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

## Practical Information

**TD Assistant**
eponiatowski@clipper.ens.psl.eu

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

### Goals of the TD

Neuronal dynamics are underlied by in the integration of electrical currents, combined with a mechanism that emits spikes (action potentials) above a threshold membrane potential. Models of point neurons aim to describe the relationship between input currents, the evolution of the membrane potential, and output spiking.

The Leaky-Integrate-and-Fire model achieves a first approximation. Nevertheless, this 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...

This TD aims to present extensions of the Leaky-Integrate-and-Fire model.

Those models can be distinguished according to their level of abstraction with respects to biological mechanisms.

- **Biophysical conductance-based models** (e.g. Hodgkin-Huxley models) provide a detailed description of the *shape of action potentials*. Indeed, they explicitly express the dynamics of different voltage-sensitive ion channels, which account for distinct components of the evolution of the membrane potential. However, those models are difficult to analyse theoretically, because they consist of *dynamical systems* of several coupled variables.
- **Generalized Integrate-and-Fire models** are more phenomenological descriptions, which only predict the *spiking times* (as discrete events). They gather all the complex phenomena in a single or a few equations, which can be tackled analytically.

**SUMMARY**

**Part 1** Non-linear Generalized Integrate-and-Fire models (one variable) : general comparison with the linear model and study of three particular cases.

**Part 2** Adaptive Integrate-and-Fire models (two variables) : two versions based on the one-dimensional models.

*The next TD will study the Hodgkin-Huxley model with more variables.*

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

**Generalized Integrate-and-fire models**

Integrate-and-fire models have two ingredients :

① A **differential equation** for 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, in which the differential equation is *linear* :

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

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.

## 1.1 General properties of non-linear models - Comparison with the linear model

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

① *Phase portrait*

Sketch an empty graph with $\frac{\mathrm{d}V}{\mathrm{d}t}$ as y-axis and $V$ as x-axis. Place vertical lines marking the firing threshold $V_{th}$ and the reset potential $V_0$.
For both the linear model and the non-linear model, 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 *Bifurcations*

Explain the effect of increasing the input current $I$. Distinguish the consequences for both models.

④ *Pulse and Step currents*

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

- **Pulse current** : Strong and transient ('instantaneous') stimulation.
- **Step current** : Moderated and prolonged current of fixed intensity.

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

⑤ *Threshold potentials for spike emission & Rheobase potential*

Justify the following qualitative difference between both models :

- The linear model is characterized by a *single threshold potential* 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 two *distinct threshold potentials* 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 each model, illustrate response time courses to pulse and step currents of different intensities in graphs $(t, I(t))$ and $(t, V(t))$ aligned one above the other.

In the following parts, three particular cases of non-linear models are studied.

### 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 $V_+ > V_-$.

Note : This model is able to generate sustained low frequency spiking regimes, 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 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 $\beta$ 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 $\beta$.

11 *Quantitative behaviors*

Separately for parameter $\beta > 0$ and $\beta < 0$ with $v_0 > \sqrt{|\beta|}$, compute :
- the evolution of $v(t)$ starting from $v_0$,
- the period of oscillations $T$.

### 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 $\theta$ represents an angle in radians.
The threshold potential for spike emission is $\theta_{th} = \pi$. The system is reset at a value $\theta_0$ 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 fixed points and their stability as a function of $I$, show that this system is topologically equivalent to the Quadratic Integrate-and-Fire model.

**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.

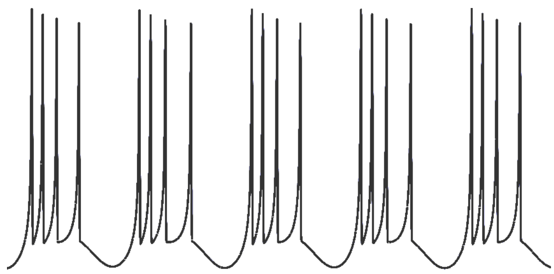
In the following questions, the input function $I(t)$ is a slow wave $I(t) = \sin(\alpha t)$, where $\alpha$ is relatively small.

**Parabolic Bursting**

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

Bursting refers to a behavior of fast spiking periods interrupted by periods of quiescence. In vivo, bursting neuronal systems are often responsible for maintaining steady rhythms (for instance, breathing is induced by a small network in the brain stem).

Parabolic bursting is a particular type of bursting, which is regulated by a slow external oscillating current. This slow current changes the frequency of spike emission during each bursting cycle (*parabolic-like* frequency curve in time : higher at the beginning and at the end relative to the middle).



**14** *Response to an slow wave current*

Explain qualitatively the emergence of parabolic 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 :

- $\Delta_T$ : "Sharpness" parameter of the exponential non-linearity.
- $\mathcal{V}$ : Critical potential.

**15** *Fixed points*

What is the condition on the parameters for the existence of at least one fixed point ? Deduce why the parameter $\mathcal{V}$ is called a "critical potential".

When this condition is met, when parameters are taken such that $\mathcal{V} \gg V_r + \Delta_T$ and with $I = 0$, justify the existence of a fixed point near $V_r$.

**16** *Phase portrait*

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* – Propose a method to verify the adequation of the exponential non-linearity chosen in the model, from times courses of $V(t)$ and $I(t)$ recorded experimentally with a sampling time step $\delta_t$.

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

### Adaptation in neuronal firing

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 mechanisms 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.

### Adaptive Integrate-and-Fire models

In the Adaptive Integrate-and-Fire models, the differential equation for the membrane potential is coupled to one or several variables for "adaptation currents". Each one obeys a differential equation linear relative to the other variables and modulated by the spiking 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 spiking history defines a sequence of spiking times $t_k$, indicated by $\delta$-functions : $\forall k,\ \delta(t - t_k) = \begin{cases} 1 \text{ when } t = t_k \\ 0 \text{ otherwise} \end{cases}$
- The membrane potential and the adaptation currents evolve with distinct time scales, depending on the time constants $\tau_m$ and $\tau_j$ respectively.
- Adaptation depends on two contributions, reflected 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 a resistance $R$.

*Note : The Adaptive Integrate-and-Fire model admits various choices of functions $f$, and can encompass various number of variables $w_j$. The choice of the parameters largely determines the firing patterns of the neuron, and can be related to the dynamics of ion channels.*

In the following sections, the Adaptive Integrate-and-Fire model is investigated using :
- only two variables : the membrane potential $V$ and a single adaptation current $w$,
- either the Leaky Integrate-and-Fire model or the Exponential Integrate-and-Fire model for the function $f$.

### 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 a single adaptation variable. The system is thus defined by two differential equations :

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

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

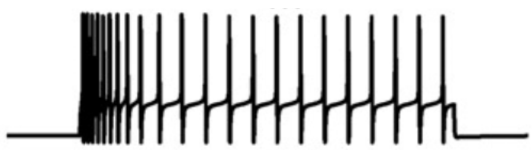
*Note : Those equations might seem not homogeneous, but an implicit resistance $R = 1$ is omitted by sake of simplicity.*

In the following questions, the model will be further simplified with a reset potential $V_0 = 0$, an initial condition $w(t = 0) = 0$, and a constant input current $I > V_{th}$.

**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 Leaky 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 $w$ (maintained constant within that interval).

#### 2.1.2 Taking decay into account

(22) Roughly, at which condition is it not possible to ignore the decay of the variable $w$ anymore ? Why should this condition be considered ?

The system is considered to have reached a stationary regime, in which it fires spikes with a constant period $T$ (hypothesis).

(23) Determine 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 $\Delta_w$ :

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

(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 verifies the implicit formula below :

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

Justify that it admits a solution $T^* > 0$ when $V_{th} > 0$ and $I > V_{th}$.

(26) Show that the asymptotic behavior of the firing rate $r(I)$ with increasing current is linear :

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

(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 :

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

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

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

In the following questions, parameters are set such that :
- $V_r < \mathcal{V} < V_{th}$
- $b > 0$
- $a < \frac{1}{R}\left(\frac{\Delta_T}{\mathcal{V} - V_r} - 1\right)$
- Separation of time scales : $\tau_m \ll \tau_w$.

(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 at an equilibrium $V_0$ 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 $(V_0, w_0)$ in the phase plane and trace the system's trajectory up to the emission of the first spike.

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