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

1 Biophysical conductance-based models

1.1 Components of conductance-based models

① *Electrical circuit*

1.2 Dynamics of voltage-sensitive conductances

② *Dynamical equations of the gating variables*
The variable a reflects the probability of a unit to be in the open state. It can be assimilated to the *fraction* of the total population of units which are in the open state.
At any time t, the total population is distributed between both states : a proportion $a(t)$ of units are the open state, and a proportion $(1 - a(t))$ are in the close state.

During a duration $\mathrm{d}t$, the fraction of units in the open state evolves from $a(t)$ to $a(t + \mathrm{d}t)$ by two contributions :

- Some units initially in the open state switch to the close state.
  The negative contribution is proportional to the initial proportion of units in the open state $a(t)$ and to their probability to close during $\mathrm{d}t$. This probability is proportional to transition rate β_a and the time elapsed $\mathrm{d}t$: $\mathbb{P}(O \to C, \mathrm{d}t) = \beta_a \,\mathrm{d}t$.
- Some units initially in the close state switch to the open state.
  The positive contribution is proportional to the initial proportion of units in the close state $1 - a(t)$ and to their probability to open during $\mathrm{d}t$. This probability is proportional to transition rate α_a and the time elapsed $\mathrm{d}t$: $\mathbb{P}(C \to O, \mathrm{d}t) = \alpha_a \,\mathrm{d}t$.

Therefore :

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

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

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

③ *Steady-states* are obtained by cancelling the derivatives :

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

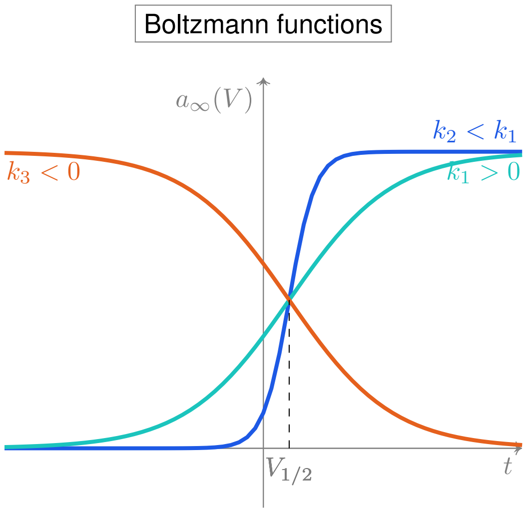
Time constants are obtained by rewriting the dynamical equation as a function of the difference between $a(t)$ and its equilibrium a_∞ (to match the target expression) :

$$\begin{aligned}
\frac{\mathrm{d}a}{\mathrm{d}t} &= \alpha_a(1 - a) - \beta_a a(t) \\
&= \alpha_a - (\alpha_a + \beta_a)a \\
&= (\alpha_a + \beta_a)\left(\frac{\alpha_a}{\alpha_a + \beta_a} - a\right) \\
&= (\alpha_a + \beta_a)\,(a_\infty - a)
\end{aligned}$$

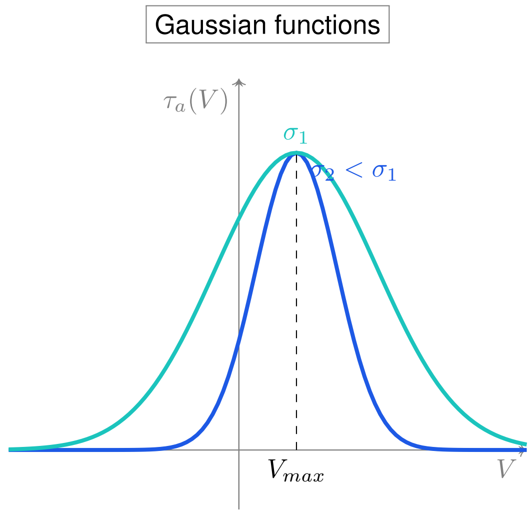
By homogeneity of the equation, the factor $(\alpha_a + \beta_a)$ has the dimension of as an inverse time :

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

④ *Shape of the functions*



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



- 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 different types of units :

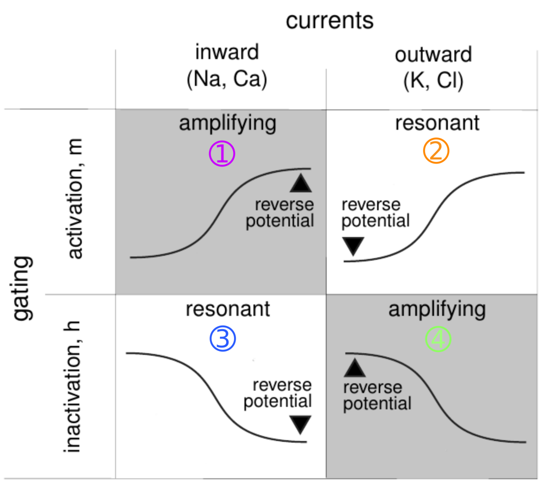
- Activation gates : the parameter k should be positive, so that the probability of the open state increases at higher membrane potentials. This will allow a stimulation to open the channels.
- Inactivation gates : the parameter k should be negative.
- Fast gates : the parameter V_{max} should be low,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

1.3 Minimal models for action potential generation

⑤ *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 : The reversal potential E_{rev} of an ion (black arrows) determines whether this ion is more prone to generate inward or outward currents. Indeed, formula of the form $\frac{dV}{dt} = -g(V - E_{rev})$ imply $\frac{dV}{dt} > 0 \iff V < E_{rev}$, which entails that the contribution of the ion favors the depolarization when the membrane potential is below its reversal potential (in the case of positively charged ions). Thus, if the reverse potential is high (e.g. for sodium Na), 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.

6 *Fast positive feedback & Delayed negative feedback*

On the one hand, *positive feedback* is due to *amplifying gates*, whereas *negative feedback* is due to *resonant gates* (question 5). On the other hand, the role of each term in the model are indicated is determined by :

- a The reversal potential of the ion, which imposes either inward or outward current in response to a depolarization.
- b The behavior of the gating variable, which can be activating or inactivating.

- *Positive feedback*

In both models, positive feedback is due to the *fast sodium current*, which is amplifying (case 1) :

- a The sodium current is inward, because its reversal potential E_{Na} is high.
- b The gate of type m is activating.

. • *Negative feedback*

In $I_{Na,p} + I_K$ model, negative feedback is due to the *slower potassium current*, which is resonant (case 2) :

- a The potassium current in outward, because its reversal potential E_K is low.
- b The gate of type n is activating.

In the $I_{Na,t}$ model, negative feedback is due to two contributions.
The first contribution is the *leak current* :

- a The leak current is outward, because the reversal potential E_l is the resting potential of the cell.
- b This conductance is always open (no gate).

The second contribution is due to the inactivating gate h for the sodium current, which is resonant (case 3).

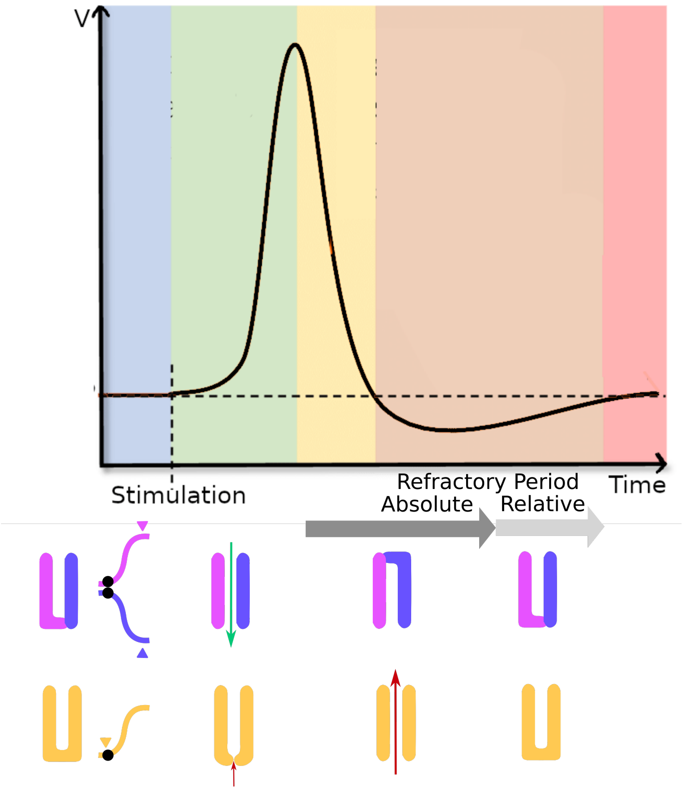
7 *Reduction to the planar system*

The lower time constant of the gate of type m compared to the other gates implies that the variable m evolves much faster than the other variables V and n. Thus, for a given value of V, 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 3).

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



⑧ *Resting state*

- At the resting state, only the varaible h is activated.
- Because n and m gating variables are close, only the leak current crosses the membrane which sets V to the leak potential E_l.

⑨ *Depolarization – Upstroke of the membrane potential*

- After the initial depolarization triggered by a stimulation, the variable m is the fastest to react, because its time constant τ_m is the smallest. It tends to activate.
- The opening of the unit m allows an inward sodium current (which is possible because the variable h is already in the open state and does not close immediately). This inward current drives the membrane potential toward E_{Na}, which further amplifies the initial depolarization and generates a positive feedback loop.

⑩ *Repolarization towards V_r*
While the membrane potential moves toward E_{Na}, the slower gating variables catch up :

- The variable h inactivates, which ceases the Na current.
- 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.

⑪ *Hyperpolarization below V_r & Refractory period*

- When $V \approx V_r$, the time constants of the variables n and h are high, therefore their recovery to the initial state is slow.
- Thus, the gate n remains activated, therefore the outward K current continues and drives V below V_r towards E_K.
- The gates h remain close, such that a new stimulation would not suffice to trigger a new action potential, because the inward Na current would still 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

(12) **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 not clear.

(13) **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

14 *Nullclines & Equilibria*

The nullclines are obtained by cancelling the derivatives :

$$\frac{\mathrm{d}V}{\mathrm{d}t} = 0 \implies V(a-V)(V-1) - w + I = 0 \implies w = V(a-V)(V-1) \tag{2}$$

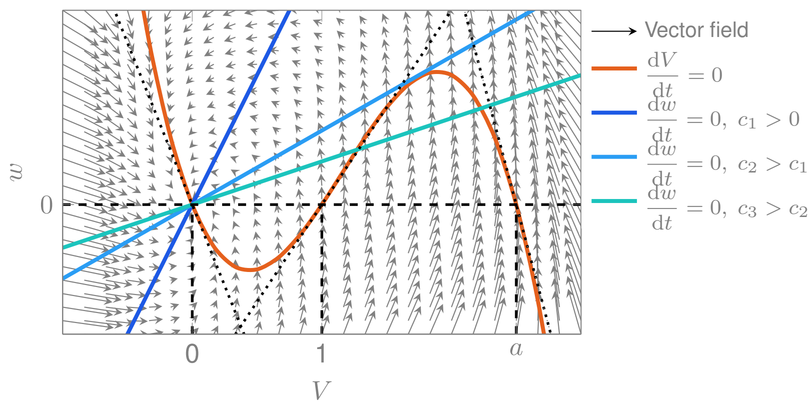
$$\frac{\mathrm{d}w}{\mathrm{d}t} = 0 \implies bV - cw = 0 \implies w = \frac{b}{c}V \tag{3}$$

- The w-nullcline is a straight line crossing the origin, of slope $\frac{b}{c} > 0$ (since $b > 0$, $c \geq 0$).
- The V-nullcline is the "N-shaped" curve of a cubic polynomial.
  - The curve crosses the abscissa at three points : $V \in \{0,\ 1,\ a\}$.
  - The outer branches are negative for $V \to +\infty$ and positive for $V \to -\infty$, as shown by the development with a negative cubic term : $-V^3 + (a+1)V^2 - aV$.
  - The derivative of the V-nullcline with respects to V is given by : $\frac{\mathrm{d}}{\mathrm{d}V}\frac{\mathrm{d}V}{\mathrm{d}t} = -3V^2 - 2V(a+1) - a$.

    The slopes at the roots are : $\begin{cases} \frac{\mathrm{d}}{\mathrm{d}V}\frac{\mathrm{d}V}{\mathrm{d}t}(0) = -a \\ \frac{\mathrm{d}}{\mathrm{d}V}\frac{\mathrm{d}V}{\mathrm{d}t}(1) = a-1 \\ \frac{\mathrm{d}}{\mathrm{d}V}\frac{\mathrm{d}V}{\mathrm{d}t}(a) = a(a-1) \end{cases}$

    Thus, the steepness of the curve is controlled by the parameter a.

The equilibria of the system 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.



15 *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 an equilibrium

When a dynamical system cannot be solved analytically, it is useful to switch to an analysis of its *local* behavior. This approach aims to to determine the stability of the equilibria, i.e. how the system evolves when it is perturbed around each of its equilibria.

The method below is presented for a dynamical system of two variables (x, y) :

$$\begin{cases} \dfrac{\mathrm{d}x}{\mathrm{d}t} = f(x, y) \\ \dfrac{\mathrm{d}y}{\mathrm{d}t} = g(x, y) \end{cases}$$

which admits an equilibrium (x^*, y^*).

The goal is to approximate the evolution of the system starting from a perturbation $(x^* + \delta x, y^* + \delta y)$ (small).

Note : This is equivalent to compute the evolution of the perturbation $(\delta x(t), \delta y(t))$ itself, since the equilibrium is constant :
$$\frac{\mathrm{d}(x^* + \delta x(t))}{\mathrm{d}t} = \cancelto{0}{\frac{\mathrm{d}x^*}{\mathrm{d}t}} + \frac{\mathrm{d}\delta x(t)}{\mathrm{d}t}$$

① Linearizing the dynamics of the system

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 around the equilibrium, at the first order in the perturbation.

The best linear approximation of the function f (resp. g) of two variables x and y is its tangent plane, whose slopes are set by the partial derivatives $\frac{\partial f}{\partial x}$, $\frac{\partial f}{\partial y}$ (resp. $\frac{\partial g}{\partial x}$, $\frac{\partial g}{\partial y}$) evaluated at the equilibrium :

$$\frac{\mathrm{d}x}{\mathrm{d}t}(x^* + \delta x,\ y^* + \delta y) = f(x^* + \delta x,\ y^* + \delta y) \qquad \approx \cancelto{0}{f(x^*, y^*)} + \frac{\partial f}{\partial x}(x^*, y^*)\ \delta x + \frac{\partial f}{\partial y}(x^*, y^*)\ \delta y \tag{4}$$
$$\frac{\mathrm{d}y}{\mathrm{d}t}(x^* + \delta x,\ y^* + \delta y) = g(x^* + \delta x,\ y^* + \delta y) \qquad \approx \cancelto{0}{g(x^*, y^*)} + \frac{\partial g}{\partial x}(x^*, y^*)\ \delta x + \frac{\partial g}{\partial y}(x^*, y^*)\ \delta y \tag{5}$$

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

② Expressing the problem in the vectorial formalism

To solve the linear system, it is convenient to use the matrix formalism, by introducing $\vec{X} = \begin{bmatrix} \delta x \\ \delta y \end{bmatrix}$ and $\frac{\mathrm{d}\vec{X}}{\mathrm{d}t} = \begin{bmatrix} \frac{\mathrm{d}\delta x}{\mathrm{d}t} \\ \frac{\mathrm{d}\delta y}{\mathrm{d}t} \end{bmatrix}$ ▷[*TD3*]. The system (6) rewrites as follows :

$$\begin{bmatrix} \dfrac{\mathrm{d}\delta x}{\mathrm{d}t} \\ \dfrac{\mathrm{d}\delta y}{\mathrm{d}t} \end{bmatrix} = \begin{bmatrix} \dfrac{\partial f}{\partial x}(x^*, y^*) & \dfrac{\partial f}{\partial y}(x^*, y^*) \\ \dfrac{\partial g}{\partial x}(x^*, y^*) & \dfrac{\partial g}{\partial y}(x^*, y^*) \end{bmatrix} \begin{bmatrix} \delta x \\ \delta y \end{bmatrix} \tag{6}$$
$$\frac{\mathrm{d}\vec{X}}{\mathrm{d}t} = \underbrace{\begin{bmatrix} \alpha & \beta \\ \gamma & \xi \end{bmatrix}}_{\mathbf{M}} \vec{X} \tag{7}$$

The next step consists in finding a linear change of variables $(\delta x, \delta y) \to (z, w)$ such that the new variables are *not coupled*, i.e. $\frac{\mathrm{d}z}{\mathrm{d}t}$ only depends on z and $\frac{\mathrm{d}w}{\mathrm{d}t}$ only depends on w. In this new basis, the matrix of is diagonal, such that the solutions are exponential functions ▷[*TD1*] :

$$\begin{bmatrix} \frac{\mathrm{d}z}{\mathrm{d}t} \\ \frac{\mathrm{d}w}{\mathrm{d}t} \end{bmatrix} = \begin{bmatrix} \lambda_1 & 0 \\ 0 & \lambda_2 \end{bmatrix} \begin{bmatrix} z \\ w \end{bmatrix} \implies \begin{cases} z(t) = z_0\ e^{\lambda_1 t} \\ w(t) = w_0\ e^{\lambda_2 t} \end{cases}$$

The evolutions of the initial variables $\delta x(t)$ and $\delta y(t)$ are just linear combinations of those exponentials.

The appropriate change of variables is obtained by diagonalizing the matrix (if possible), such that is can be written under the form :

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

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

Note : 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).

3 Diagonalizing the 2D-matrix

Diagonalizing a matrix $\mathbf{M} = \begin{bmatrix} \alpha & \beta \\ \gamma & \xi \end{bmatrix}$ requires to find a basis of eigen-vectors $(\vec{Y_1}, \vec{Y_2})$. Each eigen vector satisfies the following relation (with the eigen value to which it is associated) :

$$\mathbf{M}\vec{Y} = \lambda\vec{Y} \tag{8}$$

$$(\mathbf{M} - \lambda\mathrm{Id})\vec{Y} = \vec{0} \tag{9}$$

$$\begin{bmatrix} \alpha - \lambda & \beta \\ \gamma & \xi - \lambda \end{bmatrix} \vec{Y} = \vec{0} \tag{10}$$

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

In the particular case of a 2D-matrix, the determinant can be expressed in terms of the **trace** and the **determinant** of the initial matrix $\mathbf{M}$:

$$\det \begin{bmatrix} \alpha - \lambda & \beta \\ \gamma & \xi - \lambda \end{bmatrix} = (\alpha - \lambda)(\xi - \lambda) - \gamma\beta \tag{11}$$

$$= \lambda^2 - (\alpha + \xi)\lambda + (\alpha\xi - \gamma\beta) \tag{12}$$

$$= \lambda^2 - \mathrm{Tr}(\mathbf{M})\lambda + \det(\mathbf{M}) \tag{13}$$

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

4 Classification of the equilibria

The behavior of the system is determined by the nature of the eigen values, specifically, if they are real or complex, and the sign of their real part. Those properties depend on the *discriminant of the polynomial* :

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

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

Real vs. Complex

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

$$\Delta = \mathrm{Tr}(\mathbf{M})^2 - 4\det(\mathbf{M}) > 0 \iff \det(\mathbf{M}) < \frac{1}{4}\mathrm{Tr}(\mathbf{M})^2$$

Thus, a characteristic frontier in the graph $(\det(\mathbf{M}), \mathrm{Tr}(\mathbf{M}))$ it the parabola $y = \frac{1}{4}x^2$.

Real eigen-values

In the case $\Delta \geq 0$, the roots of the polynomial are given by :

$$\lambda_{1,2} = \frac{\mathrm{Tr}(\mathbf{M}) \pm \sqrt{\mathrm{Tr}(\mathbf{M})^2 - 4\det(\mathbf{M})}}{2}$$

The solutions of the system are : $\begin{cases} z(t) = z_0 \ e^{\lambda_1 t} \\ w(t) = w_0 \ e^{\lambda_2 t} \end{cases}$

Each variable either increases exponentially or decays exponentially, depending on the **sign** of the eigen-values. Three possible cases arise :

$\boxed{\det(\mathbf{M}) > 0}$ *Both* eigen values have the same sign, which is imposed by $\mathrm{Tr}(\mathbf{M})$.

Indeed, $\det(\mathbf{M}) > 0 \implies \sqrt{\mathrm{Tr}(\mathbf{M})^2 - 4\det(\mathbf{M})} < \sqrt{\mathrm{Tr}(\mathbf{M})^2} = |\mathrm{Tr}(\mathbf{M})|$. The square root is not large enough (in absolute value) to reverse the sign imposed by the first term $\mathrm{Tr}(\mathbf{M})$.

$\boxed{\mathrm{Tr}(\mathbf{M}) > 0}$ Both eigen values are positive, so both variable increase. The equilibrium is a **unstable node**.

$\boxed{\mathrm{Tr}(\mathbf{M}) < 0}$ Both eigen values are negative, so both variables decay. The equilibrium is a **stable node**.

$\boxed{\det(\mathbf{M}) < 0}$ One eigen value is positive, and the other is negative. The equilibrium is a **saddle**.

Indeed, $\det(\mathbf{M}) < 0 \implies \sqrt{\mathrm{Tr}(\mathbf{M})^2 - 4\det(\mathbf{M})} > |\mathrm{Tr}(\mathbf{M})|$. The square root overcomes (in absolute value) the first term $\mathrm{Tr}(\mathbf{M})$, in one case in a positive direction and in one case in a negative direction.

Complex eigen-values

In the case $\Delta < 0$, the roots of the polynomial are *complex numbers*, which can be written under the form of a real part an an imaginary part :

$$\lambda_{1,2} = \frac{\mathrm{Tr}(\mathbf{M}) \pm i\sqrt{|\mathrm{Tr}(\mathbf{M})^2 - 4\det(\mathbf{M})|}}{2} = \Re(\lambda_{1,2}) + i\,\Im(\lambda_{1,2}) \quad \text{with} \quad \begin{cases} \Re(\lambda_{1,2}) = \dfrac{\mathrm{Tr}(\mathbf{M})}{2} \\ \Im(\lambda_{1,2}) = \dfrac{\sqrt{|\mathrm{Tr}(\mathbf{M})^2 - 4\det(\mathbf{M})|}}{2} \end{cases}$$

The solutions of the system in the *complex plane* can be written by decomposing the complex exponential :

$$\begin{cases} z(t) = z_0\, e^{\lambda_1 t} = z_0\, e^{(\Re(\lambda_1) + i\,\Im(\lambda_1))t} = z_0\, e^{\Re(\lambda_1)t} e^{i\,\Im(\lambda_1)t} = z_0\, e^{\Re(\lambda_1)t}\,(\cos(\Im(\lambda_1)t) + i\sin(\Im(\lambda_1)t)) \\ w(t) = w_0\, e^{\lambda_2 t} = w_0\, e^{\Re(\lambda_2)t}\,(\cos(\Im(\lambda_2)t) + i\sin(\Im(\lambda_2)t)) \end{cases}$$

The solutions of the system in the *real domain* are obtained by keeping the real parts :

$$\begin{cases} z(t) = z_0\, e^{\lambda_1 t} = z_0\, e^{\Re(\lambda_1)t}\cos(\Im(\lambda_1)t) \\ w(t) = w_0\, e^{\lambda_2 t} = w_0\, e^{\Re(\lambda_2)t}\cos(\Im(\lambda_2)t) \end{cases}$$

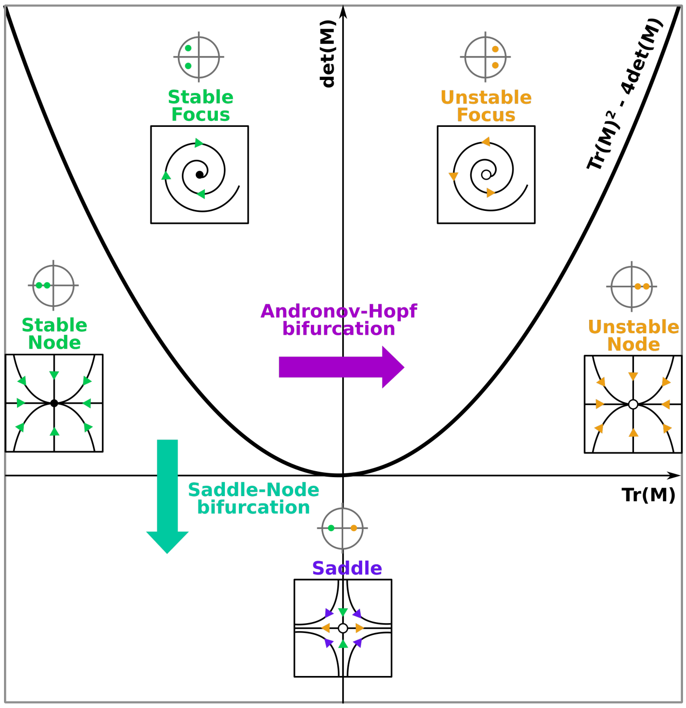
Those functions are either *dampened or amplified oscillations* :

- The factor $\cos(\Im(\lambda_2)t)[-1, 1])$ is responsible for the oscillations. Therefore, the *imaginary parts* of the eigen values sets the *speed of rotation* of the system in the space (z_1, z_2).
- The factor $e^{\Re(\lambda_{1,2})t}$ is responsible of the dampening or the amplification. Therefore, the sign of the *real parts* of the eigen values sets the *magnitude* of the system in the space (z_1, z_2)

Both eigen values have the same real part, equal to $\mathrm{Tr}(\mathbf{M})$. Two possible cases arise :

$\boxed{\mathrm{Tr}(\mathbf{M}) > 0}$ Both variables z and w increase exponentially, the equilibrium is a **unstable focus**.

$\boxed{\mathrm{Tr}(\mathbf{M}) < 0}$ Both variables z and w decay exponentially, the equilibrium is a **stable focus**.



(16) *Linearization around the equilibrum*

Partial derivatives :

$$\frac{\partial}{\partial V}\frac{\mathrm{d}V}{\mathrm{d}t}(V,w) = -3V^2 - 2V(a+1) - a \qquad \frac{\partial}{\partial w}\frac{\mathrm{d}V}{\mathrm{d}t}(V,w) = -1$$
$$\frac{\partial}{\partial V}\frac{\mathrm{d}w}{\mathrm{d}t}(V,w) = b \qquad \frac{\partial}{\partial w}\frac{\mathrm{d}w}{\mathrm{d}t}(V,w) = -c$$

Limited development around the equilibrium :

$$\begin{aligned}\frac{\mathrm{d}V}{\mathrm{d}t}(V^*+\delta V,\ w^*+\delta w) &= \cancelto{0}{\frac{\mathrm{d}V}{\mathrm{d}t}(V^*,\ w^*)} + \frac{\partial}{\partial V}\frac{\mathrm{d}V}{\mathrm{d}t}(V^*,\ w^*)\times\delta V + \frac{\partial}{\partial w}\frac{\mathrm{d}V}{\mathrm{d}t}(V^*,\ w^*)\times\delta w\\ &= (-3V^{*2} - 2V(a+1) - a)\times\delta V + (-1)\times\delta w\end{aligned}$$

$$\begin{aligned}\frac{\mathrm{d}w}{\mathrm{d}t}(V^*+\delta V,\ w^*+\delta w) &= \cancelto{0}{\frac{\mathrm{d}w}{\mathrm{d}t}(V^*,\ w^*)} + \frac{\partial}{\partial V}\frac{\mathrm{d}V}{\mathrm{d}t}(V^*,\ w^*)\times\delta V + \frac{\partial}{\partial w}\frac{\mathrm{d}V}{\mathrm{d}t}(V^*,\ w^*)\times\delta w\\ &= b\times\delta V + (-c)\times\delta w\end{aligned}$$

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

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

(17) *Evolution of the first-order perturbation*

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

Trace and determinant as a function of the parameters a, b, c :

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

(18) *Classification of the behaviors around the equilibrium*

- 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

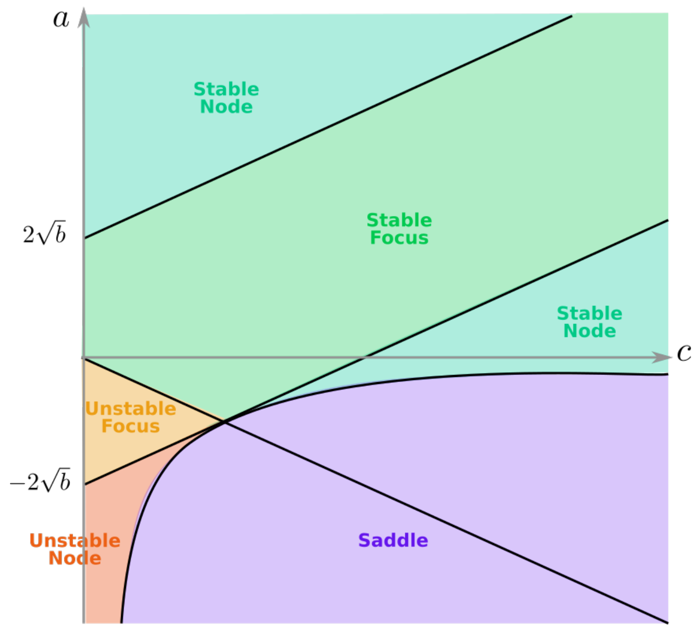
$\det(\mathbf{M}) < 0 \implies ac + b < 0 \implies a < -\frac{b}{c}$ (since $c > 0$ by hypothesis).

- Stability vs. Unstability

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

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

Parameter space



19 *Two types of bifurcations*

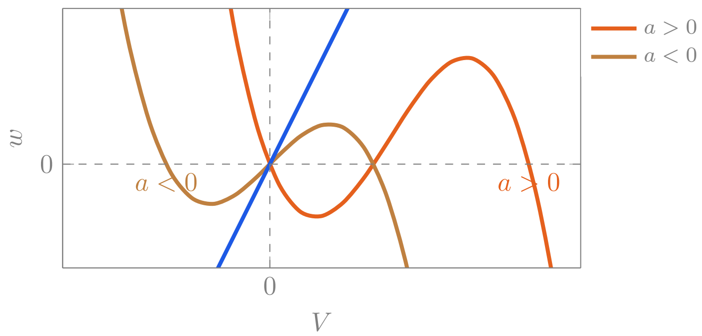
- *Saddle-Node* bifurcation – This bifurcation happens when a stable node looses its stability, which is the case when crossing the axis $\det(\mathbf{M}) = 0$.
- *Andronov-Hopf* bifurcation – This bifurcation happens when a stable focus looses its stability, which is the case when crossing the axis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

20 *Parameter a*

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

However, the stability of the equilibrium $(0,0)$ is not determined by the sing of a, but by its position relative to $-\frac{b}{c}$.

- As soon as $a > 0$, the equilibrium lies on the left-outer branch. In this case, $a > -\frac{b}{c}$, so the equilibrium is stable.
- However, when $a \in \left[-\frac{b}{c}, 0\right]$, then the equilibrum lies on the inner branch, and yet is still stable.



3.2 Explaining neuro-computational properties

3.2.1 Excitability & Responses to pulse and step currents

(21) *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.

The direction of evolution of the variable V depends on the position of w relative to the V-nullcline (and similarly for the variable w) :

$$\frac{\mathrm{d}V}{\mathrm{d}t} > 0 \implies \quad V(a-V)(V-1) - w > 0 \implies \quad w < V(a-V)(V-1) \tag{14}$$

$$\frac{\mathrm{d}w}{\mathrm{d}t} > 0 \implies \quad bV - cw > 0 \implies \quad w < \frac{b}{c}V \tag{15}$$

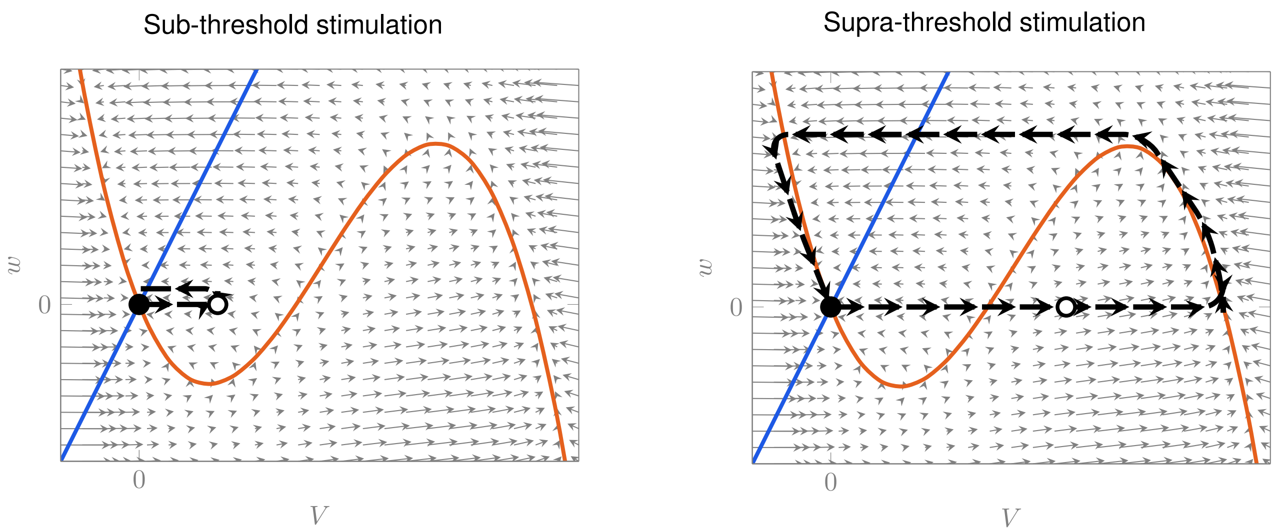
Thus, when the system is *below* the V-nullcline, then the variable V *increases*, whereas when the system is *above* the V-nullcline, then the variable V *decreases*.

(22) *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 the system remains above the V-nullcline. Therefore, iy decays towards the equilibrium without making a wide excursion (no action potential).

- In response to a supra-threshold current, the system is set in a portion of the states' space where it is below the V-nullcline. Therefore, V increases, until the system 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.



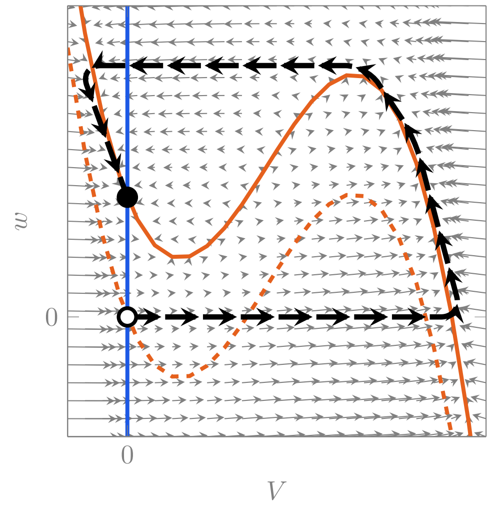
(23) *Interest of this model*

- 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. Therefore, the reset mechanism is not necessary.

- 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.

(24) *Class* `III` *excitability*

With $c = 0$, the w-null is vertical. The effect of a *step current* is to add a term I in the differential equation of the variable V, which shifts 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.



(25) *Class* II *excitability*

Class 2 behavior 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 indicates 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

(26) *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.

(27) *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.

(28) *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 :

$$I(t) = I_0 e^{i\omega t} \quad (16)$$
$$\delta V(t) = V_0 e^{i(\omega t + \phi)} \quad (17)$$
$$\delta w(t) = w_0 e^{i(\omega t + \psi)} \quad (18)$$

The steady-state oscillatory solution is found by injecting those expressions in the dynamical system.

On the one hand, by differentiating :

$$\frac{\mathrm{d}\delta V}{\mathrm{d}t} = V_0 i\omega e^{i(\omega t+\phi)} \tag{19}$$

$$\frac{\mathrm{d}\delta w}{\mathrm{d}t} = w_0 i\omega e^{i(\omega t+\psi)} \tag{20}$$

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

$$\frac{\mathrm{d}\delta V}{\mathrm{d}t} = -a\delta V - \delta w + I = -aV_0 e^{i(\omega t+\phi)} - w_0 e^{i(\omega t+\psi)} + I_0 e^{i\omega t} \tag{21}$$

$$\frac{\mathrm{d}\delta w}{\mathrm{d}t} = b\delta V - c\delta w \qquad = bV_0 e^{i(\omega t+\phi)} - cw_0 e^{i(\omega t+\psi)} \tag{22}$$

Equating (19) and (21), the time-dependent factors $e^{i\omega t}$ simplify in all members :

$$V_0 i\omega e^{i\phi} = -aV_0 e^{i\phi} - w_0 e^{i\psi} + I_0 \tag{23}$$

$$w_0 i\omega e^{i\psi} = bV_0 e^{i\phi} - cw_0 e^{i\psi} \tag{24}$$

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 :

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

29 *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 $A(\omega)$.
The numerator is always increasing with ω (> 0), so 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 $\dfrac{\beta}{2} < \alpha$.