TD 2 – 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 models which explicitly account for the **shape of response patterns**.

Contrary to the Generalized Integrate-and-Fire models investigated in the previous TD, no 'artificial' reset mechanism is implemented. Rather, a variety of phenomena such as *action potentials*, *periodic firing*, *sub-threshold resonance*, *spike adaptation*, etc, intrinsically stem from the model's equations.

To do so, biophysical conductance-based models tackle the detailed dynamics of voltage-sensitive channels responsible for ionic currents. By incorporating diverse combinations of ion channels, they can adapt to various types of neurons and firing patterns.

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 needed to trigger the firing of a given neuron, and to *what type of response* a given stimulation evokes.

This TD aims to illustrate that the fundamental aspect of a model which explains the behavior of a neuron is the *geometry of the phase plane* 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.

Part **1** *introduces the general framework of conductance-based models.*

Part **2** *presents the initial four-dimensional Hodgkin-Huxley model, and investigates the mechanisms for generating action potentials.*

Part **3** *studies the Fitz-Hugh Nagumo model, a two-dimensional model which captures the key properties of conductance-based models and affords a more convenient mathematical analysis.*

1 Biophysical conductance-based models

Conductance-based models

Conductance-based models aim to a realistic description of the neuronal membrane. They can be conceived as an extension of the leaky neuron model ▷[*TD1*], departing from it on two main points. First, conductance-based models append **several ionic currents** which selectively cross the membrane through ionic channels. Second, they take into account the complex interplay between the membrane potential and the activation of ion channels : variations in the membrane potential are generated by the opening of ion channels, and in turn the opening of ion channels is **modulated by the membrane potential** itself.

Conductance-based models can be derived from an **equivalent electrical circuit** representation of the neuronal membrane.

- Each ionic current is associated with a *driving force* (battery) due to the gradient of concentrations between intracellular and extracellular media, and with a *conductance* (inverse of resistance) reflecting the membrane permeability to the considered ions through its specific channels.
- Conductances can be *voltage-dependent*, i.e. modulated by the membrane potential itself. On a mechanistic level, this voltage-dependence reflects the change of conformation of ionic channels depending on their electrical surroundings, which makes them transition between 'open' and 'close' states.

The standard formulation of a conductance-based model is a **dynamical system**, which contains a set of differential equations for the different variables.

One variable is the *membrane potential* V, whose variation is governed by several conductances :

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

- Selective ionic currents crossing the membrane for different ions j are modeled through the first sum. Driving forces E_j correspond to the Nernt potentials of the corresponding ions, and are fixed by the concentrations of those ions in intracellular and extracellular compartments.
- External input currents are provided through the term $I(t)$ (potentially time-variable).

Other variables are the *conductances* g_j for different ions j, which are voltage-dependent functions such that :

$$g_j(V) = \overline{g}_j a_j(V)^p b_j(V)^q \tag{2}$$

$$\frac{\mathrm{d}a}{\mathrm{d}t} = \frac{1}{\tau_a(V)}(a_\infty(V) - a) \qquad \frac{\mathrm{d}b}{\mathrm{d}t} = \frac{1}{\tau_b(V)}(b_\infty(V) - b) \tag{3}$$

- The constants $\overline{g}_j$ represent the maximal conductance of ion channel types.
- The functions a and b are activation and inactivation *gating variables* for the ion channels, reflecting the state of different sub-units composing each channel. They are raised to small integer powers $p,\ q \in \mathbb{N}$ related to the number of those sub-units (stoechiometry) in a single channel. The variables a and b can be interpreted as the sub-units activity, i.e. their probability of being in a state favoring channels' opening ($a,\ b \in [0, 1]$).
- The functions a_∞ and b_∞ are the steady-state of the gating variables under a fixed voltage, which typically depend on voltage in a sigmoidal manner.
- The functions τ_a and τ_b are the activation time constants of the gating variables, which typically depend on voltage in a bell-shaped manner.

1.1 Voltage-sensitive conductances

Voltage-sensitive conductances

Experimentally, it is possible to measure the **transition rates** between the open and close states of ion channels. These opening and closing rates α and β are themselves voltage-dependent.

Thus, the dynamics of the gating variables in equation (3) stem from **first order kinetics** :

$$\frac{\mathrm{d}a}{\mathrm{d}t} = \alpha_a(V)\,(1-a) - \beta_a(V)\,a \qquad \frac{\mathrm{d}b}{\mathrm{d}t} = \alpha_b(V)\,(1-b) - \beta_b(V) \tag{4}$$

Subsequently, the steady-states a_∞, b_∞ and time constants τ_a, τ_b can be approximated by Boltzmann and Gaussian functions :

$$a_\infty(V) = \frac{1}{1+\exp\left(\frac{V_{1/2}-V}{k}\right)} \qquad \tau_a(V) = \tau_0 + \overline{\tau}\exp\left(-\frac{(V_{max}-V)^2}{\sigma^2}\right) \tag{5}$$

1 Obtain the dynamical equations (4) by a matter balance.

2 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.

3 Represent the Boltzmann and Gaussian functions (5) graphically and interpret the parameters k, $V_{1/2}$, V_{max}, τ_0.

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

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

1.2 Minimal models for action potential generation

Minimal models for action potential generation

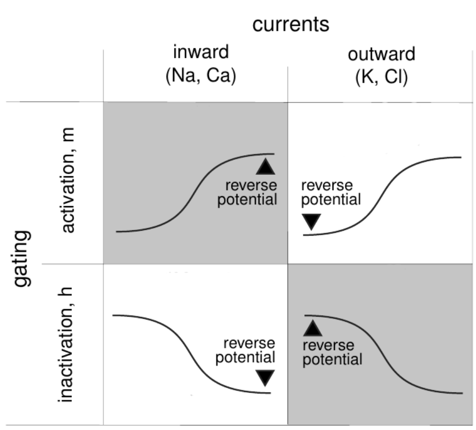
Owing to the vast repertoire of known ion channels, a huge number of conductance-based models could be built a priori ($\approx 2^{30}$). **Minimal models** consist of combinations of conductances which are *irreducible for spiking*, i.e. which are sufficient to generate action potentials, while removing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

4 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

Interestingly, distinct minimal models obtained with different conductances can nonetheless display similar dynamic repertoires and generate action potentials. Conversely, conductance-based models involving similar conductances can display radically different dynamics.

In fact, the key element for explaining neuronal responses is *not* the specific combination of ionic currents per se, but rather the *qualitative (geometric) properties of the underlying dynamical system* ▷[*Part 3*].

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

$$\begin{aligned} C\,\frac{\mathrm{d}V}{\mathrm{d}t} &= -\overline{g}_{Na}\, m\,(V - E_{Na}) \;\; - \overline{g}_K\, n\,(V - E_K) \\ \tau_m(V)\,\frac{\mathrm{d}m}{\mathrm{d}t} &= m_\infty(V) - m \qquad (6) \\ \tau_n(V)\,\frac{\mathrm{d}n}{\mathrm{d}t} &= n_\infty(V) - n \qquad (7) \end{aligned}$$

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 :

$$\begin{aligned} C\,\frac{\mathrm{d}V}{\mathrm{d}t} &= -\overline{g}_l\,(V - E_l) \;\; - \overline{g}_{Na} m^3 h\,(V - E_{Na}) \\ \tau_m(V)\,\frac{\mathrm{d}m}{\mathrm{d}t} &= m_\infty(V) - m \qquad (8) \\ \tau_h(V)\,\frac{\mathrm{d}h}{\mathrm{d}t} &= h_\infty(V) - h \qquad (9) \end{aligned}$$

By convention, the notations of are conserved across models for different types of gates with specific properties (time scale, (in)activation, ionic current) :

- 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.

⑤ In both models, which mechanisms are responsible for the fast positive feedback and the delayed negative feedback respectively ?

⑥ Knowing that experimental time constants are much lower of the sodium m gate, 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 dissection 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*, and therefore are open in all circumstances.
- The **sodium (Na) ionic 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) ionic 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 :

$$\frac{\mathrm{d}V}{\mathrm{d}t} = -\overline{g}_l\ (V(t) - E_l)\ \ - \overline{g}_{Na}\ m^3(V)\ h(V)\ (V(t) - E_{Na})\ \ - \overline{g}_K\ n^4(V)\ (V(t) - E_K) + I(t) \tag{10}$$

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

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

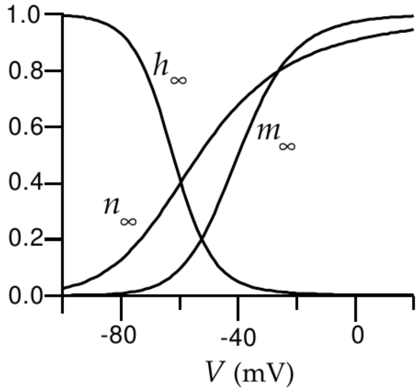
$$\frac{\mathrm{d}n}{\mathrm{d}t} = \alpha_n(V)\ (1-n) - \beta_n(V)\ n \qquad \alpha_n(V) = \frac{55+V}{100\left(1-\exp\left(\frac{55+V}{10}\right)\right)} \qquad \beta_n(V) = \frac{1}{8}\exp\left(\frac{65+V}{80}\right)$$

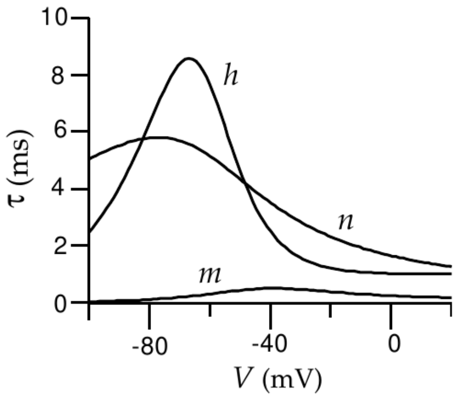
Parameters of the model take the following values :

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

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

Steady-states and time constants of the gating variable have the following shape :

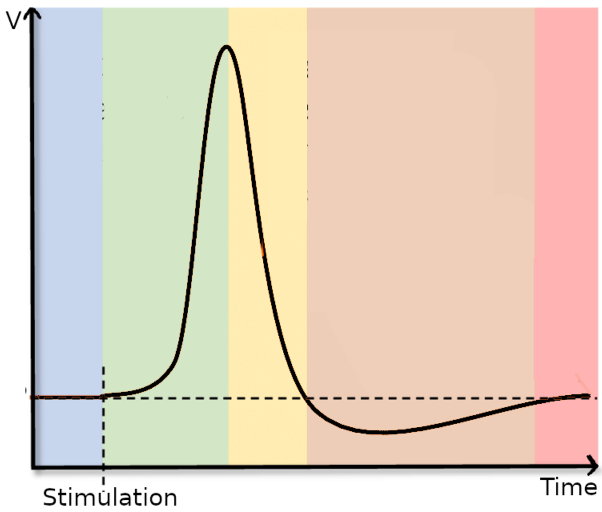


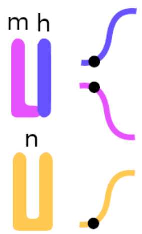


2.1 Action potential generation

By considering the gating variables' time constants and steady-state activities at a function of voltage, predict the steps of an action potential generated in response to a strong depolarizing stimulation current. Indicate the state of each type of gate during each phase of the response and its position along its activity curve.

Note : Focus on the qualitative description and graphs rather than on the exact formulas, which will be rather used for simulations. For help, answer step by step to the questions indicated below.





7 *Depolarization – Upstroke of the membrane potential*
- For each gating variable, does it tend to be activated or deactivated by a depolarization ?
- Which gating variable(s) respond(s) first ?
- What does it imply for K and Na currents and the membrane potential ? Justify that a positive feedback loop is triggered during the initial phase of response.

8 *Repolarization towards V_r*
- What it the later effect of the slower gating variable(s) ?

9 *Hyperpolarization below V_r & Refractory period*
- Comment on the recovery of variable n. What does it imply for the K current and the membrane potential ?
- Comment on the recovery of variable h. What does it imply for the ability of the neuron to respond to inputs occurring just after the action potential ?

2.2 Simulations of the model

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

11 **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 grounds on the common properties shared by a variety of minimal models. Indeed, a phase plane analyses of diverse models reveals that a key property required to generate action potentials : a *N-shaped V-nullcline*.

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 cubic nullcline.
- *Negative-feedback* is introduced through a *recovery variable* mimicking the activation of an outward current, with a linear nullcline.

$$\frac{\mathrm{d}V}{\mathrm{d}t} = V(a-V)(V-1) - w + I \tag{11}$$
$$\frac{\mathrm{d}w}{\mathrm{d}t} = bV - cw \qquad \text{with } b > 0,\ c \geq 0 \tag{12}$$

This model satisfies basic requirements for describing neuronal responses :

- The *rest potential* of the neuron is a *stable fixed point* of the system.
- *Action potentials* correspond to *large closed orbits* in the phase space, i.e. trajectories which start in a small neighborhood of the fixed point, make a wide-amplitude excursion through high potentials, and return to the fixed point.

3.1 Local analysis

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

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

14 Linearize the system around the equilibrium, i.e. approximate the response to a small perturbation

$$V(t) = V^* + \delta V(t) \tag{13}$$
$$w(t) = w^* + \delta w(t) \tag{14}$$

under the form :

$$\frac{\mathrm{d}(\delta V)}{\mathrm{d}t} = -a\delta V - \delta w \tag{15}$$
$$\frac{\mathrm{d}(\delta w)}{\mathrm{d}t} = b\delta V - c\delta w \tag{16}$$

15 Determine the time evolution 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.

16 Classify the types of behaviors around the equilibrium depending on the eigen-values of the matrix $\mathbf{M}$.
Map those possibles behaviors in a graph $(\mathbf{Tr}(\mathbf{M}), \mathbf{Det}(\mathbf{M}))$.

17 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.

18 Trace a parameter space of axes (c, a), assuming a fixed value of b. Determine the domain of stability and indicate the types of fixed points in each part of the diagram. Under which choice of parameters do bifurcations arise ?

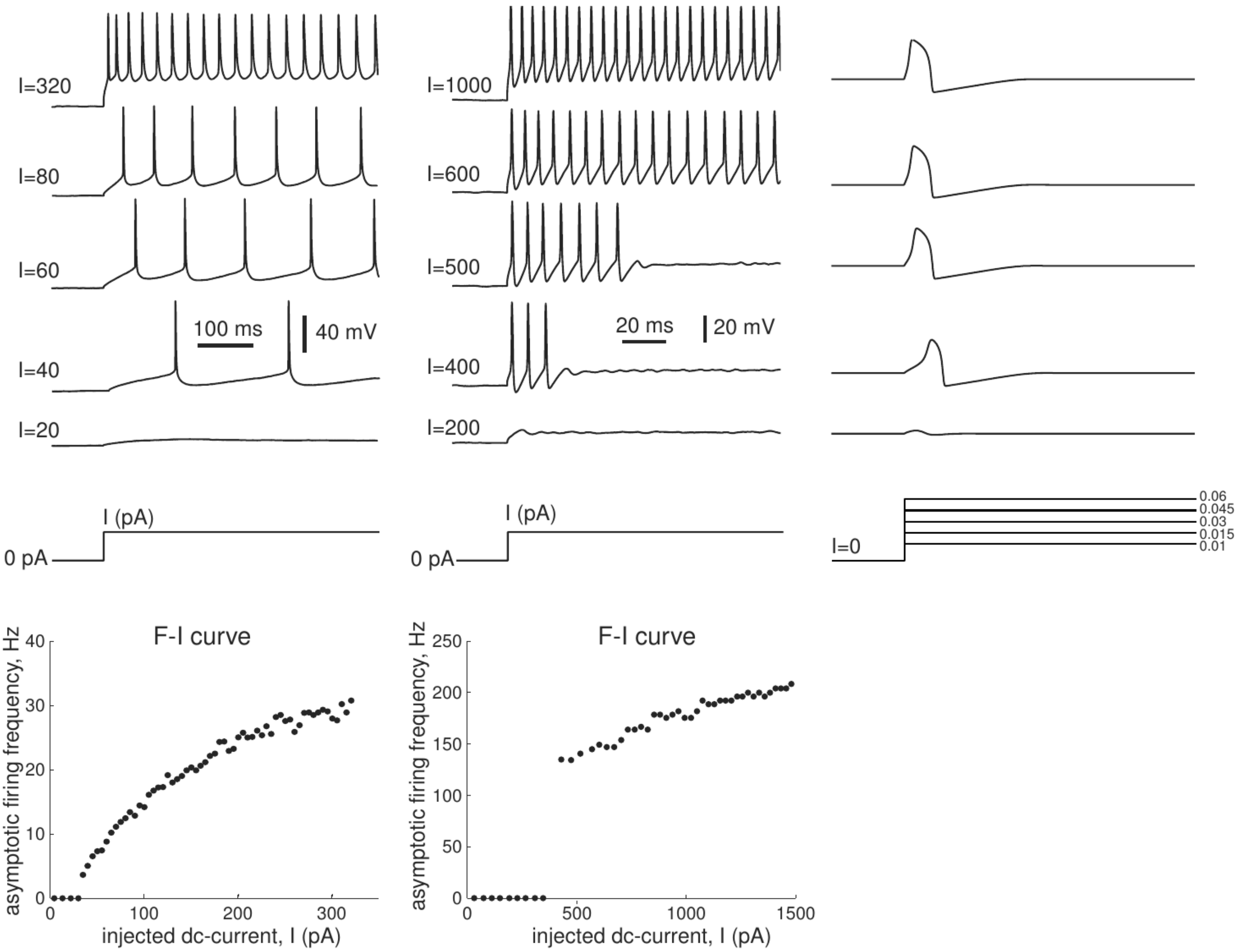
19 Relate the sign of the parameter a to the position of the fixed point along the V-nullcline. The left-outer branch of the V-nullcline is sometimes named *stable* and the inner branch *unstable*. Give one motivation for this labelling, and qualify it.

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 neurocomputational 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.



20 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.

21 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 subthrehold and a supratreshold *pulse current*, so as to explain the emission of an action potential.

(22) 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.

(23) 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 neurocomputational property is the distinction between **integrators** and **resonators**, which characterize 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*.

(24) Which type of fixed point is appropriate to obtain integrators and resonators respectively ?

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

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

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

3.3 Relaxation-oscillations – Van Der Pol oscillator

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 :

$$\frac{\mathrm{d}^2 x}{\mathrm{d}t^2} + \mu(x^2 - 1)\frac{\mathrm{d}x}{\mathrm{d}t} + x = 0 \tag{17}$$

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 $a = b = 0$:

$$\frac{\mathrm{d}x}{\mathrm{d}t} = \mu\left(x - \frac{1}{3}x^3 - y\right) \tag{18}$$

$$\frac{\mathrm{d}y}{\mathrm{d}t} = -\frac{1}{\mu}x \tag{19}$$

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 :

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

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 :

$$\begin{aligned} x_1 &= x \\ x_2 &= \frac{\mathrm{d}x}{\mathrm{d}t} + \int_0^x f(s)ds \end{aligned}$$

28 Prove that the Linéard transformation of the equation (17) indeed gives the system (18).

29 Show that an alternative form for the equation (17) can be obtained by introducing of a simple variable, such that :

$$\frac{\mathrm{d}x}{\mathrm{d}t} = v \tag{20}$$

$$\frac{\mathrm{d}v}{\mathrm{d}t} = \mu\left(1 - x^2\right) - x \tag{21}$$

3.3.2 Qualitative behavior

30 By analogy with a spring-mass mechanical system, interpret the terms of the equation (17) 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.

31 To be more rigorous, consider the Lyapunov function based on the system (20) :

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

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

32 Draw the nullclines of the Van Der Pol oscillator under its two-dimensional form (18).

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

34 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.

35 Find the behavior of the system for the case $\mu = 0$.

36 Rewrite this system (20) with polar coordinates by the following change of variables $(x, y) \rightarrow (r, \omega)$:

$$x = r\cos(\omega) \qquad r \in \mathbb{R}^+ \tag{22}$$

$$y = r\sin(\omega) \qquad \omega \in [0, 2\pi] \tag{23}$$

(37) 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 $\mu = 0$ (24), by replacing constant terms r and ω by slowly varying functions $r(t)$ and $\omega(t)$ such that :
>
> $$x(t) = r(t)\cos(t + \omega(t)) \tag{24}$$
> $$\frac{\mathrm{d}x}{\mathrm{d}t}(t) = -r(t)\sin(t + \omega(t)) \tag{25}$$
>
> The method of averaging assumes that, since the variables (r, ω) are slowly varying in time, they are acting on average as constants.

(38) Introduce the ansatz (24) in (22) to show that :

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

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

(40) 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 :

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

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

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

(42) Using the system (18), propose an approximation and draw the vector field accordingly.

(43) 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.

(44) 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 :
>
> $$\frac{\mathrm{d}^2 x}{\mathrm{d}t^2} + \mu(x^2 - 1)\frac{\mathrm{d}x}{\mathrm{d}t} + x = 0$$