TD 2 – Models of neurons II Generalized Integrate-and-Fire models

Practical Information

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

Goals of the TD

Hallmarks of neuronal dynamics roughly consist in the summation ('integration') of input currents, combined with a mechanism that outputs spikes (action potentials) above a threshold membrane potential. Spiking neuron models aim to describe the relationship between electrical currents at the input stage and membrane potential evolution, in order to predict spike emission at the output stage.

In this view, the Leaky-Integrate-and-Fire model achieves a first approximation. Nevertheless, the model is not able to account for a range of phenomena, such as the existence of a refractory period following spike emission, firing rate adaptation, bursting firing regimes... For those purposes, more complex models were developed as extensions of the Leaky-Integrate-and-Fire model.

This TD aims to present a variety of models of single point neurons' dynamics, beyond the Leaky-Integrate-and-Fire model.

Spiking neuron models can be distinguished according to their level of abstraction as opposed to their biological details.

- **Biophysical conductance-based models** (Hodgkin-Huxley models) provide a detailed description of the *shape of action potentials*. To do so, they encompass the explicit dynamics of voltage-sensitive ion channels, using first-order kinetics. Thus, those models are *dynamical systems* of several coupled variables. However, they are difficult to analyse theoretically, and computationally expensive to simulate.
- **Generalized Integrate-and-Fire models** are more abstract phenomenological descriptions, which only predict the *spike times*. Spikes are considered as discrete event, while their shape is not described. This choice is justified by the empirical observation of the stereotypical shape of action potentials for a given neuron : information is not contained in the shape of spiked but in their sequence.

Part **1** *focuses on non-linear Generalized Integrate-and-Fire models with one variable, which account for more refined spiking behaviors than the Leaky Integrate-and-Fire model.*

Part **2** *considers the Adaptive Integrate-and-Fire models with two variables, which extends the one variable models to account for the phenomenon of adaptation.*

The next TD will study the detailed Hodgkin-Huxley which explicitly models the shape of action potential, and several reductions of this model which grant more convenient theoretical analysis.

1 Non-linear Generalized Integrate-and-Fire models (1 variable)

Generalized Integrate-and-fire models

Integrate-and-fire models have two components to define their dynamics :

① A **differential equation** describing the evolution of the membrane potential as a function of input currents.

$$\tau \frac{\mathrm{d}V}{\mathrm{d}t} = f(V) + R(V)I(t) \tag{1}$$

where f and R can be *non-linear* functions of the membrane potential V.

② A mechanism for **spike emission**, generally a rule based on a threshold and reset :

If $V > V_{th}$, then $V = V_0$

with V_{th} the threshold potential for smike emission, and V_0 the reset potential after a spike.

This general model can be seen as an extension of the Leaky-Integrate-and-Fire model, whose differential equation has a *linear* form :

$$\tau \frac{\mathrm{d}V}{\mathrm{d}t} = -(V - E_l) + RI(t)$$

with E_l the 'leak potential' and $R = 1/g_l$ a constant.
In the generalized model, the leak term is replaced by the non-linear function $f(V)$, and $R(V)$ can be interpreted as a voltage-dependent input resistance.

In the following questions, the function $R(V)$ will be set to a constant $R > 0$.

1.1 General properties of non-linear models

① *Phase portrait* – Sketch an empty graph of y-axis $\frac{\mathrm{d}V}{\mathrm{d}t}$ and x-axis V. Place vertical lines marking the firing threshold V_{th} and the reset potential V_0.
For both models, trace the curve of the derivative as a function of V with $I = 0$ and :

- For the linear model, $V_0 \leq E_l < V_{th}$.
- For the non-linear model, $f(V)$ is a convex function with a minimum V_b between two zero-crossing points at V_r and V_c, such that $V_0 \leq V_r < V_b < V_c < V_{th}$.

② *Fixed points and Stability* – From the phase portraits with $I = 0$, identify the equilibria of each model and discuss their stability. Propose an interpretation for the parameters V_r and V_c in terms of 'rest' and 'critical' potentials.

③ *Bifurcation* – Explain the effect of increasing the input current. Distinguish the consequences for both models.

④ *Pulse and Step currents*

Experimentally, several types of input currents can be applied to the neuron to increase its membrane potential :

- A *pulse current* is a strong transient ('instantaneous') stimulation.
- A *step current* is a prolonged current of fixed and moderated intensity.

Distinguish the effects of a pulse and a step current in terms of the dynamics of charge and discharge of the neuronal membrane. Link those behaviors to the phase portrait.

⑤ *Voltage thresholds for spike emission and rheobase potential*

Pinpoint the following qualitative difference between both models :

- The linear model is characterized by a *single potential threshold* which has to be reached for the emission of a spike, in response to both pulse and step currents.
- The non-linear model is characterized by *distinct potential thresholds* which have to be reached for the emission of a spike, to a pulse current and a step current respectively.

⑥ *Response time courses* – For both models, predict responses to pulse and step currents of different intensities by illustrating the corresponding time courses in graphs $(t, I(t))$ and $(t, V(t))$ aligned one above the other.

1.2 Quadratic Integrate-and-Fire

Quadratic Integrate-and-Fire model (QIF)

In the **Quadratic Integrate-and-Fire model**, the differential equation for the membrane potential is given by :

$$\tau \frac{\mathrm{d}V}{\mathrm{d}t} = a(V - V_+)(V - V_-) + RI \tag{2}$$

with $a \in \mathbb{R}^+$ and $V_c > V_r$.

This model was motivated by the inability of standard models to generate sustained low frequency spiking, while networks with low firing rates are often observed in biological systems.

In the following questions, the model is simplified by taking $I = 0$.

⑦ Propose an interpretation for the parameters V_+ and V_-.

⑧ Justify that the system is topologically equivalent to the normal form :

$$\frac{\mathrm{d}V}{\mathrm{d}t} = c(b - b_n) + a(V - V_n)^2 \tag{3}$$

and propose a change of variable to study a system of the form :

$$\frac{\mathrm{d}v}{\mathrm{d}t} = \beta + v^2 \tag{4}$$

The following questions aim to study the simplified system following the above equation (4). This simplified system evolves from an initial condition v_0 (analogous of the reset potential V_0), until it reaches a value v_{th} (analogous of the threshold potential V_{th}), after which it is reset to v_0.

The parameter β can be varied so that it can be positive or negative. In the initial version of the equation, this is analogous to increasing the current I or the parameter b to slide the parabola along the vertical axis.

⑨ *Qualitative behaviors* – Separately for parameter $\beta > 0$ and $\beta < 0$, determine the possible behaviors as a function of the parameter v_0, by analysing the steady-states and their stability.

⑩ *Bifurcation diagram* – Represent the bifurcation diagram of the system in a parameter space of axes v_0 and β.

⑪ *Quantitative behaviors* – Separately for parameter $\beta > 0$ and $\beta < 0$ with $v_0 > \sqrt{|\beta|}$, compute the period of oscillations T. Deduce the evolution of $v(t)$ starting from v_0.

1.3 Theta model

Theta model

In the **Theta model** (also named Ermentrout–Kopell canonical Type I model), the differential equation for the membrane potential is given by :

$$\frac{\mathrm{d}\theta}{\mathrm{d}t} = 1 - \cos(\theta(t)) + [1 + \cos(\theta(t))] \cdot I(t) \tag{5}$$

The state variable θ represents an angle in radians.
The threshold potential for spike emission is $\theta_{th} = \pi$. The system is reset at a value θ_0 after a spike.

In the following questions, the input function $I(t)$ is set to a constant I.

⑫ *Qualitative equivalence with the QIF model* – By analysing the steady-states as a function of I, show that this system is topologically equivalent to the Quadratic Integrate-and-Fire model. To do so, proceed by a change of variable, inspiring from the expression of v found at question ⑨.

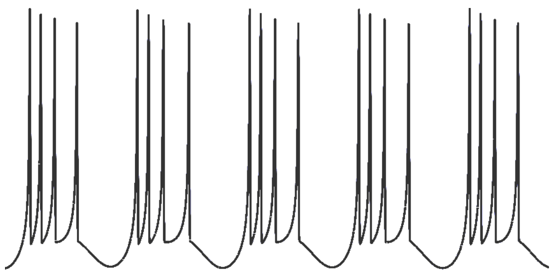
(13) *Quantitative equivalence with the QIF model* – Find an appropriate change of variable to transform the Theta model into the Quadratic Integrate-and-Fire model.

Parabolic Bursting

The Theta model is particularly well suited to describe **bursting**.

Bursting refer to rapid oscillations in the membrane potential interrupted by periods of quiescence (slow evolution). Bursting neuronal systems are often responsible for controlling and maintaining steady rhythms, such as breathing, induced by a small network in the brain stem.

Parabolic bursting is a type of bursting regulated by a slow external oscillation. This slow oscillation changes the frequency of the fast bursting oscillation, such that frequency of spikes at the beginning and end of each burst is high relative to the frequency at the middle of the burst. Therefore, the frequency curve of the burst pattern resembles a parabola, which explains the name given to this behavior.



In the following questions, the input function $I(t)$ is a slow wave $I(t) = \sin(\alpha t)$, where α is relatively small.

(14) *Response to an slow wave current* – Explain qualitatively the emergence of bursting, by considering the behavior of the model on appropriate time intervals during the evolution of the slow wave current.

1.4 Exponential Integrate-and-Fire

Exponential integrate-and-fire model (EIF)

In the **Exponential Integrate-and-Fire model**, the differential equation for the membrane potential is given by :

$$\tau \frac{\mathrm{d}V}{\mathrm{d}t} = -(V - V_r) + \Delta_T \exp\left(\frac{V - \mathcal{V}}{\Delta_T}\right) + RI \tag{6}$$

with Δ_T the sharpness parameter of the exponential non-linearity and $\mathcal{V}$ a critical potential.

(15) Justify the existence of a fixed point near V_r, if parameters are taken such that $\mathcal{V} \gg V_r + \Delta_T$ and with $I = 0$.

(16) On a phase portrait similar to question (1), approximately sketch the function $f(V)$ (on different domains, consider the dominant term of the sum). How do the parameters influence the shape of the function f ?

Experimental fit of the non-linearity

The exponential non-linearity is strongly supported by experimental evidence, as it can be directly extracted from experimental data.

Fitting the non-linearity can be performed through the *dynamic I-V curve method*. In such electrophysiological experiments, the time course of the membrane potential is recorded with an electrode in response to the injection of a time-varying current into the neuron.

(17) Show that for the general equation (1), the non-linear function can be rescaled and expressed in the form :

$$\tilde{f}(V(t)) = \frac{1}{C_m} I(t) - \frac{\mathrm{d}}{\mathrm{d}t} V(t)$$

(18) *Fitting to data* – From times courses of $V(t)$ and $I(t)$ recorded experimentally, propose a method to verify the adequation of the exponential non-linearity chosen in the model.

2 Adaptive Generalized Integrate-and-Fire (2 variables)

Adaptive models

Experimentally, in response to a step current, neuronal responses can exhibit specific **firing patterns**, defined by a stereotypical arrangement of short, long or variable inter-spike intervals. Various firing patterns have been observed, encompassing tonic, adapting, or delayed firing.

This diversity of firing patterns can be explained to a large extent by **adaptation** mechanisms, which refer to the modulation of subsequent responses due to preceding stimulation of the neuron. Adaptation patterns themselves depend on the variety of ion channels repertoires characterizing different neuronal types.

In order to model the variety of firing patterns through adaptation, a single equation is not sufficient.

In the **Adaptive Integrate-and-Fire models**, the membrane potential differential equation is coupled to abstract current variables obeying a linear differential equation modulated by the stimulation history :

$$\tau_m \frac{\mathrm{d}V}{\mathrm{d}t} = f(V) - R\sum_j^{w_j} w_j + RI(t) \tag{7}$$

$$\tau_j \frac{\mathrm{d}w_j}{\mathrm{d}t} = a_j(V - V_r) - w_j + b_j\tau_j \sum_k \delta(t - t_k) \tag{8}$$

- As in other integrate-and-fire models, a spike is emitted as soon as the membrane potential reaches a threshold V_{th}, and the membrane potential is subsequently reset to a potential V_0.
- The sequence of spikes defines the spiking times t_j. Spiking events are indicated by the δ-functions of spike times $\delta(t - t_k)$, which equal 1 at all times t_k when a spike is produced, and 0 otherwise.
- The membrane potential and the adaptation currents evolve with distinct time scales, with time constant τ_m and τ_j respectively.
- Adaptation is characterized by two types of parameters :
  - The parameters b_j control spike-triggered adaptation : they reflect the 'jumps' by which the adaptation variables w_j are modified immediately after one spiking event.
  - The parameters a_j control sub-threshold adaptation : they couple adaptation to the membrane potential.
- In turn, adaptation currents are fed back to the membrane potential dynamics with resistance R.

The choice of the parameters largely determines the firing patterns of the neuron, and can be related to the dynamics of ion channels.

The Adaptive Integrate-and-Fire model can be adapted to various choices of functions f, and encompass various number of variables w_j. In the following sections, it will be investigated with the Leaky Integrate-and-Fire model and the Exponential Integrate-and-Fire model, and with only two variables (the membrane potential V and a single adaptation current w).

2.1 Adaptive Leaky Integrate-and-Fire model

Adaptive Leaky Integrate-and-Fire model (AdLIF)

The **Adaptive integrate-and-fire model** combines the leaky integration of the membrane potential with one adaptation variable. The system is thus defined by two differential equations :

$$\tau_m \frac{\mathrm{d}V}{\mathrm{d}t} = -V - w + I \tag{9}$$

$$\tau_w \frac{\mathrm{d}w}{\mathrm{d}t} = -w + \Delta_w \sum_k \delta(t - t_k) \tag{10}$$

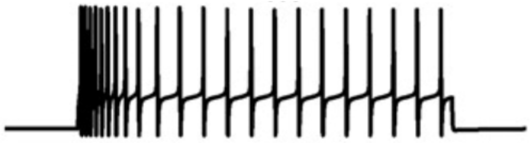
with a reset potential $V_0 = 0$, an initial condition $w(t = 0) = 0$, and a constant input current $I > V_{th}$.

Note : Those equations might seem not homogeneous, but an implicitly resistance $R = 1$ is omitted by sake of simplicity.

Firing rate adaptation

A classical adaptation phenomenon is the progressive slowing down of firing in response to a maintained input current. A possible biophysical interpretation is the accumulation of calcium into the cell during repetitive spiking, which induces a counteracting calcium-dependent potassium current.

The Adaptive integrate-and-fire model above is well suited to reproduce the classical adaptation effect, because the adaptation variable w here reflects an negative current (negative sign in $\frac{\mathrm{d}V}{\mathrm{d}t}$ in equation (9)).



2.1.1 Neglecting the decay of the adaptation variable

As a first approximation, the decay of the adaptation variable can be neglected, and w is considered to be piece-wise constant on each inter-spike interval (i.e. between two spikes).

19 Discuss qualitatively how the system is modified after the first spike.

20 Find the value of w at which the neuron stops spiking, and the corresponding number of spikes emitted.

21 Compute the duration of an inter-spike interval as a function of w in that interval.

2.1.2 Taking into account decay

22 Roughly, at which condition is it not possible anymore to ignore the decay of the variable w ? Is it possible for the neuron to stop spiking ?

The system is considered to have reached its equilibrium firing rate and to fire spikes with a period T.

23 Compute the time course of w between two successive spikes, assuming that immediately after the first spike the adaptation variable starts at $w = w_0$.

24 Proof the following relation between w_0 and Δ_w :

$$w_0 = \frac{\Delta_w}{1 - \exp(-T/\tau_w)}. \tag{11}$$

25 Assuming that w can be approximated by its average value during the whole inter-spike interval, show that the period T of spike emission is given by :

$$T = \tau_m \ln\left(\frac{I - w}{I - w - V_{th}}\right) \tag{12}$$

26 Show that the asymptotic behavior of the firing rate $r(I)$ with increasing current is linear (the same method as in TD1 can be used) :

$$r(I) \sim \frac{1}{\tau_w \Delta_w + \tau_m V_{th}} I \tag{13}$$

27 Compare this asymptotic behavior an integrate-and-fire model without firing rate adaptation.

2.2 Adaptive Exponential Integrate-and-Fire

Adaptive Exponential Integrate-and-Fire model (AdEx)

The **Adaptive Exponential Integrate-and-Fire model** combines the exponential non-linearity of the membrane potential equation with a single adaptation variable

$$\tau_m \frac{\mathrm{d}V}{\mathrm{d}t} = -(V - V_r) + \Delta_T \exp\left(\frac{V - \mathcal{V}}{\Delta_T}\right) - Rw + RI \tag{14}$$

$$\tau_w \frac{\mathrm{d}w}{\mathrm{d}t} = a(V - V_r) - w + b\tau_w \sum_k \delta(t - t_k) \tag{15}$$

In the following questions, parameters will be chosen such that : $V_r < V_0 < \mathcal{V} < V_{th}$, $b > 0$ and $a \in \mathbb{R}$, and a *separation of time scales* : $\tau_m \ll \tau_w$.

This model is able to reproduce a large variety of firing patterns observed experimentally. Those behaviors can be understood through a *phase plane analysis*.

28 Sketch a graph of x-axis V and y-axis w.
Place a vertical line for the threshold potential V_{th}.
Trace the nullclines before any spike has been emitted, with a current $I > 0$ such that both nullclines do not cross.
Represent the direction of the gradient of the system in each area of the graph.

29 What does the separation of time scales imply for the dynamics of w relative to V ? Adjust the norm of the gradient on the graph accordingly.

Before any current is injected, the membrane potential lies near the equilibrium V_r and the adaptation variable starts at $w_0 = 0$. As soon as the step current is applied, the dynamics can be depicted by the phase plane of question 28.

30 Place the initial point (V_r, w_0) in the phase plane and trace the system's trajectory up to the emission of the first spike.

31 Place the reset point after the first spike in two possible cases depending on the reset potential : $V_0 < \mathcal{V}$ and $V_0 > \mathcal{V}$ (with a small δ_w). In both cases, trace multiple successive trajectories and reset points after each spike.

32 Represent the corresponding time courses of $V(t)$ as a function of time. Which firing pattern does each case model (regular tonic spiking, bursting) ?