a linear function for large values of I.
- Show that the slope tends to infinity for a particular value of I.

19 Graph the f-I curve. Comment on its implications in light of biological plausibility.

3.3 Response to an oscillating input current

In this part, the neuron is receiving a small oscillating current :

$$I_{app}(t) = 2I_0 \cos(\omega t) \tag{10}$$

with $\omega > 0$ and $I_0 > 0$.

By integrating this current, the membrane potential also reaches an **oscillatory steady state** : it oscillates around its equilibrium potential, at the same frequency as the input current, with a certain time lag.

Thus, this steady-state behavior for the membrane potential can be expressed under the following form :

$$V_m(t) = E_l + 2A\cos(\omega t + \phi) \tag{11}$$

with $A > 0$ and ϕ two constants.

20 Interpret the parameters ω, I_0, A and ϕ in physical terms. Graph an example of I_{app} and V_m as a function of time.

21 Express the cosinus with complex numbers and provide a representation in the complex plane.
Write the expressions of I_{app} and V_m with this formalism.

22 Show that :

$$A\exp(i\phi) = \frac{I_0}{g_l + i\,C_m\omega} \tag{12}$$

23 Compute the amplitude $A(\omega)$ and phase $\phi(\omega)$ of the response as functions of ω. Introduce the characteristic time constant τ_m (question 12) in those expressions.

24 Represent the amplitude A and phase ϕ of the response as a function of ω.
Comment on the limiting behaviours at low ($\omega \ll 1/\tau_m$) and high frequency ($\omega \gg 1/\tau_m$). Justify that the membrane behaves as a low-pass filter.