TD 3 – Models of neurons `III` – Biophysical Conductance-based models

1 Biophysical conductance-based models

1.1 Voltage-sensitive conductances

① *Dynamical equations of the gating variables*
Let us assimilate the probability a of a unit to be in the open state as the fraction of the total population of the units which are in this state.
Knowing that the system is in a given distribution among open and close states at time t, let us express the fraction of units in the open state at time $t + \mathrm{d}t$. Two flows have to be added to the initial fraction of channels $a(t)$:

$$a(t + \mathrm{d}t) = a(t) - a(t)\beta_a \,\mathrm{d}t + (1 - a(t))\alpha_a \,\mathrm{d}t$$

- Some units initially in the open state switch to the close state.
  The amount of units in this case is proportional to the initial number of channels in the open state $a(t)$ and to their probability to close during $\mathrm{d}t$ $\mathbb{P}(O \to C, \mathrm{d}t)$.
  The latter probability is proportional to transition rate β_a and the time elapsed $\mathrm{d}t$: $\mathbb{P}(O \to C, \mathrm{d}t) = \beta_a \,\mathrm{d}t$.
  This flow appears in the mass balance with a negative sign because those units leave the open state.
- Some units initially in the close state switch to the open state.
  The amount of units in this case is proportional to the initial number of channels in the close state $1 - a(t)$ and to their probability to open during $\mathrm{d}t$ $\mathbb{P}(C \to O, \mathrm{d}t)$. The latter probability is proportional to transition rate α_a and the time elapsed $\mathrm{d}t$: $\mathbb{P}(C \to O, \mathrm{d}t) = \alpha_a \,\mathrm{d}t$.
  This flow appears in the mass balance with a positive sign because those units enter in the open state.

Taking the limit $t \to 0$ yields the derivative as the limit of the growth rate :

$$\frac{a(t + \mathrm{d}t) - a(t)}{\mathrm{d}t} = \alpha_a(1 - a(t)) - \beta_a a(t) \tag{1}$$

② *Steady-states* are obtained by cancelling the derivatives :

$$\frac{\mathrm{d}a}{\mathrm{d}t} = 0 \implies \alpha_a(1 - a) - \beta_a a \implies a_\infty(V) = \frac{\alpha_a(V)}{\alpha_a(V) + \beta_a(V)}$$

Time constants are obtained by rewriting the dynamical equation as a function of the difference between $a(t)$ and its equilibrium a_∞ :

$$\begin{align}
\frac{\mathrm{d}a}{\mathrm{d}t} &= \alpha_a(1 - a) - \beta_a a(t) \tag{2}\\
&= \alpha_a - (\alpha_a + \beta_a)a \tag{3}\\
&= (\alpha_a + \beta_a)\left(\frac{\alpha_a}{\alpha_a + \beta_a} - a\right) \tag{4}\\
&= (\alpha_a + \beta_a)\left(a_\infty - a\right) \tag{5}
\end{align}$$

By homogeneity of the equation, the factor $(\alpha_a + \beta_a)$ has the dimension of as an inverse time :

$$(\alpha_a + \beta_a) = \frac{1}{\tau_a} \implies \tau_a = \frac{1}{\alpha_a + \beta_a}$$

③ *Shape of the functions*

Roles of the parameters for the Boltzmann function :

- $V_{1/2}$: value at which $a_\infty(V_{1/2}) = 0.5$,
- : k : slope at $V_{1/2}$.

Roles of the parameters for the Boltzmann function :

- τ_0 : lower bound of the function,
- $\overline{\tau}$: amplitude,
- V_{max} : value at which the peak is reached,
- σ : characteristic width of the function.

Modeling choices :

- Activation gates : the parameter k should be positive, so that the probability of the open state increases at higher membrane potentials. This will allow a stimulation to open the channels.
- Inactivation gates : the parameter k should be negative.
- Fast gates : the parameter V_{max} should be low, so that the gates react at their maximum speed for small stimulations.

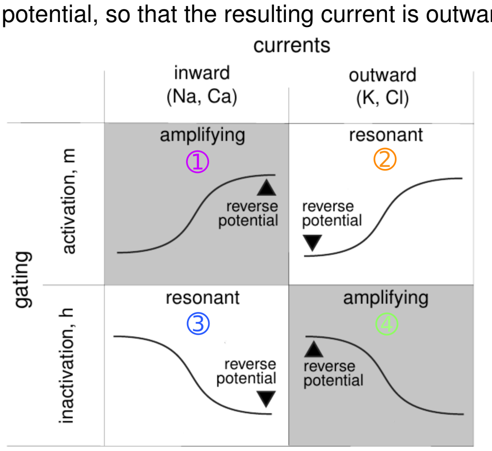
1.2 Minimal models for action potential generation

4 *Classification of the gates*

• Amplifying gates should strengthen a small depolarization triggered by a small inward current. Thus, when the membrane potential increases, they should either produce an additional inward current (column 'inward', row 'activation') or prevent a pre-exiting outward current (column 'outward', row 'inactivation').

• Resonant gates should counteract depolarization. Thus, when the membrane potential increases, they should either produce an compensatory outward current (column 'outward', row 'activation') or prevent a pre-existing inward current (column 'inward', row 'inactivation').

Note that the position of the reversal potential indicates the direction of the current. Indeed, the contributions of the different currents in the membrane potential equations are of the form $\frac{\mathrm{d}V}{\mathrm{d}t} = -g_{ion}(V - E_{ion})$ (wtih g_{ion} the conductance and E_{ion} the reversal potential of the considered ion). Thus, the contribution of one current produces a depolarization when the membrane potential is below the reverse potential of the ion (for positively charged ions such as sodium and potassium), i.e. $\frac{\mathrm{d}V}{\mathrm{d}t} > 0 \iff V < E$. Thus, if the reverse potential is high (e.g. for sodium), then an initial depolarization triggered by a stimulation brings the membrane potential higher, but not above the reverse potential, so that the resulting current is inward. Conversely, if the reverse potential is low (e.g. for potassium), then an initial depolarization triggered by a stimulation brings the membrane potential above the reverse potential, so that the resulting current is outward.



⑤ *Fast positive feedback & Delayed negative feedback*
According to question ④, positive feedback is due to amplifying gates, negative feedback is due to resonant gates. Thus, the roles of the different terms in the model are read out from their position in the table, which is determined by (1) the reversal potential of the ion, which imposes if the current is inward or outward in response to a depolarization, (2) the behavior of the gating variable, which can be activating or inactivating.

• In both models, positive feedback is due to the fast sodium current. Indeed, it has an amplifying behavior (case ①), since (1) the sodium current is inward, because its reversal potential E_{Na} is high, (2) the gate of type m is activating.

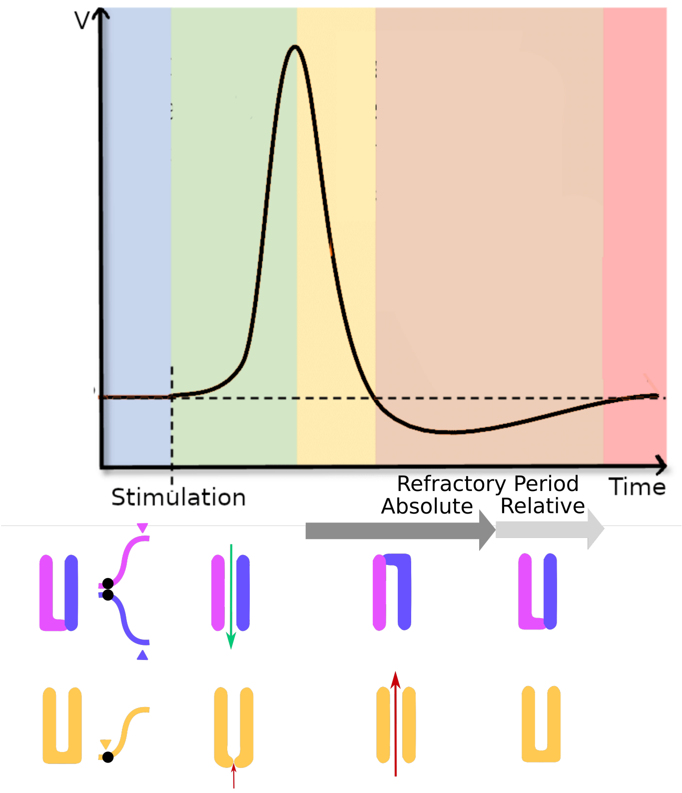
• In the persistent sodium plus potassium model $I_{Na,p} + I_K$, negative feedback is due to the slower potassium current. Indeed, it has a resonant behavior (case ②), since (1) the potassium current in outward, because its reversal potential E_K is low, (2) the gate of type n is activating.

• In the transient sodium model $I_{Na,t}$, negative feedback is due to two contributions. The first contribution is the leak current, since (1) the leak current is outward, because the reversal potential E_l is close to the potassium potential (and is the resting potential of the cell), (2) this conductance is always open (no gate). The second contribution is due to the inactivating gate h for the sodium current, which has a resonant behavior (case ③).

⑥ *Reduction to the planar system*
The fact that the time constant of the gate type m are much lower than the other implies that the variable m in the model evolves much faster than the other variables V and n. Thus, for a given value of V, of the variable m can be assumed to reach its equilibrium instantaneously, such that at any time $m(t) = m_\infty$ (which is a function of V according to question ②).
Thus, the three-dimensional system can be reduced to two differential equations, for the variables V and n.

2 Hodgkin-Huxley model (4 variables)

2.1 Action potential generation



⑦ *Depolarization – Upstroke of the membrane potential*
• An initial depolarization triggered by a stimulation tends to increase the activation variables m and n and to decrease the inactivation variable h.
• The variable m is the fastest to react, because its time constant τ_m is the smallest for an initial depolarization.
• The opening of the gate variable m allows a An inward sodium current is made possible by (1) the fast activation of

gate m, (2) the slow reaction of the gate h, which was already in the open state (and thus does not close immediately). This inward current drives the membrane potential toward E_{Na}, which amplifies the initial depolarization. This further activates the Na conductance, generating a positive feedback loop.
The outward K current does not compensate the Na current, because the gate n opens slowly.

8 *Repolarization towards V_r*
While the membrane potential moves toward E_{Na}, the slower gating variables catch up : the fate h inactivates, which ceases the Na current, and the variable n activates, which induces the an outward K current. Both effects contribute to repolarize the membrane potential towards the rest potential V_r.

9 *Hyperpolarization below V_r & Refractory period*
• When $V \approx V_r$, the recovery of variable n is slow because its time constant τ_n is large at low potentials. Therefore, the outward K current continues to be activated, thereby driving V below V_r towards E_K.
• Similarly, the recovery of variable h is slow because its time constant τ_h is large at low potentials. Therefore, the gates h are close, such that a new stimulation would not suffice to trigger a new action potential, because the inward Na current would continue to be prevented (absolute refractory period). Then, when the gate h starts to deinactivate, a new stimulation could potentially trigger a new action potential, but should be stronger than in resting conditions, because the membrane potential is still below its resting state V_r (relative refractory period).

2.2 Simulations of the model

10 **num** *Existence of a threshold for firing*
It can be observed that the transition to an action potential is gradual : increasing the stimulation leads to progressively wider depolarization waves, rather than an all-or-none behavior. Thus, the definition of a threshold is less clear.

11 **num** *Linear relation between the variables h and m*
The linear relation can be put forward by plotting $h(t)$ as a function of $m(t)$.
This implies that the variable h can be written as a multiple of m : $h(t) = \alpha m(t)$, with α a constant. Thus, the model can be reduced to three differential equations for the variables V, n, m.

3 FitzHugh-Nagumo model

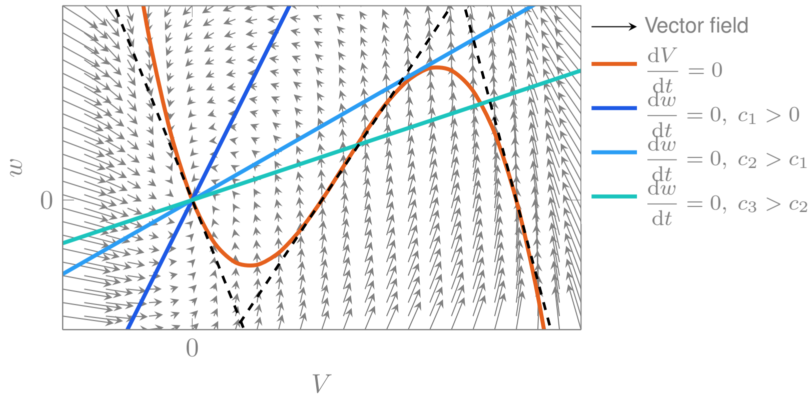
3.1 Local analysis

12 *Nullclines & Equilibria*
The nullclines are obtained by cancelling the derivatives :

$$\frac{\mathrm{d}V}{\mathrm{d}t} = 0 \implies \quad V(a-V)(V-1) - w + I = 0 \implies \quad w = V(a-V)(V-1) \tag{6}$$

$$\frac{\mathrm{d}w}{\mathrm{d}t} = 0 \implies \quad bV - cw = 0 \implies \quad w = \frac{b}{c}V \tag{7}$$

The w-nullcline is a straight line crossing the origin, whose slope is $\frac{b}{c}$.
The V-nullcline is a 'N-shaped' curve of a cubic polynomial. The development of the polynomial gives : $-V^3 + (a+1)V^2 - aV$, whose negative cubic term implies that the outer branches are negative for $V > 0$ and positive for $V < 0$. The curve crosses the abscissa at three points : $V \in \{0,\ 1,\ a\}$. The derivative of the V-nullcline is given by : $-3V^2 - 2V(a+1) - a$, such that slopes at points 0, 1 and a are $-a$, $a-1$ and $a(a-1)$ respectively. This shows that the parameter a controls the steepness of the V-nullcline.
The equilibria correspond to the points were both curves cross each other. Depending on the slope of the w nullcline, it can cross the V-nullcline at either 1, 2 or 3 points, illustrated by the three configurations below. The system can have at most 3 equilibria.



13 *Trivial equilirbium*
The curve of the polynomial and the straight line always cross the origin, so a trivial equilibrium $(V^*, w^*) = (0, 0)$ always exists.

Studying a dynamical system around a point

When a dynamical system cannot be solved analytically, it is useful to switch to an analysis of its *local* behavior. It is particularly interesting to determine how the system evolves around its equilibria, to determine their stability.

To do so, the goal is to consider a small perturbation of the system around the point under consideration, and to determine if the system will go back to the equilibrium of evolve farther away.

1 Linearizing the differential equations

The first step is to approximate the initial dynamical system by a *linear* system, because such systems can be solved explicitly.

This can be done thanks to a limited development of each derivative at the first order in the perturbation.

For instance, for a dynamical system of variables (x, y) around an equilibrium (x^*, y^*), the goal is to study the response to a perturbation $(\delta x, \delta y)$. This means computing the derivatives $\frac{\mathrm{d}x}{\mathrm{d}t}$ and $\frac{\mathrm{d}y}{\mathrm{d}t}$ evaluated at $(x^* + \delta x,\ y^* + \delta y)$. In fact, this also mean to compute the evolution of the perturbation $\delta x(t)$ and $\delta y(t)$, since it is equivalent to compute the derivative of the function $t \mapsto x^* + \delta x(t)$, which is the function $t \mapsto x(t)$ translated by a constant x^* :

$$\frac{\mathrm{d}(x^* + \delta x(t))}{\mathrm{d}t} = \cancelto{0}{\frac{\mathrm{d}x^*}{\mathrm{d}t}} + \frac{\mathrm{d}\delta x(t)}{\mathrm{d}t}$$

The best linear approximation of the derivative functions f and g of two variables x and y is their tangent plane, which gives :

$$\frac{\mathrm{d}x}{\mathrm{d}t}(x^* + \delta x,\ y^* + \delta y) = f(x^* + \delta x,\ y^* + \delta y) \approx \cancelto{0}{f(x^*, y^*)} + \frac{\partial f}{\partial x}(x^*, y^*)\ \delta x + \frac{\partial f}{\partial y}(x^*, y^*)\ \delta y \quad (8)$$

$$\frac{\mathrm{d}y}{\mathrm{d}t}(x^* + \delta x,\ y^* + \delta y) = g(x^* + \delta x,\ y^* + \delta y) \approx \cancelto{0}{g(x^*, y^*)} + \frac{\partial g}{\partial x}(x^*, y^*)\ \delta x + \frac{\partial g}{\partial y}(x^*, y^*)\ \delta y \quad (9)$$

(10)

The terms $f(x^*, y^*)$ and $g(x^*, y^*)$ cancel out by definition of the equilibrium.

In practice, two methods can be followed to compute this expression :

Computing the partial derivatives
This involves deriving the functions f and g relative to each of their two variables x and y, to obtain the partial derivatives $\frac{\partial f}{\partial x}$, $\frac{\partial f}{\partial y}$ and $\frac{\partial g}{\partial x}$, $\frac{\partial g}{\partial y}$ (which hold at any point (x, y)).
The next step is to evaluate those expressions at the equilibrium (x^*, y^*).

Developing the full expression and truncating

Alternatively, it is possible to compute explicitly $f(x^* + \delta x,\ y^* + \delta y)$ and $g(x^* + \delta x,\ y^* + \delta y)$ (by injecting $(x^* + \delta x,\ y^* + \delta y)$ as arguments in the expressions of the functions). Then, the terms have to be reorganized according to the order at which the perturbations δx and δy appear, so as to conserve only the linear ones :

- The 'constant' terms which do not contain δx and δy correspond to $f(x^*, y^*)$ and $g(x^*, y^*)$, which can be cancelled out.
- The linear terms in δx and δy correspond to $\frac{\partial f}{\partial x}(x^*, y^*)\ \ \delta x$ and $\frac{\partial f}{\partial y}(x^*, y^*)\ \ \delta y$ in the first equation, $\frac{\partial g}{\partial x}(x^*, y^*)\ \delta x$ and $\frac{\partial g}{\partial y}(x^*, y^*)\ \delta y$ in the second equation, which have to be conserved.
- The cross terms in $\delta x \delta y$ or higher orders δx^2, δy^2 (or higher) are be negligible compared to the linear terms when $\delta x \to 0$, $\delta y \to 0$, thus they can be ignored.

2 Behaviors of the linearized system

The second step is to determine the evolution of the linear system. To study such systems, it is convenient to use the matrix formalism, by introducing $\vec{X} = \begin{bmatrix} \delta x \\ \delta y \end{bmatrix}$ and $\frac{\mathrm{d}X}{\mathrm{d}t}$. The system (11) rewrites as follows :

$$\frac{\mathrm{d}X}{\mathrm{d}t} = \begin{bmatrix} \frac{\partial f}{\partial x}(x^*, y^*) & \frac{\partial f}{\partial y}(x^*, y^*) \\ \frac{\partial g}{\partial x}(x^*, y^*) & \frac{\partial g}{\partial y}(x^*, y^*) \end{bmatrix} \begin{bmatrix} \delta x \\ \delta y \end{bmatrix} \tag{11}$$

$$= \begin{bmatrix} \alpha & \beta \\ \gamma & \xi \end{bmatrix} \vec{X} \tag{12}$$

Linear system can be solved straightforward if the variables are *not coupled*, i.e. if $\frac{\mathrm{d}x}{\mathrm{d}t}$ only depends on x and $\frac{\mathrm{d}x}{\mathrm{d}t}$ only depends on y, which means that the matrix of is diagonal : $\begin{bmatrix} \alpha & 0 \\ 0 & \xi \end{bmatrix}$.

The solutions are exponential functions ▷[*TD1*] :

$$\delta x(t) = \delta x_0\ e^{\alpha t} \tag{13}$$

$$\delta y(t) = \delta y_0\ e^{\xi t} \tag{14}$$

Otherwise, it is nonetheless possible to find a linear change of variables such that the new variables are not coupled. The system can then be solved in this new basis, and the evolution of the initial variables x and y are just linear combinations of the new variables.

Find the appropriate change of variables is equivalent to diagonalize the matrix (if possible), such that is can be written under the form :

$$\mathbf{P}\mathbf{D}\mathbf{P}^{-1} \qquad \mathbf{D} = \begin{bmatrix} \lambda_1 & 0 \\ 0 & \lambda_2 \end{bmatrix}$$

with $\mathbf{P}$ an matrix composed of eigen-vectors and $\mathbf{D}$ the diagonal matrix containing the eigen-values.

If the goal is only to predict the stability of the fixed point, it is not necessary to compute the change of variable with the eigen-vectors, because the signs of the real parts of the eigen-values suffice to determine if the perturbation will follow an exponential decay of an exponential growth (see below).

14 *Linearization around the equilibrum*

With the second method :

Derivative of the variable V (using the developed expression) :

$$\frac{\mathrm{d}V}{\mathrm{d}t}(V^* + \delta V,\ w^* + \delta w) = -(V^* + \delta V)^3 + (a+1)(V^* + \delta V)^2 - a(V^* + \delta V) - (w^* + \delta w) \tag{15}$$

$$\frac{\mathrm{d}V}{\mathrm{d}t}(V^* + \delta V,\ w^* + \delta w) = -(V^{*3} + 3V^{*2}\delta V + 3V^*\delta V^2 + \delta V^3) \tag{16}$$

$$+ (a+1)(V^{*2} + 2V^*\delta V + \delta V^2) \tag{17}$$

$$- a(V^* + \delta V) \tag{18}$$

$$- (w^* + \delta w) \tag{19}$$

$$\frac{\mathrm{d}V}{\mathrm{d}t}(V^* + \delta V,\ w^* + \delta w) = -V^{*3} + (a+1)V^{*2} - aV^* - w^* \quad (= 0, \text{equilibrium}) \tag{20}$$

$$+ (-3V^{*2} + 2(a+1)V^* - a)\ \delta V - \delta w \tag{21}$$

$$+ \dots \tag{22}$$

Derivative of the variable w :

$$\frac{\mathrm{d}w}{\mathrm{d}t}(V^* + \delta V,\ w^* + \delta w) = b(V^* + \delta V) - c(w^* + \delta w) \tag{23}$$

$$= bV^* - cw^* \quad (= 0, \text{equilibrium}) \tag{24}$$

$$+ b\delta V - c\delta w \tag{25}$$

In particular, at the equilibrium $(0, 0)$:

$$\frac{\mathrm{d}V}{\mathrm{d}t}(\delta V,\ \delta w) = -a\delta V - \delta w \tag{26}$$

$$\frac{\mathrm{d}\delta w}{\mathrm{d}t}(\delta V,\ \delta w) = b\delta V - c\delta w \tag{27}$$

15 *Evolution of the first-order perturbation*

In the vectorial formalism : $\frac{\mathrm{d}\vec{X}}{\mathrm{d}t} = \begin{bmatrix} -a & -1 \\ b & -c \end{bmatrix} \vec{X}$.

16 *Classification of the behaviors around the equilibrium*

Diagonalizing a 2D-matrix

Diagonalizing a matrix $\mathbf{M} = \begin{bmatrix} \alpha & \beta \\ \gamma & \xi \end{bmatrix}$ requires to find a basis of eigen-vectors $(\vec{Y_1}, \vec{Y_2})$ such that :

$$\mathbf{M}\vec{Y_1} = \lambda_1 \vec{Y_1} \tag{28}$$

$$(\mathbf{M} - \lambda_1 \mathrm{Id})\vec{Y_1} = \vec{0} \tag{29}$$

$$\begin{bmatrix} \alpha - \lambda_1 & \beta \\ \gamma & \xi - \lambda_1 \end{bmatrix} \vec{Y_1} = \vec{0} \tag{30}$$

and similarly for $\vec{Y_2}$.

This condition implies that the matrix $\mathbf{M} - \lambda_1 \mathrm{Id}$ is not inversible (because $\vec{Y_1} \neq \vec{0}$, to obtain a basis). This means that the area spanned by the vectors $\begin{bmatrix} \alpha - \lambda_1 \\ \gamma \end{bmatrix}$ and $\begin{bmatrix} \beta \\ \xi - \lambda_1 \end{bmatrix}$ is null, in other words the determinant of this family of vector is null.

With a 2D-matrix, the determinant can be expressed in terms of the trace and the determinant of the initial matrix to be diagonalized :

$$\det \begin{bmatrix} \alpha - \lambda & \beta \\ \gamma & \xi - \lambda \end{bmatrix} = (\alpha - \lambda)(\xi - \lambda) - \gamma\beta \tag{31}$$

$$= \lambda_1^2 - (\alpha + \xi)\lambda + (\alpha\xi - \gamma\beta) \tag{32}$$

$$= \lambda_1^2 - \mathrm{Tr}(\mathbf{M})\lambda + \det(\mathbf{M}) \tag{33}$$

The eigen-values λ_1 and λ_2 are obtained by computing the roots of this characteristic polynomial.

The *discriminant of the polynomial* is given by :

$$\Delta = \mathrm{Tr}(\mathbf{M})^2 - 4\mathrm{det}(\mathbf{M})$$

Classification of the equilibria

The behavior of the system is determined by the nature of the eigen-values.

In all generality, the eigen-values can be written under the form of a complex number :

$$\lambda_{1,2} = \Re(\lambda_{1,2}) + i\ \Im(\lambda_{1,2})$$

The evolution of the new variables (after the change of variables) are multiples of exponential functions :

$$z_{1,2}(t) = z_{1,2}(0)\ e^{\lambda_{1,2}t} = z_{1,2}(0)\ e^{(\Re(\lambda_{1,2})+i\ \Im(\lambda_{1,2}))t} = z_{1,2}(0)\ e^{\Re(\lambda_{1,2})t} e^{i\Im(\lambda_{1,2})t}$$

The factor $e^{i\Im(\lambda_{1,2})} = \cos(\Im(\lambda_{1,2})) + i \sin(\Im(\lambda_{1,2}))$ lies on the unit circle in the complex plane, thus is sets the *speed of rotation* of the system in the space (z_1, z_2).

The factor $e^{\Re(\lambda_{1,2})t}$ is a real number, which sets the *magnitude* of the system in the space (z_1, z_2). Its limit for $t \to +\infty$ depends on whether it is superior of inferior to 1, which itself depends on the sign of the real parts $\Re(\lambda_{1,2})$.

- Both negative real parts, $\Re(\lambda_1) < 0,\ \Re(\lambda_2) < 0$: **Stable equilibrium**.
  Indeed, the variables (z_1, z_2) decay exponentially, and so do the initial variables (x, y).
- At least one positive real part, for instance $\Re(\lambda_1) > 0,\ \Re(\lambda_2) < 0$: **Saddle-point**.
  Indeed, one variable will decay exponentially, while the other one will grow exponentially.
- Both positive real parts, $\Re(\lambda_1) > 0,\ \Re(\lambda_2) > 0$: **Unstable equilibrium**.
  Indeed, the variables (z_1, z_2) grow exponentially

The behavior of the system can be summarized in a graph $(\mathrm{det}(\mathbf{M}), \mathrm{Tr}(\mathbf{M}))$.

Real vs. Complex

The sign of the discriminant determines if the eigen-values are real or complex :

$$\Delta = \mathrm{Tr}(\mathbf{M})^2 - 4\mathrm{det}(\mathbf{M}) > 0 \iff \mathrm{Tr}(\mathbf{M})^2 > 4\mathrm{det}(\mathbf{M})$$

Thus, a characteristic frontier in the graph $(\mathrm{det}(\mathbf{M}), \mathrm{Tr}(\mathbf{M}))$ it the parabola $y = 4x^2$.

Real eigen-values

In this case, $\lambda_{1,2} = \dfrac{\mathrm{Tr}(\mathbf{M}) \pm \sqrt{\mathrm{Tr}(\mathbf{M})^2 - 4\mathrm{det}(\mathbf{M})}}{2}$.
The sign of those eigen-values depend on the sign of $\mathrm{det}(\mathbf{M})$:

$$\mathrm{det}(\mathbf{M}) > 0 \implies \sqrt{\mathrm{Tr}(\mathbf{M})^2 - 4\mathrm{det}(\mathbf{M})} < \sqrt{\mathrm{Tr}(\mathbf{M})^2} = |\mathrm{Tr}(\mathbf{M})|$$

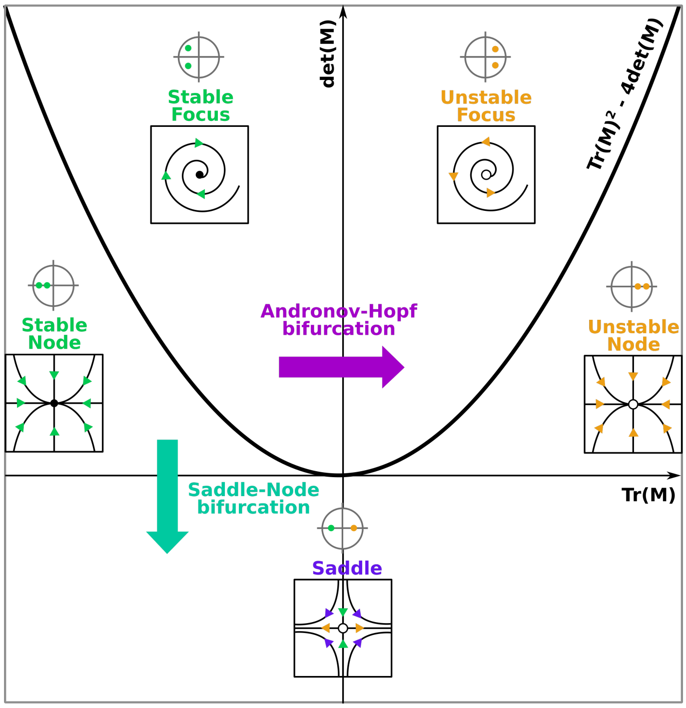
In this case, the square root is not large enough (in absolute value) to reverse the sign imposed by the first term $\mathrm{Tr}(\mathbf{M})$ (either both eigen-values are positive, either both are negative). Thus, the equilibrium is stable if and only if $\mathrm{Tr}(\mathbf{M}) > 0$, and is unstable otherwise.

$$\mathrm{det}(\mathbf{M}) < 0 \implies \sqrt{\mathrm{Tr}(\mathbf{M})^2 - 4\mathrm{det}(\mathbf{M})} > |\mathrm{Tr}(\mathbf{M})|$$

In this case, one eigen-value is positive, and the other is negative. The equilibrium is a saddle.

Complex eigen-values

In this case, $\lambda_{1,2} = \dfrac{\mathrm{Tr}(\mathbf{M}) \pm i\sqrt{|\mathrm{Tr}(\mathbf{M})^2 - 4\mathrm{det}(\mathbf{M})|}}{2}$.
The real part of the eigen-values is exactly $\mathrm{Tr}(\mathbf{M})$, which imposes the nature of the equilibrium according to the above analysis.



⑰ *Two types of bifurcations*

- *Saddle-Node* bifurcation – This bifurcation happens when a stable node looses its stability, which is the case when crossing the axis $\det(\mathbf{M}) = 0$.
- *Andronov-Hopf* bifurcation – This bifurcation happens when a stable focus looses its stability, which is the case when crossing the axis $\mathrm{Tr}(\mathbf{M}) = 0$.

⑱ *Parameter space*
Applying the general method to the system under study requires to investigate $\mathrm{Tr}(\mathbf{M})$ and $\det(\mathbf{M})$ depending on the parameters a, b, c.

$$\mathrm{Tr}(\mathbf{M}) = -(a + c) \qquad \det(\mathbf{M}) = ac + b$$

- Real vs. Complex eigen-values

$\Delta = (a + c)^2 - 4(ac + b) = a^2 + 2ac + c^2 - 4ac - 4b = a^2 - 2ac + c^2 - 4b = (a - c)^2 - 4b$
$\Delta < 0 \implies (a - c)^2 < 4b \implies |a - c| < 2\sqrt{b} \implies c - 2\sqrt{b} < a < c + 2\sqrt{b}$

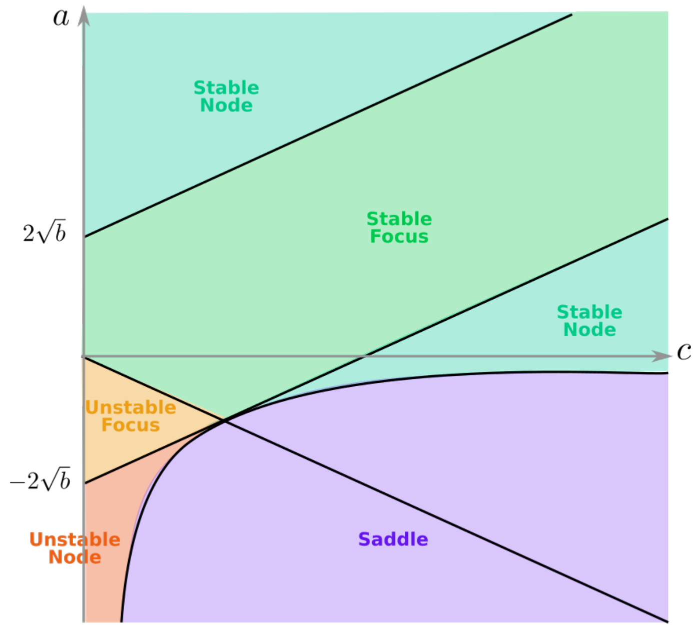
- Saddle vs. Node

$\det(\mathbf{M}) < 0 \implies ac + b < 0 \implies a < -\dfrac{b}{c}$ (since $c > 0$ by hypothesis).

- Stability vs. Unstability

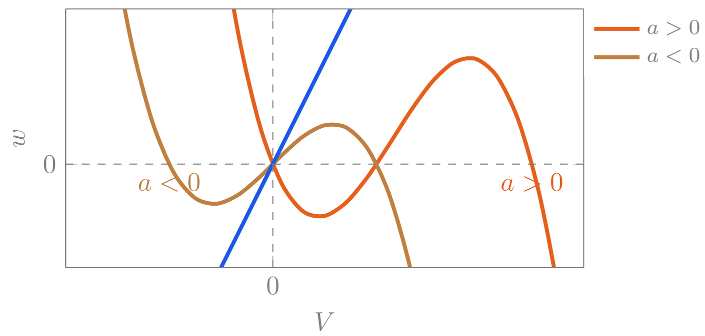
$\mathrm{Tr}(\mathbf{M}) < 0 \implies a + c > 0 \implies a > -c$.

- Bifurcations : a *saddle-node* bifurcation occurs on the curve $a = -\dfrac{b}{c}$ (which is the slope of the w-nullcline).



(19) *Parameter a*
The sign of the parameter a determines if the fixed point $(0, 0)$ occurs on the left-outer branch or the inner-branch of the V-nullcline.

It is true that as soon as $a > 0$, then $a > -\frac{b}{c}$, thus the equilibrium lies on the left-outer branch and is stable. However, when $a \in \left[-\frac{b}{c}, 0\right]$, then the equilibrum lies on the inner branch, and yet is unstable.



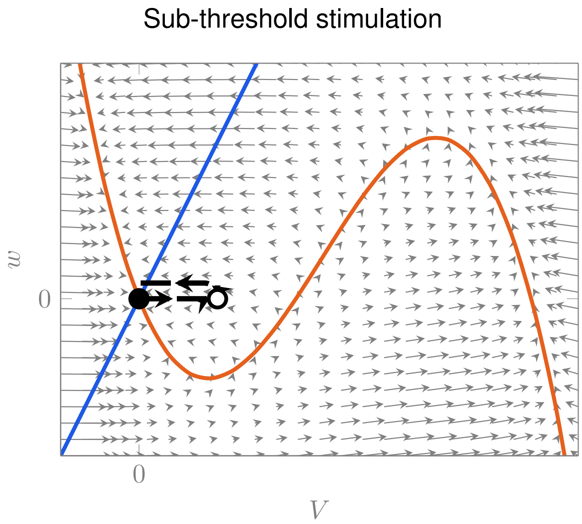
3.2 Explaining neurocomputational properties

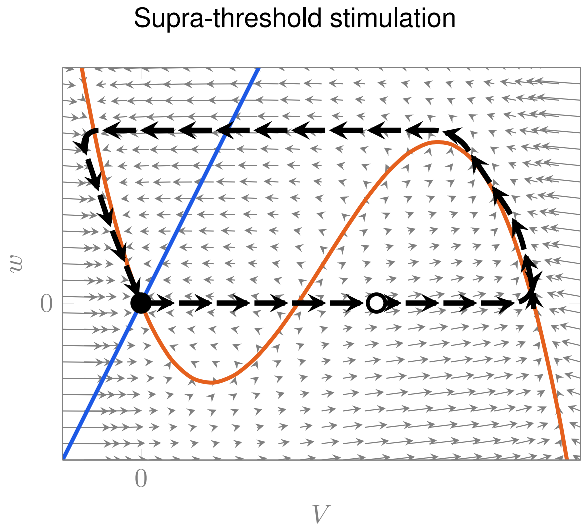
3.2.1 Excitability & Responses to pulse and step currents

(20) *Vector field*
Under the hypothesis of a separation of time scales, w evolves much slower than V, thus the vector field can be considered to be almost parallel to the abscissas (i.e. in the direction of V, as only V evolves substantially), except along the V-nullclines.

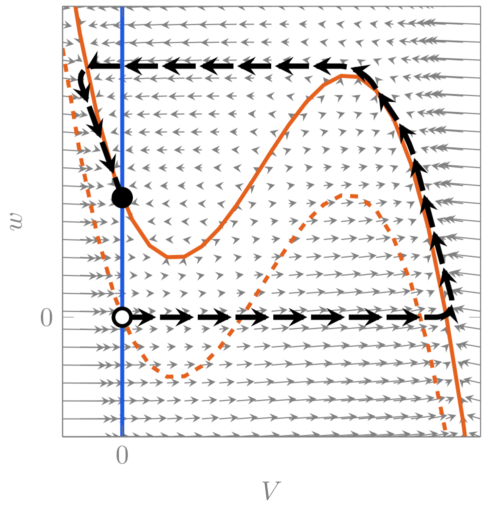
(21) *Trajectories in response to a pulse*
The effect of a pulse current is to perturb the variable V to an upper value.
• In response to a sub-threshold current, the variable V does not cross the inner branch of the V-nullcline, such that it decays towards the equilibrium without making a wide excursion (no action potential).
• In response to a supra-threshold current, the variable V is crosses the inner branch of the V-nullcline, in a portion of the states' space in which it is driven to even higher values. It keeps increasing until it reaches the right-outer branch of the V-nullcline. At this point, only the variable w evolves, driving the system in the upper part of the states' space, running alongside the V-nullcline. • The interest of a cubic nullcline compared to a quadratic nullcline is to allow both a positive feedback and a negative feedback in different portions of the states' space.

• The second variable w is necessary for switching the system between positive and negative feedback. Without it, the system would be locked onto its upper fixed point along the V nullcline.





(22) *Class* III *excitability*
With $c = 0$, the w-null is vertical. The effect of a *step current* is to add a maintained term in the differential equation of the variable V, which induces a shift of the V-nullcline upwards. The fixed point suddenly jumps upwards along w, such that the system makes a single tour in the states' space. Only one action potential is generated, which is the characteristic of Class III excitability.



(23) *Class* II *excitability*
In the condition where the $c \neq 0$ which types of bifurcations could a priori account for Class II excitability ? Class 2 neural corresponds to the sudden transition to an oscillatory regime. This means that the resting state $(0, 0)$ looses its stability at a threshold value, which indicated a bifurcation. A priori, this behavior could be due to a Andronov-Hopf bifurcation for instance.
Note : It could also be due to a saddle-node off invariant circle bifurcation, but the latter is a global bifurcation which could not be predicted by the local analysis above.

3.2.2 Integrators & Resonators

(24) *Integrators and resonators*
• Integrator behaviors require the transition from a stable node to become unstable (saddle-node bifurcation). Thus, the initial fixed point should be a stable node.
• Resonator behaviors require an oscillatory behavior, thus the transition to an unstable stable focus. The initial fixed point could be a stable focus near an Andronov-Hopf bifurcation.

Note : Two aspects of the resonator behavior can be explained further.
Dampened oscillations. In response to a brief stimulation, the system deviates from the focus equilibrium, then returns to the equilibrium along a spiral trajectory, thereby producing a damped oscillation. Persistent noisy perturbations create a random sequence of damped oscillations which sustain small amplitude activity.
Selective amplification of inputs. The effect of inputs depend on their timings. A first input triggers a rotation in the states space. If a second input arrives when the trajectory finishes one full rotation around the equilibrium, it pushes the membrane potential above the equilibrium, and the neuron may fires an action potential. In contrast, if it arrives before the end of the rotation, while it is still below the equilibrium, it will push the membrane potential closer to the equilibrium, thereby canceling the effect of the first pulse.

25 *Dampened oscillations*
According to question 18, an Andronov-Hopf bifurcation could be obtained with :
- $|a - c| < 2\sqrt{b}$, so that the behavior is oscillatory.
- $a \gtrsim -c$, so that the fixed point is near unstability.

26 *Amplitude and phase of the response to a small oscillating perturbation*
Under an oscillatory stimulation around the equilibrium, the response can be assumed to be also oscillatory at the same frequency, with a phase relative to the stimulation. Using the complex notation :

$$I(t) = I_0 e^{i\omega t} \tag{34}$$
$$\delta V(t) = V_0 e^{i(\omega t + \phi)} \tag{35}$$
$$\delta w(t) = w_0 e^{i(\omega t + \psi)} \tag{36}$$

The steady-state oscillatory solution is found by injecting those expressions in the constraint of the dynamical system. On the one hand, by differentiating :

$$\frac{\mathrm{d}\delta V}{\mathrm{d}t} = V_0 i\omega e^{i(\omega t + \phi)} \tag{37}$$
$$\frac{\mathrm{d}\delta w}{\mathrm{d}t} = w_0 i\omega e^{i(\omega t + \psi)} \tag{38}$$
$$\tag{39}$$

On the other hand, according to the expressions of the derivatives :

$$\frac{\mathrm{d}\delta V}{\mathrm{d}t} = -a\delta V - \delta w + I = -aV_0 e^{i(\omega t + \phi)} - w_0 e^{i(\omega t + \psi)} + I_0 e^{i\omega t} \tag{40}$$
$$\frac{\mathrm{d}\delta w}{\mathrm{d}t} = b\delta V - c\delta w \qquad = bV_0 e^{i(\omega t + \phi)} - cw_0 e^{i(\omega t + \psi)} \tag{41}$$
$$\tag{42}$$

Equating (37) and (40), the time-dependent factors $e^{i\omega t}$ simplify in all members :

$$V_0 i\omega e^{i\phi} = -aV_0 e^{i\phi} - w_0 e^{i\psi} + I_0 \tag{43}$$
$$w_0 i\omega e^{i\psi} = bV_0 e^{i\phi} - cw_0 e^{i\psi} \tag{44}$$
$$\tag{45}$$

The second equation allows to express $w_0 e^{i\phi}$:

$$w_0 e^{i\phi}\,(i\omega + c) = bV_0 e^{i\phi} \implies w_0 e^{i\phi} = \frac{bV_0 e^{i\phi}}{i\omega + c}$$

Replacing in the first equation gives :

$$V_0 e^{i\phi}\left(i\omega + a + \frac{b}{i\omega + c}\right) = I_0 \implies V_0 e^{i\phi} = \frac{I_0}{i\omega + a + \dfrac{b}{c + i\omega}}$$

To obtain a quotient of two simple complex numbers, it is possible to multiply numerator and denominator by $c + i\omega$ and to develop :

$$V_0 e^{i\phi} = \frac{I_0(c + i\omega)}{(a + i\omega)(c + i\omega) + b} = \frac{I_0(c + i\omega)}{(ac + b - \omega^2) + i\omega(c + a)}$$

The amplitude is the norm of this complex number, which is the quotient of the norms of the complex number in the numerator and the denominator :

$$A(\omega) = \frac{I_0(\omega^2 + c^2)}{(ac + b - \omega^2)^2 + \omega^2(c + a)^2}$$

27 *Resonance*

Resonance occurs if the amplitude of the response exhibits a peak for a specific frequency ω. Thus, it requires to determine the maximum of the function $A(\omega)$.

As the numerator is always increasing with ω (> 0), then it suffices to determine the minimum of the denominator. Developing its expression gives :

$\omega^4 + \omega^2(\beta - 2\alpha) + \alpha^2$, with $\alpha = ac + b$ and $\beta = (a + c)^2$

It can be written under the form : $X^2 + X(\beta - 2\alpha) + \alpha^2$

The extremum is obtained by cancelling its derivative :

$$2X + (\beta - 2\alpha) = 0 \implies X = \alpha - \frac{\beta}{2}$$

As $X = \omega^2 > 0$, solutions exist if $\frac{\beta}{2} < \alpha$.