Applications of computer algebra in the identifiability study and the parameter estimation. Application in neurosciences.

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- estimating quantities for which no sensor is available from indirect measurements

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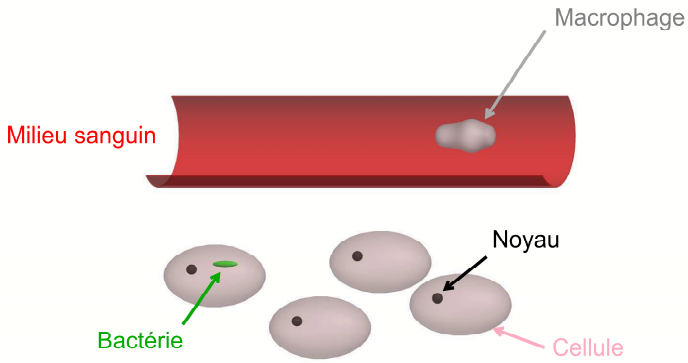
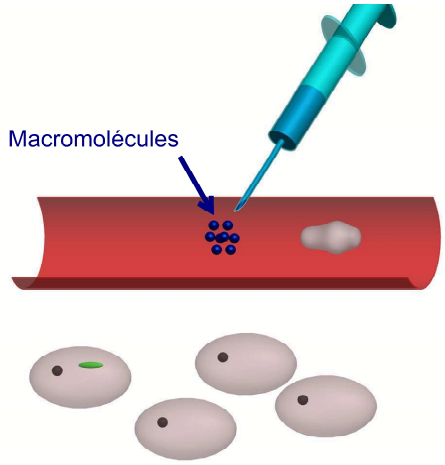
- testing hypotheses (in pharmacokinetic)

1. Infection of a cell by an extracellular bacterium



2 Injection of macromolecules



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- testing hypotheses (in pharmacokinetic)
- Method for doing fault diagnosis (system of neural network)

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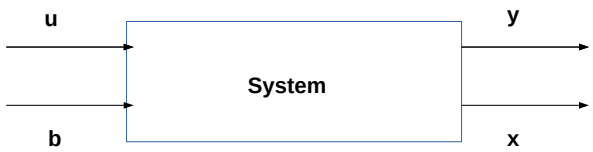
- testing hypotheses (in pharmacokinetic)
- Method for doing fault diagnosis (system of neural network)
- Teaching (simulators of aircrafts,...), predicting short-term behaviour....

Given a system (mechanical, biological...), the modeling depends on the aim of the modeler.

Any model depends on some parameters to be estimated!

Given a *system* or a *process*, some quantities interact:



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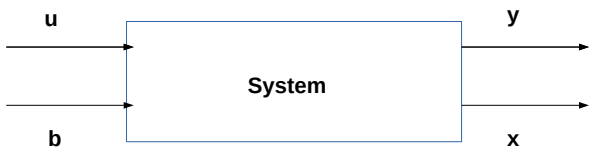

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- Some characteristic quantities of the system are observed: *output* vector y

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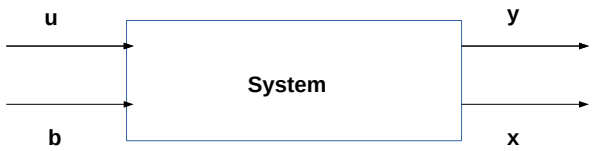

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- The system (or the measurements taken from the system) endures the action of some quantities that are not under control and/or more or less unknown: *perturbations* or *noises* vector b.

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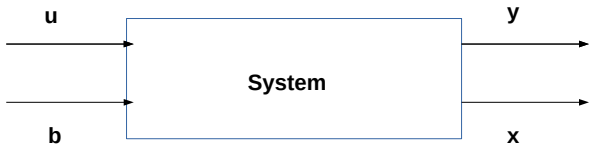

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- The system (or the measurements taken from the system) endures the action of some quantities that are not under control and/or more or less unknown: *perturbations* or *noises* vector b.
- Some quantities of the system can not be directly measured (denoted x).

Assume that the process can be modeled by

$$G(x, u, p) = y$$

- x state variables
- p parameter vector
- u input vector
- y output vector.

G defines a rule of calculus which, from quantities *a priori* known or measured form the system permits to estimate quantities that interest us.

- ✓ choice of G = *characterization of the system*
- ✓ G = *parametric model*

Several models can be considered and are not all equivalent (linear or not linear model), continuous or discrete, deterministic or stochastic....

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Two problems can be considered:

- ✓ The *forward problem*: given p, u, find x and y.
- ✓ The *inverse problem*: given y and u, estimate p.

1. Identifiability problem
2. Identification problem

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Two problems can be considered:

- ✓ The *forward problem*: given p, u, find x and y.
- ✓ The *inverse problem or identification problem*: given y and u, estimate p.
  A property of lots of inverse problems: *ill-posedness*.

Definition

A problem is said well-posed in the sense of Hadamard if it satisfies the following properties:

1. Existence: For all (suitable) data, there exists a solution of the problem (in an appropriate sense)
2. Unicity : for all available data, the solution is unique
3. Stability : the solution depends continuously of the data.

Example: The differentiation and integration

Goal of the lesson: Propose a method based on algebra tools to study inverse problems on systems of nonlinear differential equations.

$$\Gamma^p \begin{cases} \dot{x}(t,p) = f(x(t,p),u(t),p), \\ y(t,p) = h(x(t,p),p). \end{cases} \tag{1}$$

- ✓ $x(t,p) \in \mathbb{R}^n$: state variables at time t,
- ✓ $y(t,p) \in \mathbb{R}^m$: output vector at time t,
- ✓ $u(t) \in \mathbb{R}^r$: input vector at time t,
- ✓ f, h: real functions, analytic on M (an open set of $\mathbb{R}^n$),
- ✓ $p \in \mathcal{U}_\mathcal{P}$: vector of parameters, $\mathcal{U}_\mathcal{P} \subset \mathbb{R}^p$: an a priori known set of admissible parameters.

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Question

From measurements of the output(s) of the system, is it possible to estimate uniquely the parameter vector p?
If the answer is YES, then the model is said identifiable.

Tools

- ✓ Similarity method (S. Vajda),
- ✓ Method of invariants (M. Petitot),
- ✓ Input-output method based on the Rosenfeld-Groebner algorithm (implemented in Maple by F. Boulier, CRIStAL) and based on differential algebra approach (Kolchin and al., 1973)

- ✓ Microscopic worm Caenorhabditis elegans ($\approx 1mm$ de long) has .... neurons
- ✓ The insects have approximatively ..... of neurons
- ✓ Modern man has ..... of neurons in its best form
- ✓ Every day we loose approximatively ..... neurons, which is the equivalent of .....
- ✓ At 80 years old, the brain is only ..... percent of what it was around 20 years
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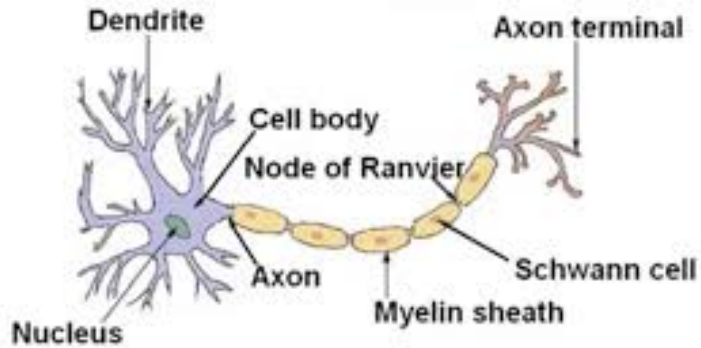
A neuron is a nerve cell, that is an electrically excitable cell that receives, processes, and transmits information through electrical and chemical signals.

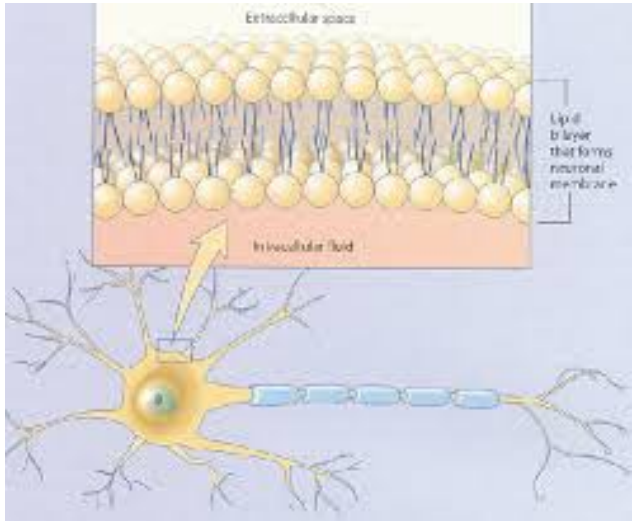


REPRESENTATION OF A NEURON

Membrane

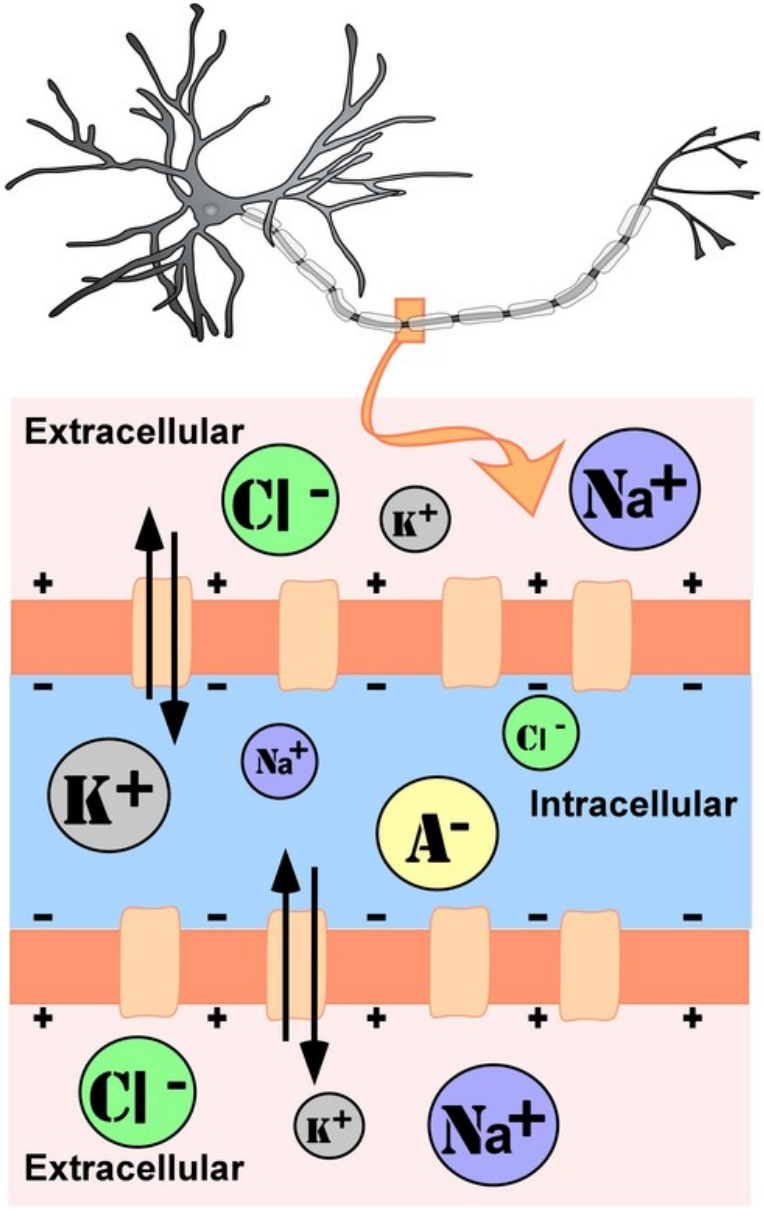
A lipid membrane

A membrane is composed of a lipid bilayer which separates the intracellular milieu and the extracellular milieu.



The main ions in a neuron are:

- Sodium (Na^+)
- Potassium (K^+)
- Calcium (Ca^{2+})
- Chlorure (Cl^-)



Ions are unequally distributed

on both sides of the membrane

There exist channels, specific for

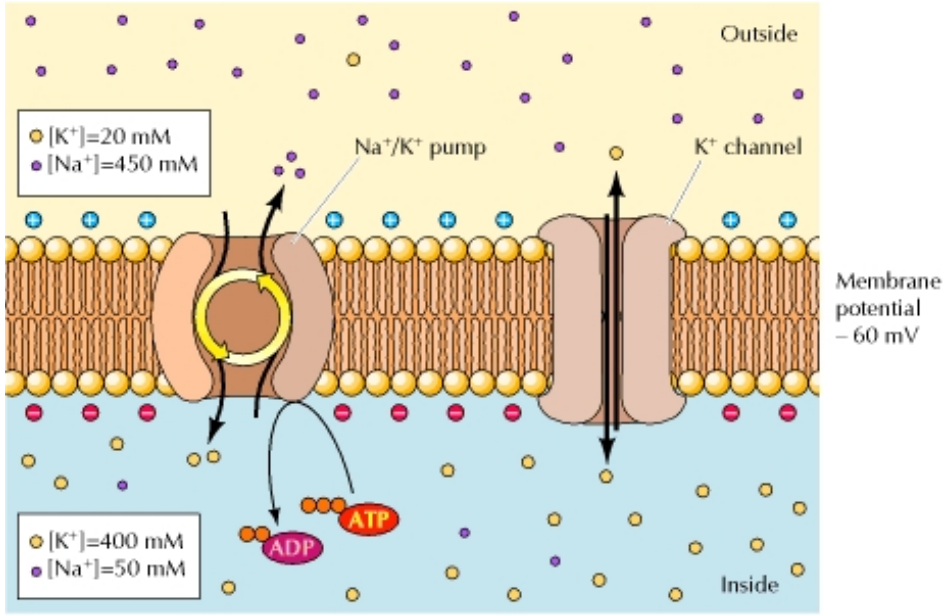
each ion through which the ions cross

the membrane.

Channels can be:

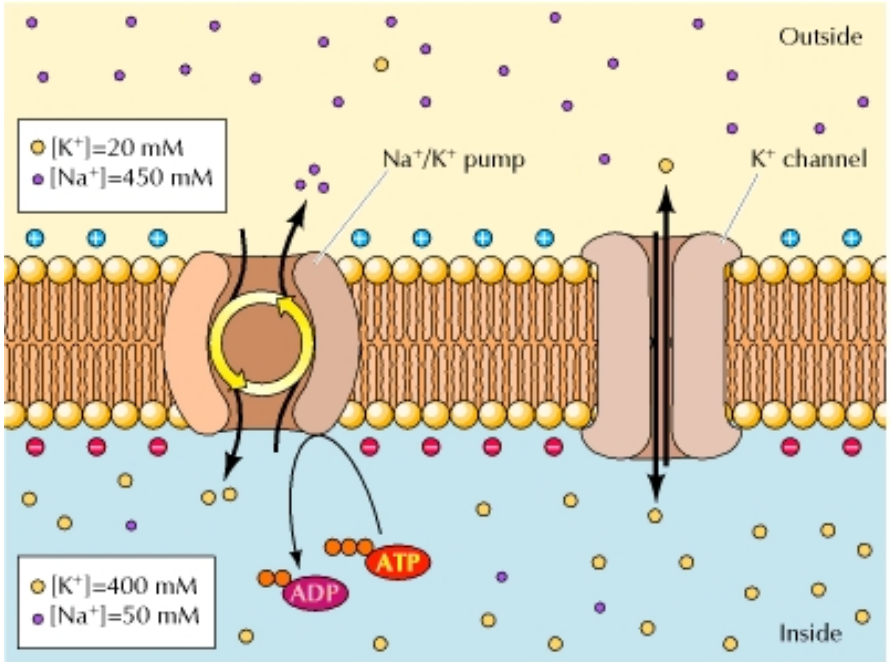
- ✓ open or close
- ✓ active or inactive.

However there is electroneutrality!



Some mechanisms permit to regulate ionic concentrations and to maintain them constant. Two types of transport:

- ✓ passive transport:
  - concentration gradient: ions go from the most concentrated milieu to the least concentrated milieu
    extracellular → intracellular: Cl^- , Na^+ , Ca^{2+}
    intracellular → extracellular: K^+
  - electrical gradient: the membrane is electrically charged: negatively inside, positively outside
    extracellular → intracellular: K^+, Na^+ and Ca^{2+}
    intracellular → extracellular: Cl^-
- ✓ active transport (NA/K pomp) requiring energy.



Potential differences:

- ✓ the potential difference of the membrane:
  $V_m = \underbrace{V_i}_{\text{intracellular potential}} - \underbrace{V_e}_{\text{extracellular potential}}$
- ✓ the potential difference due to the passage of an ion:
  $V_m - \underbrace{E_{ion}}_{\text{equilibrium potential of an ion}}$.

The current due to the passage of an ion in a channel:

$$\underbrace{V_m - E_{ion}}_{mV} = \underbrace{r}_{\text{resistance of channel}} \times \underbrace{I_{ion}}_{\text{ionic current (pA)}} \Leftrightarrow I_{ion} = \underbrace{G}_{\text{conductance (siemens } S\text{)}} (V_m - E_{ion}).$$

Modeling of a simple ion channel with one activation (m):

$$I = G(V - E) \text{ where } G = g\,m$$

where

- V (mV): voltage
- g (nS): maximal conductance
- E (mV): reversal potential
- m is the probability of a channel to be open

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The equation describing the activation of the gates to the answer of the potential of membrane is

$$\frac{dm}{dt} = \frac{m_\infty(V) - m}{\tau(V)}$$

where

- $m_\infty(V)$: the equilibrium value of m
- $\tau(V)$: times at which the equilibrium is attained.

What can we measure?

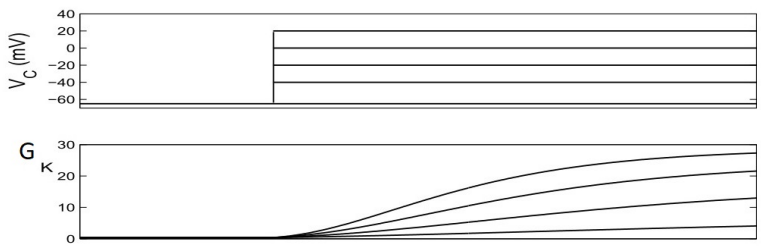
The *voltage-clamp protocol*

- characterizes the activation or inactivation properties of the ionic canal
- necessitates to treat the membrane of the neuron (tetrodoxine)
- consists in holding the voltage ($= V$) piecewise constant $\Rightarrow$ during each interval, m_∞ , τ can be considered as constant and we have

$$\frac{dm}{dt} = \frac{m_\infty - m}{\tau}$$

.

For example, the potassium: $I_K(t) = G_K(t)(V - E_K) \Rightarrow G_K(t) = \frac{I_K(t)}{(V - E_K)}$



Assumptions:

- ✓ V = constant input
- ✓ I = output (= y)
- ✓ m = state variable (= x)

Example 1

The equation of one ion channel with one activation variable:

$$\left\{ \begin{array}{ll} \dfrac{dm}{dt} & = \dfrac{m_\infty - m}{\tau}, \, m_0 = m(0) \\ I(t) & = g\, m\, (V - E) \end{array} \right. \Leftrightarrow \left\{ \begin{array}{ll} m(t) & = m_\infty + (m(0) - m_\infty)\, e^{-\frac{t}{\tau}} \\ y(t) & = g\, m\, u \end{array} \right. \tag{2}$$

where $u := V - E = cst$ and $y := I$.

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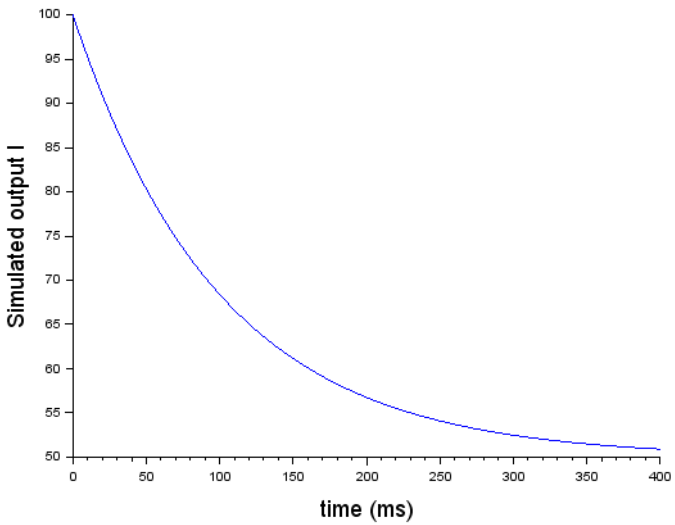
For $\tau = 100ms$, $u = 20mV$, $(m(0), m_\infty, g) = (1, 0.5, 5)$ and $(m(0), m_\infty, g) = (2, 1, 2.5)$:



During the voltage step protocol, the model can produce exactly the same output for different parameter/initial condition values!

Formalization

Controlled models ($u \neq 0$) WITHOUT initial condition; ($\tilde{x}$, $\tilde{y}$) = unique set of solutions

- The model is **globally identifiable** if there exists an input u such that, for all $p \in \mathcal{U}_p$, one gets

$$\left.\begin{array}{r} \tilde{y}(t,p) \neq \emptyset, \\ \tilde{y}(t,p) \cap \tilde{y}(t,\bar{p}) \neq \emptyset, \ \forall\, t \geq 0, \ \bar{p} \in \mathcal{U}_p \end{array}\right\} \quad \Rightarrow \quad p = \bar{p}. \tag{3}$$

- The model is **locally identifiable** if it is globally identifiable in an open neighborhood $v(p) \subset \mathcal{U}_p$ of p.

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Controlled model ($u \neq 0$) WITH initial conditions; (x, y) unique solution

- The model is **globally identifiable** if there exists an input u such that, for all p, $\bar{p} \in \mathcal{U}_p$, there exists $t_1 > 0$ such that if for all $t \in [0, t_1]$, the equalities $y(t,p) = y(t,\bar{p})$ implies that $p = \bar{p}$.
- The model is **locally identifiable** if it is globally in an open neighborhood $v(p) \subset \mathcal{U}_p$ of p.

Example 1: WITHOUT initial condition

The equation of one ion channel with one activation variable:

$$I(t) = g\, m\, (V - E) \tag{4}$$

where

$$\frac{dm}{dt} = \frac{m_\infty - m}{\tau}. \tag{5}$$

m_∞: the equilibrium value of m,
τ: times at which the equilibrium is attained,
E known constant reversal potential.

Proposition

If V is a constant input and I is an output of the model then the model is not identifiable, in particular with respect to τ and m_∞.

Proof.

...

□

Example 1: WITH initial condition

$$\begin{cases} I(t) = g(V - E)m \\ \dfrac{dm}{dt} = \dfrac{m_\infty - m}{\tau}, m(0) = m_0. \end{cases} \tag{6}$$

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Proof.

Results obtained in the case without initial conditions stay valid: τ et gm_∞ are identifiable.
The solution of the second equation is

$$m(t) = m_0 e^{-t/\tau} + m_\infty (1 - e^{-t/\tau})$$

In taken $y(t) = g\,u\,m(t)$ and in substituting m by its expression, one gets:
$\dfrac{y(t)}{m_\infty\, g\, u} = \dfrac{m_0}{m_\infty} e^{-t/\tau} + 1 - e^{-t/\tau}$. Since the product $g\,m_\infty$ is identifiable, $\dfrac{y(t)}{m_\infty\, g\, u}$ can be estimated and the model is identifiable with respect to m_∞. □

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Remarks

- Identifiability result based on specific relations called Input-Output (IO) polynomials
- Differential algebra permit to obtain them owing to the Rosenfeld-Groebner algorithm.

General case:

$$\Gamma^p \begin{cases} \dot{x}(t,p) = f(x,u,p),\ x \in \mathbb{R}^n,\ u \in \mathbb{R}^q,\ p \in \mathbb{R}^p \\ y(t,p) = h(x,p) \in \mathbb{R}^m. \end{cases} \tag{7}$$

1. Rewrite (7) :

$$\begin{cases} p(x,u,p) = 0 \\ q(x,y,u,p) = 0 \\ r(x,y,y,p) \neq 0 \\ \dot{p}_i = 0,\ i = 1,\ldots,p. \end{cases} \tag{8}$$

2. Use the Rosenfeld-Groebner algorithm with the elimination order $[p] \prec [y,u] \prec [x]$:

$$\mathcal{C}(p) = \{\dot{p}_1,\ldots,\dot{p}_p, P_1(y,u,p),\ldots,P_m(y,u,p), Q_1(x,y,u,p),\ldots,Q_n(x,y,u,p)\}.$$

   This set is called the *characteristic presentation* (general case).

3. Identifiability study done from the *input-output polynomials*

$$P_i(y,u,p) = m_0^i(y,u) + \sum_{k=1}^{q} \gamma_k^i(p) m_k^i(y,u) = 0. \tag{9}$$

Remark

Under some technical assumptions, (9) are contained in the characteristic presentation obtained with p as a constant vector and $[y,u] \prec [x]$ as the elimination order.

Afterwards, 1 observation $\Rightarrow i = 1$.

$$P(y, u, p) = m_0(y, u) + \sum_{k=1}^{q} \gamma_k(p) m_k(y, u) = 0.$$

Proposition

If $(m_k(y, u))_{1 \leq k \leq q}$ are linearly independent then the model is globally identifiable at p if for all $\bar{p} \in \mathcal{U}_p$

$$\forall k = 1, \ldots, q, \ \gamma_k(\bar{p}) = \gamma_k(p) \Rightarrow p = \bar{p}. \tag{10}$$

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Remark

- ✓ If $\phi(p) = (\gamma_k(p))_{k=1,\ldots,q}$, (10) consists in verifying that ϕ is injective.
- ✓ The functions $(m_k(y,u))_{k=1,\ldots,q}$ are linearly independent if the functional determinant is not identically equal to zero. It is sufficient to find a time point at which the Wronskian is non-zero.
- ✓ We recall that the Wronskian of the sequence of functions $(\phi_1,\ldots,\phi_s)$ is defined by:

$$\text{Wronskian} = Det(\phi_1,\ldots,\phi_s) = \begin{vmatrix} \phi_1 & \cdots & \phi_s \\ \dot{\phi}_1 & \cdots & \dot{\phi}_s \\ \vdots & \cdots & \vdots \\ \phi_1^{(s-1)} & \cdots & \phi_s^{(s-1)} \end{vmatrix}. \tag{11}$$

The identifiability when initial conditions are considered:

$$\Gamma^p = \begin{cases} \dot{x}(t,p) = f(x(t,p),p), x(0,p) = x_0 \\ y(t,p) = h(x(t,p),p). \end{cases} \tag{12}$$

f and h are supposed to be rational and analytical.

$$P(y,u,p) = m_0(y,u) + \sum_{k=1}^{q} \gamma_k(p)\ m_k(y,u) = 0$$

Proposition

Let l the highest order derivative in the polynomial P. If $(m_k(y,u))_{1\leq k\leq q}$ are linearly indépendant then the model is globally identifiable at p if for all $\bar{p} \in \mathcal{U}_p$

$$\begin{cases} \forall k = 1,\dots,q,\ \gamma_k(\bar{p}) = \gamma_k(p) \\ 1 \leq s \leq l-1,\ y^{(s)}(0^+,p) = y^{(s)}(0^+,\bar{p}) \end{cases} \Rightarrow p = \bar{p} \tag{13}$$

Moreover, if the coefficient of $y^{(l)}$ in P is not equal to 0 at $t = 0$ then the reciprocal is true.

Example 2: the FitzHugh-Nagumo model

R. FitzHugh (1961) and Nagumo (1962) proposed a simplification in two dimensions of the Hodgkin-Huxley (HH; Hodgkin Huxley, 1952) model:

- HH or conductance-based model: mathematical model describing how action potentials in neurons are initiated and propagated
- HH model is constructed in using an analogy with a circuit.

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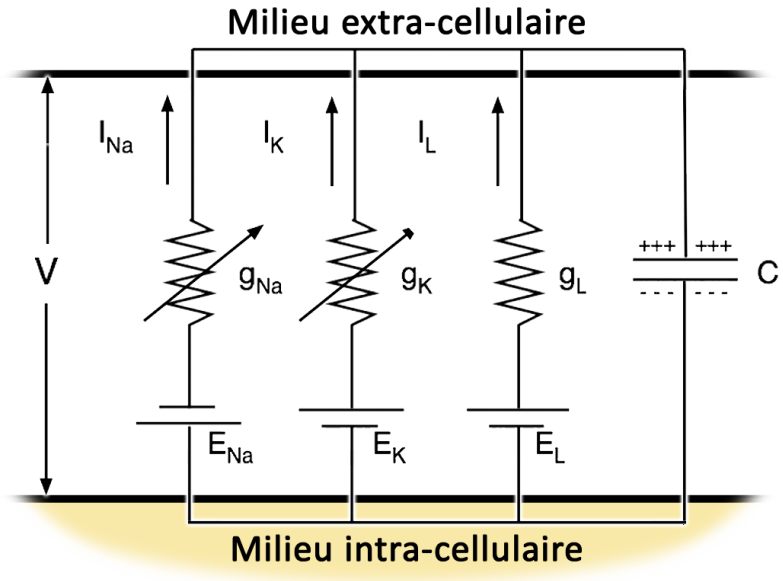
- HH or conductance-based model: mathematical model describing how action potentials in neurons are initiated and propagated
- HH model is constructed in using an analogy with a circuit.

✓ Membrane = capacitor of capacity C and ionic channels = variable resistors

✓ Kirchhof's law: at any node (junction) in an electrical circuit, the sum of currents flowing into that node is equal to the sum of currents flowing out of that node



$$-C\frac{dV}{dt} = I_K + I_{Na} + I_L - I$$

$$\text{Model HH} \begin{cases} -C\dot{V} &= m^3 h\overline{g_{Na}}(V - E_{Na}) + n^4\overline{g_K}(V - E_K) + \overline{g_L}(V - E_L) - I \\ \dot{n} &= \dfrac{n_\infty - n}{\tau_n} \\ \dot{m} &= \dfrac{m_\infty - m}{\tau_m} \\ \dot{h} &= \dfrac{h_\infty - h}{\tau_h} \end{cases} \tag{14}$$

- ✓ V: potential of the membrane
- ✓ I: injected current
- ✓ C: capacitor
- ✓ E_K, E_{Na} are E_L: reversal potentials.
- ✓ n: probability that a potassium channel is opened
- ✓ m: probability that a sodium channel is opened
- ✓ h: probability that a sodium channel is activated

Simulations show that the HH model can be approximated by the FitzHugh-Nagumo model:

$$\begin{cases} \dfrac{dx_1}{dt} &= a(x_2 - f(x_1) + I) \quad f \text{ cubic function} \\ \dfrac{dx_2}{dt} &= b(g(x_1) - x_2) \quad g \text{ linear function} \end{cases}$$

x_1: potential.

FitzHugh-Nagumo model ($c \neq 0$):

$$\begin{cases} \dfrac{dx_1}{dt} = c(x_1 - \dfrac{x_1^3}{3} + x_2) \\ \dfrac{dx_2}{dt} = -\dfrac{1}{c}(x_1 - a + bx_2) \end{cases} \tag{15}$$

Proposition

Given $y := x_1$ the output of the model, the model is identifiable with respect to a, b, c.

Proof.

Using the *DifferentialAlgebra* package of Maple with the elimination order $[y] \prec [x_1, x_2]$, the Rosenfeld-Groebnerr algorithm gives the characteristic presentation:

$$i := [-y + x_1,\ -c\,y^3 + 3\,c\,x_2 + 3\,c\,y - 3\,\dot{y},$$
$$b\,c\,y^3 + 3\,c^2\,y^2\,\dot{y} - 3\,b\,c\,y - 3\,c^2\,\dot{y} - 3\,a\,c + 3\,b\,\dot{y} + 3\,c\,y + 3\,c\,\ddot{y}].$$

Hence, $P(y) = \ddot{y} - a\,1 + \dfrac{b}{3}\,y^3 + c\,\dot{y}\,y^2 + (-b+1)\,y + \dfrac{-c^2+b}{c}\,\dot{y}$.

- ✓ $det(1, y^3, \dot{y}\,y^2, y, \dot{y})$ is not identically null.
- ✓ If $p = (a, b, c)$, the function $\phi(p) = (-a, \frac{b}{3}, c, -b+1, \frac{-c^2+b}{c})$ is injective.

In conclusion, the model is identifiable. □

Exercise

Consider an ion channel model with one activation (m) and one inactivation variable (h) in the case of a voltage clamp protocol.

$$\begin{cases} I & = gmh(V_0 - E) = gmh(u - E), \\ \dfrac{dm}{dt} & = \frac{m_\infty - m}{\tau_m}, \\ \dfrac{dh}{dt} & = \frac{h_\infty - h}{\tau_h}, \\ y & = I,\ u = V_0 = cst. \end{cases} \tag{16}$$

By a change of variables: $x_1 = m$, $x_2 = h$, $p_1 = \tau_m$, $p_2 = m_\infty$, $p_3 = \dfrac{1}{\tau_h}$, $p_4 = h_\infty$, $p_5 = g$, $k_1 = u - E$, the model can be rewritten:

$$\begin{cases} \dfrac{dx_1}{dt} & = p_1(p_2 - x_1), \\ \dfrac{dx_2}{dt} & = p_3(p_4 - x_2), \\ y & = k_1 p_5 x_1 x_2. \end{cases} \tag{17}$$

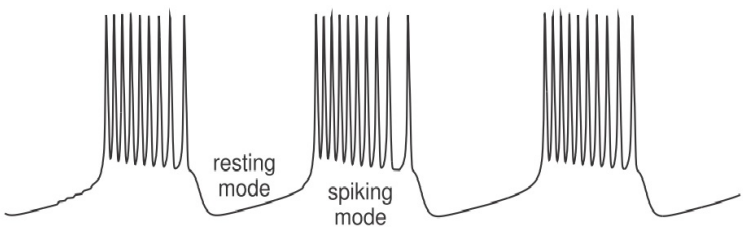
Study the identifiability of model (17).

2 types of algorithms:

- global algorithm: genetic algorithm
- local algorithms: Gauss-Newton and Levenberg-Marquardt algorithms.

- $y = (y(t_1), \ldots, y(t_n))^T$ = vector coming from experimental results.

In neurosciences, measurable characteristic: mean between the height of spikes and the length of spikes, resting potential of the membrane, potential after a hyperpolarisation, firing rate, bursting rate....



- $y = (y(t_1), \ldots, y(t_n))^T$ = vector coming from experimental results.
- Given a model, $y_m(t, p)$: $(y_m(t_1), \ldots, y_m(t_n))^T$ = output vector calculated from the model and the parameter vector p

Goal

Given y, calculate p such that $y_m(t, p)$ "approximate" experimental data y.
Define the output error:

$$e(t, p) = y_m(t, p) - y(t).$$

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Problem

Perturbations of the system $\Rightarrow$ $e(t, p)$ can never been equal to 0.
The model outputs can never fit the system outputs with these perturbations.

Solution

Define the differentiable cost function

$$j(p) = \frac{1}{2} \parallel e(t,p) \parallel_2^2 = \frac{1}{2} \parallel y_m(t,p) - y(t) \parallel_2^2, \text{ où } p \in \mathcal{U}_{ad} \tag{18}$$

and solve the problem

$$\text{find } \hat{p} \text{ such that } j(\hat{p}) = \min_p j(p).$$

Choose an optimization algorithm to minimize $j(p)$. In general, the error must be near 0.

Examples

- ✓ Compare simulated ionic currents (I_{est}) and registered ionic currents (I_{ref}):

$$j(p) = \sum_t \sum_{stim} (I_{est}(stim,t) - I_{ref}(stim,t))^2.$$

- ✓ Compare simulated potentials $V_{est}(stim,t)$ and registered potentials:

$$j(p) = \sum_t \sum_{stim} (V_{est}(stim,t) - V_{ref}(stim,t))^2.$$

- ✗ Classical local algorithms (least-squares): Gauss-Newton, Levenberg-Marquardt
- ✗ Problem: necessitate a first initial guess for the parameter vector
- ✗ Solution: Use the IO polynomial to obtain a first initial guess.

Principle of the method

Observations are supposed to be done at discrete times $t_1, \ldots, t_M$ ($y_k := y(t_k)$, $u_k := u(t_k)$).

- ✓ The input-output polynomial:

$$P(y, u, p) = m_0(y, u) + \sum_{l=1}^{q} \gamma_l(p) m_l(y, u) = 0.$$

- ✓ Rectangular linear system ($\gamma = (\gamma_1(p), \ldots, \gamma_q(p))^T$):

$$A\gamma = b, \quad (A)_k = (m_l(y_k, u_k))_{l=1,\ldots,q}, \; b_k = -m_0(y_k, u_k). \tag{19}$$

$((A)_k = (m_j(y_k, u_k))_{j=1,\ldots,q}, \; b_k = -m_0(y_k, u_k))$ solve with the QR factorization.

Example 2

FitzHugh-Nagumo model ($c \neq 0$):

$$\begin{cases} \dfrac{dx_1}{dt} = c(x_1 - \dfrac{x_1^3}{3} + x_2) \\ \dfrac{dx_2}{dt} = -\dfrac{1}{c}(x_1 - a + bx_2) \end{cases} \tag{20}$$

- ✓ $P(y) = \ddot{y} - a\,1 + \dfrac{b}{3}\,y^3 + c\,\dot{y}\,y^2 + (-b+1)\,y + \dfrac{-c^2+b}{c}\,\dot{y}$.
- ✓ Rectangular linear system $A\gamma = b$ such that $(A)_k = (1,\ y_k^3,\ \dot{y}_k\,y_k^2,\ y_k,\ \dot{y}_k)$, $b_k = -\ddot{y}_k$.

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- ✗ Problem: Estimation of derivatives of order 2
- ✗ Solution: Integrate twice the IO polynomial (over a sliding time window of fixed length):

  $I_n x(t) := \int_{t-\tau}^{t} \int_{\tau_1-\tau}^{\tau_1} \dots \int_{\tau_n-1-\tau}^{\tau_{n-1}} x(\tau_n) d\tau_n \dots d\tau_1$, n higher derivative order.

  For example: $I_2 \ddot{y}(t) = \int_{t-\tau}^{t} \int_{\tau_1-\tau}^{\tau_1} \ddot{y}(\tau_2) d\tau_2 d\tau_1 = y(t) - 2y(t-\tau) + y(t-2\tau)$.

Consider the FitzHugh-Nagumo with a=0.2, b=0.2, c=0.6 and the program Scilab:

1. run the program with different values of τ
2. test this program in adding noises on the output.

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