TD 1 – Models of Neurons

Practical Information

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

Goals of the TD

This TD aims to study models describing the electrical behavior of **single neurons**.

Overall, one neuron can be conceived as an electrical device performing signal transmission.

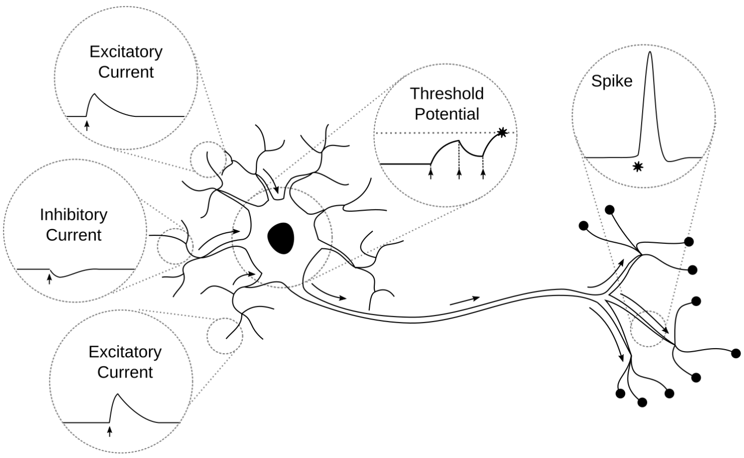
- The **input signal** received by the neuron is modeled as a global 'apparent' *electrical current* I_{app}, which corresponds to the sum of individual signals received from neighboring neurons (not specified explicitly).
- The **output signal** sent by the neuron is reflected by discrete *spikes*, which are brief events when the neuron suddently emits a strong discharge. Often, the informative signal is considered to be contained in the *continuous firing rate* rather than in binary single spikes.
- The transformation from input to output signals is achieved through an **internal variable**, the neuron's *membrane potential* V, which corresponds to the difference in electrical potential between inside and outside the neuron. The computation performed by the neuron is *integration up to threshold* : at each time step, the instantaneous input current tends to increase the membrane potential of the neuron, until the latter reaches the threshold for spike emission.

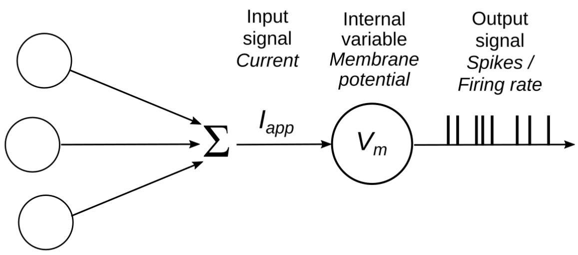
This TD focuses on **point neurons** models, the simplest types of single neuron models.

In those models, a neuron's complex morphology is simplified to a point, characterised by a single homogeneous membrane potential $V(t)$ evolving in time. Specifically, these models do not consider signal propagation across distinct locations of the membrane, which would require to add a spatial dimension to the membrane potential $V(t, x)$.

Thus, the goal of those models is to predict the temporal evolution of the membrane potential in response to a known input current (which can either be fixed or variable in time). To do so, models use the mathematical tool of **differential equations**.

The first part of the TD aims to revise mathematical and numerical tools for handling differential equations. Then, the behaviors of several point neuron models are investigated.





1 Mathematical tools for Differential equations

1.1 Analytical solutions

First order differential equations

A **differential equation** is a formula specifying the expression of a function's derivative at any (time) point. This derivative can be interpreted as the pace at which the function evolves at this time point.

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

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

The **initial condition** is given by $y(t = 0) = y_0$.

The models considered here use a subclass of differential equations in which the derivative only depends *linearly* on the instantaneous value of the function and an *independent term* :

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

in which τ is a positive time constant rescaling the formula (for homogeneity).

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

① *General solution* – Justify that the analytical expression for the unknown function (in the general case (1)) is obtained by integrating the differential equation from the initial condition y_0 up to an arbitrary time point t :

$$y(t) = y_0 + \int_0^t f(y(t), t)\,\mathrm{d}t \tag{3}$$

Provide a graphical interpretation of this result.

② *Constant independent term* – Compute the time evolution of $y(t)$ for the particular case (2) when $c(t)$ is constant, equal to c_0.

③ *Arbitrary independent term (Bonus)* – For an arbitrary function $c(t)$, verify that a general solution to the differential equation is given by :

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

1.2 Numerical approximation with Euler Method

Euler tangent method for numerical approximation

In practice, it is not always possible to find an *explicit analytical expression* for the unknown function y, especially when the primitives of the function to be integrated cannot be written as compositions of standard functions.

However, it is possible to obtain a *numerical approximation* $\tilde{y}$ of the unknown function y.

To do so, the **Euler's method** proceeds by *iteration*, starting from the initial condition, as follows :

- The time interval $[0, t_{max}]$ is discretized in N intermediate points, regularly spaced by a small interval Δ_t :
  $0 < t_1 < ... < t_N = t_{max}$ such that $t_{k+1} = t_k + \Delta_t, \ \forall k \in [[0, N]]$.
- At each intermediate point, an approximated value of the function y is computed from the value at the previous time point :

$$\tilde{y}_0 = y_0,\ \tilde{y}_1 \approx y(t_1),\ ...\ \tilde{y}_k \approx y(t_k),\ ...,\ \tilde{y}_N \approx y(t_N)$$

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

4 Write the Taylor expansion of $f(t + \Delta_t)$ for a real function f of a variable t which is infinitely differentiable.
The Euler method is also named the *tangent method*. By approximating the Taylor expansion to the first order in Δ_t, 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.

5 **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_t.
Execute this algorithm with the differential equation (2) and $c(t) = 0$.

Instability of the approximation

With respects to certain differential equations, a numerical approximation method can be **unstable**, when the accumulation of estimation errors can lead the approximated solution to diverges from the exact solution (unless the step size is taken to be extremely small compared to the smoothness of the solution). Such problematic differential equations are labelled *stiff equations*.

With the Euler method, even simple linear equations can be stiff, such as :

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

where $k > 0$ is a large number (for instance, > 10).

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

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

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

8 **num** Illustrate the problem of the Euler method numerically with the Python algorithm from question 5.

2 Models of Point Neurons

Parameters of the models

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

2.1 Leaky Neuron

Leaky Neuron model

The simplest model describes the **passive behavior** of a neuronal membrane, in absence of any stimulation.

Neuronal membranes separate two aqueous media (extracellular and intracellular), which both contain ions (electrical charges) maintained at distinct concentrations. Differences in ion concentrations and in electric potentials between the interior and the exterior of the neuron drive a *flow of ions* (current) across the membrane, until an *equilibrium* is reached (i.e. a situation at which no net current crosses the membrane). Any perturbation

in concentrations induces a compensatory flow which restores a new equilibrium. Mechanistically, the flow of ions achieves an equilibrium by modifying the distribution of electrical *charges* between both sides of the membrane, which has large effects on electrical potentials (but only negligible effects on concentrations, which are assumed to be fixed).
The membrane is *selectively* permeable to specific ions through dedicated channels, which implies that at the equilibrium, potentials and concentrations *do not equate* across both sides of the membrane, even though no more current is driven through it.

By modeling membranes as electrical components, physics laws can be applied to predict the current flow and the membrane potential with any distribution of ionic concentrations in external and internal media. The ionic current is due to two components :

- The difference in *ionic concentrations* between internal and external media favor the diffusion of ions towards the compartment in which they are less concentrated. This effect is modelled as a *generator* of current with constant driving force.
- The difference in *electrical potentials* between internal and external media favor the displacement of positive charges towards the compartment which exhibits the more negative (or less positive) polarity, and conversely for negative charges. This effect is modeled as a *resistor* obeying Ohm's law, in which the electrical current through the dipole is set by the difference in potentials at its terminals.

Thus, the current flowing through the membrane at any time is governed by the following expression :

$$I = -g_l(V_m - E_l) \tag{6}$$

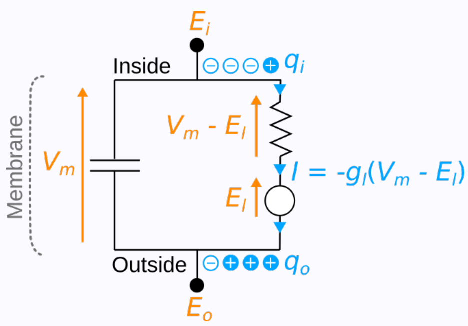
with :

- I : instantaneous current flowing across the membrane,
- $V_m = E_i - E_o$: instantaneous membrane potential, which is the difference between the internal and external potentials (the external media being the reference),
- E_l : equilibrium potential imposed by the ionic concentrations, which is the value of the membrane potential at which no more current is driven across the membrane,
- g_l : overall leak conductance of the membrane, due to all the parallel channels inserted in it.

The membrane potential resulting from the distribution of charges between both sides is given by the equation of a *capacitor* :

$$Q = C_m V_m \tag{7}$$

with C_m the membrane capacitance.



⑨ Knowing that 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.

⑩ Solve this equation for an initial condition V_0. Introduce a characteristic relaxation time τ_m and give its expression. Interpret what this constant represents for the dynamics.

⑪ Distinguish different behaviors depending on the initial value V_0 relative to the equilibrium potential E_l.

2.2 Leaky Integrate-and-Fire model (LIF)

Leaky Integrate-and-Fire model

The Leaky Integrate-and-Fire model extends the previous model to simulate some qualitative features of the membrane potential dynamics in **active behaviors**, when the neuron can be submitted to external inputs.

To do so, two elements are added :

- An input current can be applied to the neuron is modeled by an additional term I_{app} in the differential equation.
- When the membrane potential reaches a *threshold* value, a spike is emitted and the membrane potential is returned to a *reset* value.

Thus, the dynamical equation for the membrane potential is :

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

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

with I_{app} the 'apparent' current applied to the neuron, which can be constant or variable in time.

Different regimes can be observed depending on the injected current. This model introduces a framework on which more realistic models can be elaborated.

(12) *Threshold current* – With a constant current I_{app}, find the condition on this parameter for the neuron being 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.

(13) **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}.

(14) *Firing rate as a function of current (f-I curve)* – Compute the inter-spike interval T_{ISI} as well as the firing rate f of the neuron.

(15) Study the function $f(I)$ to represent it graphically : determine the limits depending on I and show that the $f(I)$ curve is asymptotically equivalent to a linear function for large values of input current.
Comment on this in light of biological plausibility.

(16) **num** Plot the function numerically and verify the results found at question (15).

2.3 Response to an oscillating input current

The neuron is receiving a small oscillating current :

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

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

The membrane potential integrates this current, therefore it reaches its steady state at which it oscillates around its equilibrium potential at the same frequency as the input current, with a certain time lag. Thus, this steady-state solution 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 the phase of oscillations compared to the input current.

(17) Represent I_{app} and V_m as a function of time, and interpret the parameters ω, I_0, A and ϕ.

(18) 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.

(19) Show that :

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

(20) Compute the amplitude A and phase ϕ of the response. Represent them as functions of ω.

(21) Comment on the limiting behaviours at low ($\omega \ll g_l/C_m$) and high frequency ($\omega \gg g_l/C_m$). At low frequency, relate the phase difference to the characteristic time constant τ_m (question (10)).
Justify that the membrane behaves as a low-pass filter.