TD 4 – Models of neurons III – Biophysical Conductance-based models

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 a class of **biophysical conductance-based models**, which explicitly tackle the detailed dynamics of **voltage-sensitive ion channels** generating ionic currents. By incorporating diverse combinations of ion channels, those models can adapt to various types of voltage response patterns, such as action potentials, periodic firing, sub-threshold resonance, spike adaptation...

In those models, various voltage responses intrinsically stem from the model's equations. Thus, contrary to the Generalized Integrate-and-Fire models investigated in the previous TD, conductance-based models models do not resort to an 'artificial' reset mechanism.

Response patterns are interesting because they reflect distinct **neurocomputational properties**, i.e. different ways neurons can react to stimulations and transform input signals. Modeling helps to understand *what kind of stimulation* is required to trigger a given response pattern, and conversely, *what type of response* is evoked by a given stimulation.

This TD aims to illustrate that the fundamental aspect of a system to exhibit a specific behavior is the *geometry of its phase space* as well as on the *bifurcations* of the underlying dynamical system. A specific type of response pattern can thus be achieved by multiple combinations of ionic currents, provided they constitute a dynamical system with an appropriate geometry.

Part1 General framework of conductance-based models.

Part 2 Hodgkin-Huxley model, with 4 variables. Mechanisms for generating action potentials.

Part 3 Fitz-Hugh Nagumo model, reduction of the Hodgkin-Huxley model with 2 variables.

1 Conductance-based models

1.1 Components of conductance-based models

Equivalent electrical circuit

Conductance-based models aim to a "biophysical", i.e. realistic, description of the neuronal membrane.

They extend the Leaky Neuron model ▷[*TD1*] on two main points :

- **Several currents** can cross the membrane through selective ionic channels.
- The opening of ion channels (and consequently, the currents flowing through the membrane) is **voltage-dependent**, i.e. modulated by the membrane potential itself.

Conductance-based models can be associated with a representation of the neuronal membrane as an **electrical circuit**.

- The ability of the membrane to accumulate charges is modeled by a *capacitor*.
- Each ionic current corresponds to two components :
  ▷ A constant *driving force* (battery), due to the fixed gradient of concentrations between the intracellular and the extracellular media.
  ▷ A (voltage-dependent) *conductance* (inverse of resistance) reflecting the membrane permeability to the considered ion through its selective channels.

The standard formulation of a conductance-based model leads to a **dynamical system**, which includes several variables.

The main variable is the *membrane potential* V. Its evolution is governed by the total net current which crosses it, which is the sum of the different ionic currents flowing through the channels (indexed by j below) and external inputs :

$$C_m \frac{\mathrm{d}V}{\mathrm{d}t} = -\sum_j g_j(V)(V - E_j) + I(t) \tag{1}$$

with :
- C_m : Capacitance of the membrane.
- $g_j(V)$: Conductance for ion j (potentially voltage-dependent, see below).
- E_j : Driving force for ion j (fixed by the concentrations of this ions in intracellular and extracellular media).
- $I(t)$: External input currents (potentially time-varying).

① Draw the equivalent electrical circuit representing the neuronal membrane.

Dynamics of voltage-sensitive conductances

Biologically, the voltage-dependence of ion channels reflects their change of conformation depending on their electrical surroundings, which makes them transition between 'open' and 'close' states when the charge of the membrane evolves.

Furthermore, each single ions channels is usually composed of distinct **voltage-dependent sub-units**, which should all be in an "active" state so that the channel is open.

Therefore, the conductance g of an ion channel (index j is omitted) can be described as a **voltage-dependent function** of the following form :

$$g(V) = \overline{g}\ a(V)^p b(V)^q \tag{2}$$

- The constant $\overline{g}$ represents the maximal conductance of a channels selective for its ion.
- The variables a and b ($\in [0, 1]$) are activation and inactivation **gating variables** for the ion channel, which can be interpreted as the activity of the different sub-units composing the channel (i.e. the probability that each type of sub-unit is in an active state). The integer powers $p,\ q \in \mathbb{N}$ (small) are related to the number of those sub-units (stoechiometry) in a single channel.

Experimentally, it is possible to measure the **opening and closing rates** of an ion channel (voltage-clamp). These opening and closing rates turn out to be themselves voltage-dependent.

Thus, in the model, the dynamics of the gating variables (equation (4)) follow **first order kinetics** :

$$\frac{\mathrm{d}a}{\mathrm{d}t} = \alpha_a(V)\ (1-a) - \beta_a(V)\ a \qquad \frac{\mathrm{d}b}{\mathrm{d}t} = \alpha_b(V)\ (1-b) - \beta_b(V) \tag{3}$$

with α and β the activation and inactivation rates of the respective units.

② Obtain the dynamical equations (3) by a matter balance.

Steady-states & Time constants

The dynamics of the gating variables can be rewritten under the following form :

$$\frac{\mathrm{d}a}{\mathrm{d}t} = \frac{1}{\tau_a(V)}(a_\infty(V) - a) \qquad \frac{\mathrm{d}b}{\mathrm{d}t} = \frac{1}{\tau_b(V)}(b_\infty(V) - b) \tag{4}$$

- The functions a_∞ and b_∞ are the **steady-states** of the gating variables under a fixed voltage.
They typically depend on voltage in a sigmoidal manner, and thus can approximated by Boltzmann functions :

$$a_\infty(V) = \frac{1}{1 + \exp\left(\frac{V_{1/2} - V}{k}\right)} \tag{5}$$

- The functions τ_a and τ_b are the **activation time constants** of the gating variables under a fixed voltage.
They typically depend on voltage in a bell-shaped manner, and thus can be approximated by Gaussian functions :

$$\tau_a(V) = \tau_0 + \overline{\tau} \exp\left(-\frac{(V_{max} - V)^2}{\sigma^2}\right) \tag{6}$$

③ Express the steady-states a_∞, b_∞ and time constants τ_a, τ_b as a function of α_a, β_a, α_b, β_b.

④ Sketch Boltzmann (5) and Gaussian functions (6) and interpret the parameters k, $V_{1/2}$, V_{max}, τ_0.

Which choice of parameters could be used to model *activation* gates (i.e. units which open when V increases) and *inactivation* gates (i.e. units which close when V increases) respectively ?

Which choice of parameters could be used to model *fast* and *delayed* currents in response to a stimulation ?

1.2 Minimal models for action potential generation

Minimal models for action potential generation

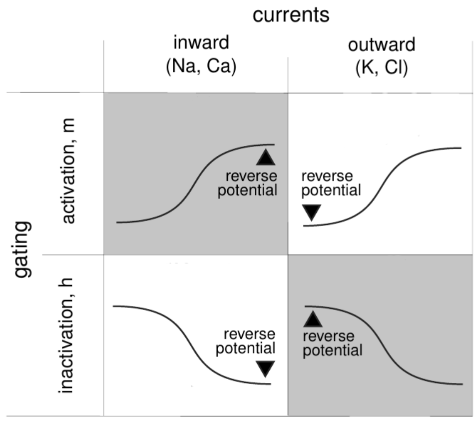
Owing to the vast repertoire of existing ion channels, a huge number of conductance-based models could be built a priori ($\approx 2^{30}$). **Minimal models** consist of combinations of conductances which are *irreducible for spiking*, i.e. which are sufficient to generate action potentials, while removing one conductance abolishes this property.

Minimal models are interesting to understand the **fundamental mechanisms** for the generation of action potentials. The following mechanisms are required :

- In absence of stimulation, the system lies at a *resting state* with a low membrane potential.
- In response to a stimulation, a *fast positive feedback* triggers a rapid upstroke of the membrane potential.
- During a later phase, a *slower negative feedback* counteracts the increase of the membrane potential and drives the system back to the resting state.

⑤ Channels' gates can be classified according to :
- their reaction to voltage changes (activation / inactivation),
- the direction of the current (outward/inward) flowing through this gate.

Determine the role of the four types of gates in the table, between :
- Amplifying gates, which enhance voltage changes via a positive feedback loop.
- Resonant gates, which resist voltage changes via a negative feedback loop.



Multiple realizations – Examples of minimal models

Among the classical minimal models, the **persistent sodium plus potassium model** $I_{Na,p} + I_K$ includes a sodium (inward) current and a potassium (outward current), both voltage-sensitive :

$$\begin{aligned} C\,\frac{\mathrm{d}V}{\mathrm{d}t} &= -\bar{g}_{Na}\, m\,(V - E_{Na}) \;\; -\bar{g}_K\, n\,(V - E_K) \\ \tau_m(V)\,\frac{\mathrm{d}m}{\mathrm{d}t} &= m_\infty(V) - m \qquad (7) \\ \tau_n(V)\,\frac{\mathrm{d}n}{\mathrm{d}t} &= n_\infty(V) - n \qquad (8) \end{aligned}$$

Note : This model is analogous to the $I_{Ca} + I_K$ model proposed by Morris and Lecar (1981) to describe voltage oscillations in the barnacle giant muscle fiber.

An alternative model is the **transient sodium model** $I_{Na,t}$, which encompasses a voltage-insensitive leak (outward) current, and a voltage-sensitive sodium (inward) current :

$$\begin{aligned} C\,\frac{\mathrm{d}V}{\mathrm{d}t} &= -\bar{g}_l\,(V - E_l) \;\; -\bar{g}_{Na} m^3 h\,(V - E_{Na}) \\ \tau_m(V)\,\frac{\mathrm{d}m}{\mathrm{d}t} &= m_\infty(V) - m \qquad (9) \\ \tau_h(V)\,\frac{\mathrm{d}h}{\mathrm{d}t} &= h_\infty(V) - h \qquad (10) \end{aligned}$$

By convention, the notations of are conserved across models for different types of gates :

- Variables m correspond to fast activation gates for the sodium channel.
- Variable h correspond to slow inactivation gates for the sodium channel.

- Variables n correspond to slow activation gates for the potassium channel.

Interestingly, distinct sets of conductances can nonetheless display similar dynamics and generate action potentials. Conversely, conductance-based models involving some common conductances can display radically different dynamics.

In fact, the key element explaining the dynamics of a model is *not* the specific combination of ionic currents per se, but rather the *qualitative properties of the underlying dynamical system* ▷[*Part 3*].

6 In both models, which mechanisms are responsible for the fast positive feedback and the delayed negative feedback respectively ?

7 Experiments have shown that the time constant of the sodium gate m is much lower compared to the other units. Propose a reduction of the three-dimensional $I_{Na,p} + I_K$ system to a planar system (i.e. two-dimensional).

2 Hodgkin-Huxley model

Hodgkin–Huxley model

The **Hodgkin–Huxley model** was the first detailed conductance-based model, built from the experimental identification of the currents contributing to the action potential.

In the Hodgkin-Huxley model, three types of currents cross the membrane with different time scales :

- The **leak current** is responsible for the *passive* properties of the cell (as in the Leaky Neuron model). It tends to set the system to a low resting potential.
  The leak channels are *voltage-independent*, they remain open in all circumstances.
- The **sodium (Na) current** tends to drive positively charged ions inside the cell, triggering its *depolarization*. It is thus responsible for the *generation of the action potential*.
  The selective sodium channels are *voltage-dependent*, they contain both *activation and inactivation gates* with *fast and slow dynamics* respectively.
- The **potassium (K) current** tends to drive positively charged ions outside the cell, triggering its *hyperpolarization*. It is thus responsible for the *reset* (repolarisation) after a spike and the following *refractory period*.
  The selective potassium channels are *voltage-dependent*, they contain only an *activation gate* with *slow dynamics*.

The dynamics obey a four-dimensional system of non-linear differential equations :

$$\frac{\mathrm{d}V}{\mathrm{d}t} = -\overline{g}_l\ (V(t) - E_l)\quad -\overline{g}_{Na}\ m^3(V)\ h(V)\ (V(t) - E_{Na})\quad -\overline{g}_K\ n^4(V)\ (V(t) - E_K) + I(t) \tag{11}$$

$$\frac{\mathrm{d}m}{\mathrm{d}t} = \alpha_m(V)\ (1-m) - \beta_m(V)\ m \qquad \alpha_m(V) = \frac{40+V}{10\left(1-\exp\left(-\frac{40+V}{10}\right)\right)} \qquad \beta_m(V) = 4\exp\left(-\frac{65+V}{18}\right)$$

$$\frac{\mathrm{d}h}{\mathrm{d}t} = \alpha_h(V)\ (1-h) - \beta_h(V)\ h \qquad \alpha_h(V) = 0.07\exp\left(-\frac{65+V}{20}\right) \qquad \beta_h(V) = \frac{1}{\exp\left(-\frac{35+V}{10}\right)+1}$$

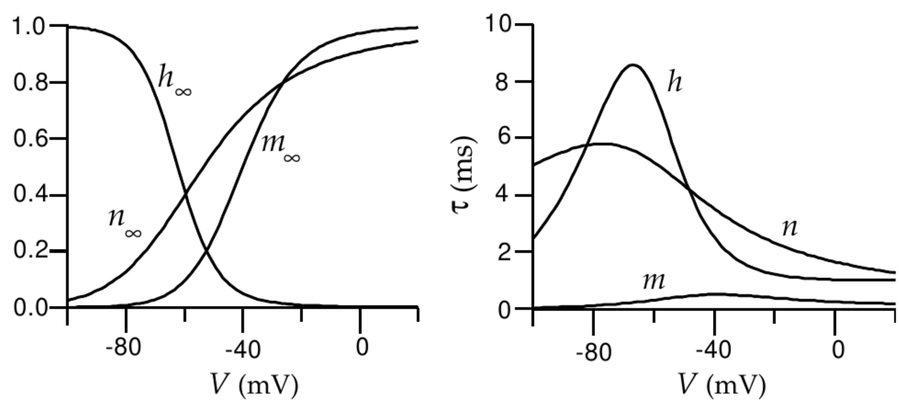
$$\frac{\mathrm{d}n}{\mathrm{d}t} = \alpha_n(V)\ (1-n) - \beta_n(V)\ n \qquad \alpha_n(V) = \frac{55+V}{100\left(1-\exp\left(\frac{55+V}{10}\right)\right)} \qquad \beta_n(V) = \frac{1}{8}\exp\left(\frac{65+V}{80}\right)$$

Parameters of the model :

$E_l = -54$ mV $\qquad E_{Na} = 50$ mV $\qquad E_K = -77$ mV

$\overline{g}_l = 0.3$ mS/cm^2 $\qquad \overline{g}_{Na} = 120$ mS/cm^2 $\qquad \overline{g}_K = 36$ mS/cm^2 $\qquad C = 1\ \mu$F/cm^2

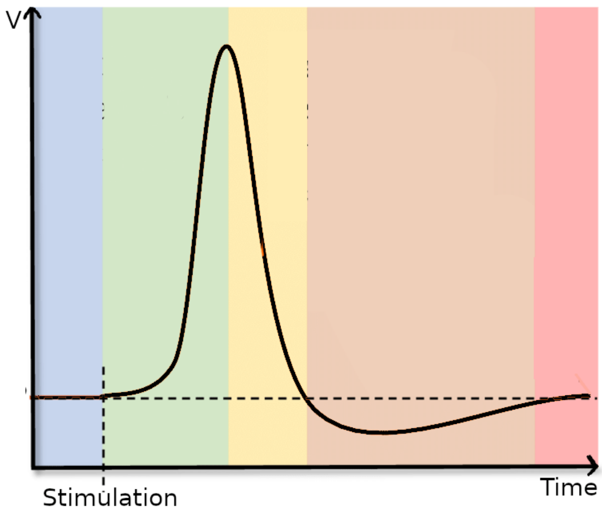
Steady-states and time constants of the gating variables :

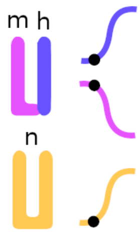


2.1 Action potential generation

In response to a strong depolarizing stimulation current, the steps of an action potential can be predicted qualitatively by considering the gating variables' time constants and steady-state activities at a function of voltage.

Note : For each step below, draw the state of the activation gates under the action potential curve.





8 *Resting state*
- At the resting state, in which state is each gating variable ?
- Do currents cross the membrane ?

9 *Depolarization – Upstroke of the membrane potential*
- After the initial depolarization induced by an external stimulation, which gating variable(s) respond(s) first ? Do(es) it/they activate or inactivate ?
- Which is/are the dominant current(s), and what does it entail for the evolution of the membrane potential ? Justify that a positive feedback loop is triggered during the initial phase of response.

10 *Repolarization towards V_r*
- What are the later effects of the slower gating variable(s) ?

11 *Hyperpolarization below V_r & Refractory period*
- How are the time constants of the variables n and h during the repolarization phase ? What does it imply for their recovery to the initial state ?
- Justify that the remaining K current fosters a hyperpolarization.
- Justify that the variable h is responsible for a refractory period, during which the neuron is prevented to respond to new stimulations.

2.2 Simulations of the model

12 **num** Implement the model in Python and simulate it for various input currents. Comment on the existence of a threshold for firing.

13 **num** Show the existence of an approximate linear relation between the variables h and m. How could this relation be exploited to simplify the model ?

3 FitzHugh-Nagumo model

FitzHugh-Nagumo model

The **FitzHugh-Nagumo model** is an abstraction of minimal conductance-based model, which captures their key property to generate action potentials.

The FitzHugh-Nagumo model is a two-dimensional system, in which :

- *Positive-feedback* is incorporated directly in the *membrane potential variable*, through a non-linear *N-shaped nullcline*.
- *Negative-feedback* is provided by a *recovery variable* mimicking the activation of an outward current, with a *linear nullcline*.

$$\frac{\mathrm{d}V}{\mathrm{d}t} = V(a-V)(V-1) - w + I \tag{12}$$

$$\frac{\mathrm{d}w}{\mathrm{d}t} = bV - cw \qquad \text{with } b > 0,\ c \geq 0 \tag{13}$$

This model satisfies basic requirements for describing neuronal behaviors :

- The system displays *stable fixed point*, which can be assimilated to the *rest potential* of the neuron.
- *Action potentials* correspond to *large closed orbits* in the phase space in response to a sufficient perturbation (i.e. trajectories starting in a certain neighborhood of the fixed point make a wide-amplitude excursion through high potentials, and return to the fixed point).

3.1 Local analysis

(14) In the case $I = 0$, draw the nullclines of the model. How many equilibria can the system have ?

(15) Find a trivial equilirbium (V^*, w^*).

(16) Linearize the system around the equilibrium, i.e. approximate the response to a small perturbation

$$V(t) = V^* + \delta V(t) \tag{14}$$

$$w(t) = w^* + \delta w(t) \tag{15}$$

under the form :

$$\frac{\mathrm{d}(\delta V)}{\mathrm{d}t} = -a\delta V - \delta w \tag{16}$$

$$\frac{\mathrm{d}(\delta w)}{\mathrm{d}t} = b\delta V - c\delta w \tag{17}$$

(17) Rewrite the differential system of the first-order perturbation by introducing the vector formalism $X = (\delta V,\, \delta w)$ and the matrix $\mathbf{M}$ of the associated linear system.
Express the trace and the determinant of this matrix as a function of the parameters a, b, c.

(18) Classify the types of behaviors around the equilibrium depending on the trace and the determinant.
Map those possibles behaviors in a parameter space of axes (c, a), assuming a fixed value of b. Determine the domains of each type of equilibria and their stability.

(19) Under which choice of parameters do bifurcations arise ? Identify in this graph two types of bifurcations :

- *Saddle-Node* bifurcation – A stable node becomes unstable.
- *Andronov-Hopf* bifurcation – A stable focus transforms into a limit cycle.

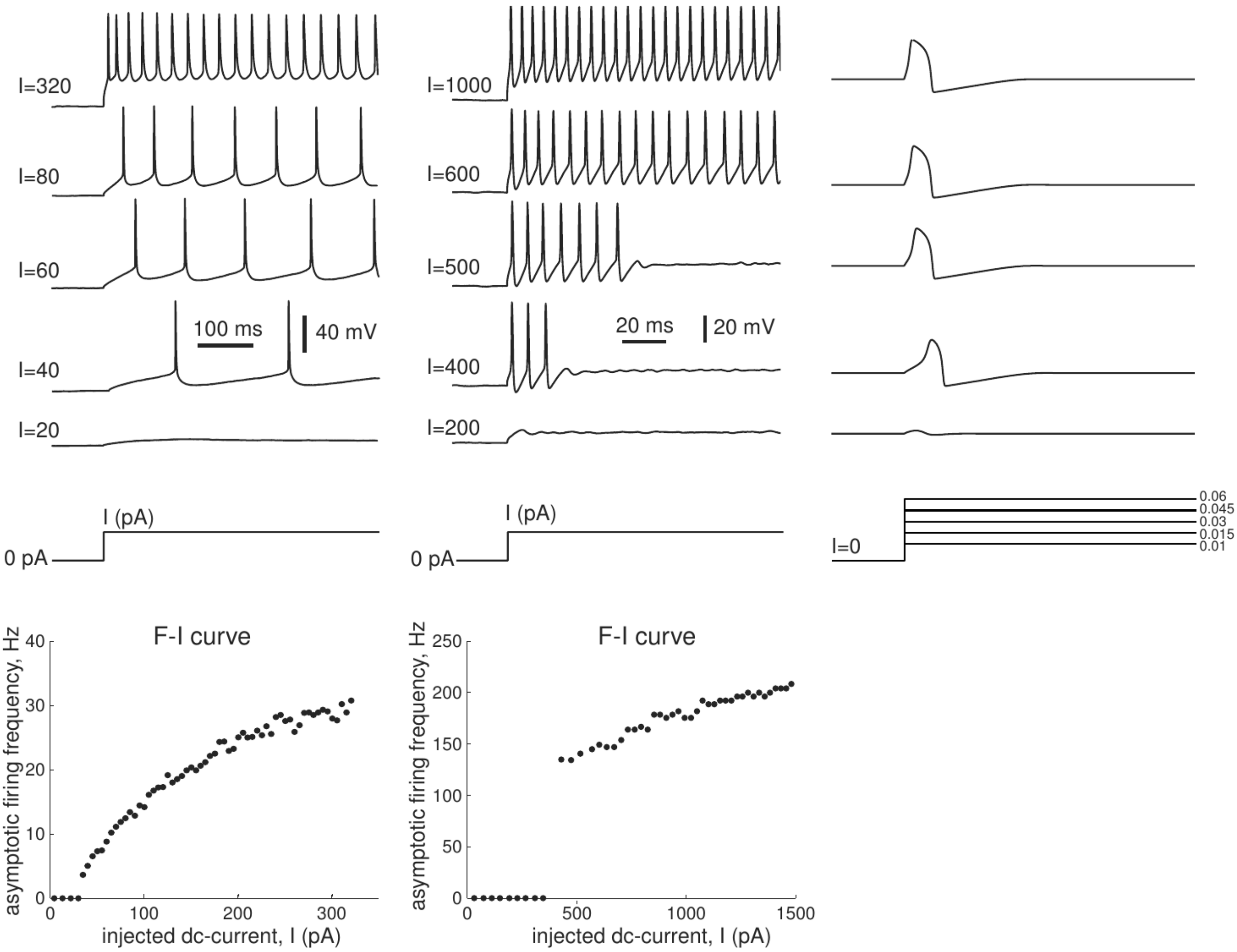
(20) Relate the sign of the parameter a to the position of the equilibrium along the V-nullcline.
The left-outer branch of the V-nullcline is sometimes named *stable* and the inner branch *unstable*. Is this labelling accurate ?

3.2 Explaining neurocomputational properties

Several types of neuronal responses can be understood through the **phase plane analysis** of the model.

3.2.1 Excitability & Responses to pulse and step currents

> **Classes of excitability**
>
> One type of neuro-computational property is the **class of excitability**, which describes the relation between the input strength and the output firing pattern.
>
> Three main types of excitability have been put forward :
> - *Class* `I` – Action potentials can be generated with low input currents, leading to a continuous f-I curve.
> - *Class* `II` – Action potentials can be generated only above a threshold current, leading to a discontinuous f-I curve.
> - *Class* `III` – At most a single action potential can be generated above a threshold current, thus no f-I curve can be defined.



21 Under the hypothesis of a separation of time scales ▷[*TD2*] with w evolving much slower than V, and with a single fixed point, sketch the vector field in the phase diagram.

22 In response to a *pulse* of current, the potential is perturbed from its fixed point to a higher value ▷[*TD2*]. Trace the trajectories of the system in response to a sub-threshold and a supra-threshold pulse current, so as to explain the emission of an action potential.

(23) What is the interest of a cubic nullcline compared to a quadratic nullcline ▷[TD2] in order to generate an action potential ? Why is a second variable necessary ?

(24) In the condition $c = 0$ and $a > 0$, justify that the effect of a *step current* cannot induce a bifurcation. Explain how this choice of parameters could account for Class `III` excitability.

(25) In the condition where the $c \neq 0$ which types of bifurcations could a priori account for Class `II` excitability ?

Note : Class `I` excitability can be explained by still another type of bifurcation in this model, the 'saddle-node on invariant cycle' bifurcation. It can also be explained in QIF and EIF models.

3.2.2 Integrators & Resonators

Integrators and Resonators

Another neuro-computational property is the distinction between **integrators** and **resonators**, which characterizes how neurons react to successive inputs received with a specific timing.

- *Integrators* respond preferentially to high-frequency inputs because they are most sensitive to inputs arriving simultaneously or in close temporal windows. They fire all-or-none spikes, and have well-defined thresholds. Functionally, they act as *coincidence detectors*.
- *Resonators* respond preferentially to oscillatory inputs at a specific resonance frequency. However, increasing the stimulation frequency beyond their resonance frequency may delay or even terminate their response. They often display *sub-threshold dampened oscillations*, and their firing threshold often depends on the previous stimulation.
  Functionally, they act as *frequency detectors*.

(26) Which type of equilibrium is appropriate to obtain integrators and resonators respectively ?

(27) Under which conditions does the system display dampened oscillations around the fixed point ?

(28) Close to this point, determine the amplitude and phase of the response to a small oscillating perturbation $I(t) = I_0 \sin(\omega t)$ ▷[TD1].

(29) Show that the response can exhibit resonance for particular input frequency ω.

3.3 Relaxation-oscillations – Van Der Pol oscillator

⚠ This exercise is **optional**. It proposes to compare the Fitz-Hugh Nagumo model to a classical model in physics. For the final exam, it is **NOT** required to master the mathematical tool of Laplace transform. ⚠

Van Der Pol oscillator

The Fitz-Hugh Nagumo model is also called the **Bonhoeffer–Van der Pol oscillator** because it contains the Van der Pol oscillator as a special case.

The standard form of the **Van Der Pol oscillator** is :

$$\frac{\mathrm{d}^2 x}{\mathrm{d}t^2} + \mu(x^2 - 1)\frac{\mathrm{d}x}{\mathrm{d}t} + x = 0 \tag{18}$$

It can also be written under the form of a first-order system with two variables, which is analogous to the Fitz-Hugh Nagumo model with $a = b = 0$:

$$\frac{\mathrm{d}x}{\mathrm{d}t} = \mu\left(x - \frac{1}{3}x^3 - y\right) \tag{19}$$

$$\frac{\mathrm{d}y}{\mathrm{d}t} = -\frac{1}{\mu}x \tag{20}$$

The Van Der Pol model helps to understand the spontaneous emergence of repetitive firing patterns in some neurons.

3.3.1 Two transformations in two-dimensional systems

Theorem – Linénard system

For a differential system given by :

$$\frac{\mathrm{d}^2 x}{\mathrm{d}t^2} + f(x)\frac{\mathrm{d}x}{\mathrm{d}t} + g(x) = 0$$

with f and g two continuously differentiable functions on $\mathbb{R}$, the second order ordinary differential equation can be transformed into an equivalent two-dimensional system of ordinary differential equations :

$$x_1 = x$$

$$x_2 = \frac{\mathrm{d}x}{\mathrm{d}t} + \int_0^x f(s)ds$$

(30) Prove that the Linéard transformation of the equation (18) indeed gives the system (19).

(31) Show that an alternative form for the equation (18) can be obtained by introducing of a simple variable, such that :

$$\frac{\mathrm{d}x}{\mathrm{d}t} = v \tag{21}$$

$$\frac{\mathrm{d}v}{\mathrm{d}t} = \mu\left(1 - x^2\right) - x \tag{22}$$

3.3.2 Qualitative behavior

(32) By analogy with a spring-mass mechanical system, interpret the terms of the equation (18) in terms of *dampening* and *restoring forces*, and propose a role for the parameter μ.
By comparing those forces when $|x| > 1$ and $|x| < 1$, predict qualitatively that the system could evolve according to a limit cycle in the phase space.

(33) To be more rigorous, consider the Lyapunov function based on the system (21) :

$$L(x, y) = x^2 + v^2$$

What does it represents ?
Compute its derivative, and interpret for the cases $|x| > 1$ and $|x| < 1$.

(34) Draw the nullclines of the Van Der Pol oscillator under its two-dimensional form (19).

(35) Show that the system admits a single fixed point, and determine its stability according to the parameter μ.

(36) Comment on the differences between the Van Der Pol and Fitz-Hugh Nagumo models. What dynamical properties do they provide, in the purpose of describing neuronal dynamics ?

3.3.3 Small dampening ($\mu \ll 1$)

> **Perturbation method**
>
> If the non-linearity remains small ($\mu \ll 1$), then it can be assumed that the trajectories in the phase space will be a small distortion of those of the harmonic oscillator (case $\mu = 0$). In particular, the system may display near-circular orbits.

(37) Find the behavior of the system for the case $\mu = 0$.

(38) Rewrite this system (21) with polar coordinates by the following change of variables $(x, y) \to (r, \omega)$:

$$x = r\cos(\omega) \qquad r \in \mathbb{R}^+ \tag{23}$$
$$y = r\sin(\omega) \qquad \omega \in [0, 2\pi] \tag{24}$$

(39) Comment on the first-order term of the derivatives $\frac{\mathrm{d}r}{\mathrm{d}t}$ and $\frac{\mathrm{d}r}{\mathrm{d}t}$, and then on its second order for small and large values of r.

> **Averaging method**
>
> An ansatz for the solution is to express it in a form close to the case $\mu = 0$ (25), by replacing constant terms r and ω by slowly varying functions $r(t)$ and $\omega(t)$ such that :
>
> $$x(t) = r(t)\cos(t + \omega(t)) \tag{25}$$
> $$\frac{\mathrm{d}x}{\mathrm{d}t}(t) = -r(t)\sin(t + \omega(t)) \tag{26}$$
>
> The method of averaging assumes that, since the variables (r, ω) are slowly varying in time, they are acting on average as constants.

(40) Introduce the ansatz (25) in (23) to show that :

$$\frac{\mathrm{d}r}{\mathrm{d}t} = -\mu r\left(r^2\cos^2(t+\omega) - 1\right)\sin^2(t+\omega)$$
$$\frac{\mathrm{d}\omega}{\mathrm{d}t} = -\mu\left(r^2\cos^2(t+\omega) - 1\right)\sin(t+\omega)\cos(t+\omega)$$

(41) Compute the averages of the variables r and ω over one cycle of oscillation.

(42) Deduce that the polar variable r obeys the following separable differential equation :

$$\frac{\mathrm{d}r}{\mathrm{d}t} = \frac{\mu}{8}r(4 - r^2)$$

Solve this system using partial fraction decomposition, so as to obtain :

$$r(t) = \frac{2e^{\frac{\mu}{2}t}}{\sqrt{e^{\mu t} - 1 + \frac{4}{r_0}}}, \quad \text{with } r_0 \in \mathbb{R}$$

(43) Conclude that the system evolves towards a limit cycle, and give its limit radius.

3.3.4 Large dampening ($\mu \gg 1$)

(44) Using the system (19), propose an approximation and draw the vector field accordingly.

(45) Qualitatively, start a trajectory on the vertical axis. What happens when this trajectory meets one branch of the cubic nullcline ?
By symmetry, argue that this trajectory forms a limit cycle.
This is the idea underlying the Liénard theorem to prove the existence of limit cycles.

(46) Which parts of the trajectory mainly determine the period of oscillations ?

3.3.5 Equivalent circuit

Electrical circuit of the Van Der Pol oscillator (for information)

At the beginning of the twentieth century, vacuum tubes were used to control the flow of electricity in the circuitry of transmitters and receivers. To model such a device, Van Der Pol inspired from a classical RLC circuit.
The classical RLC circuit consists of an inductance L, a capacitor C, a resistor R and a constant battery E. The current $I(t)$ flowing into the circuit obeys Kirchhoff's Voltage Law :

$$E = U_L + U_R + U_C = L\frac{\mathrm{d}I}{\mathrm{d}t} + RI + \frac{Q}{C}$$

with Q the charge of the capacitor, verifying $\frac{\mathrm{d}Q}{\mathrm{d}t} = I$.
Differentiating both sides of the equation lead to the standard equation of a damped harmonic oscillator :

$$0 = L\frac{\mathrm{d}^2 I}{\mathrm{d}t^2} + R\frac{\mathrm{d}Q}{\mathrm{d}t} + \frac{1}{C}I$$

The circuit that was considered by Van der Pol replaces the passive resistor by an active semiconductor (array of vacuum tubes). Unlike a resistor which simply dissipates energy, the semiconductor depends on the state of the system itself, injecting energy when the current is low, and absorbing energy when the current is high. This interplay results in a periodic oscillation in voltages and currents. The action of the semiconductor is modelled by the function $I^2 - \alpha$, where α is the threshold level of current. The dynamical equation for the current becomes :

$$E = L\frac{\mathrm{d}I}{\mathrm{d}t} + (I^2 - \alpha)I + \frac{Q}{C}$$

Differentiating leads to :

$$0 = L\frac{\mathrm{d}^2 I}{\mathrm{d}t^2} + 3\left(I^2 - \frac{\alpha}{3}\right) + \frac{1}{C}I$$

The model was generalized under the form :

$$\frac{\mathrm{d}^2 x}{\mathrm{d}t^2} + \mu(x^2 - 1)\frac{\mathrm{d}x}{\mathrm{d}t} + x = 0$$