

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

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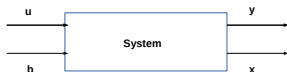


Aim of modeling (E. Walter and L. Pronzato, Identification of parametric models from experimental data, 1997):

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



- We act on the system by means of some quantities which are more or less under control: *input* vector u
- Some characteristic quantities of the system are observed: *output* vector y
- 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.

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.

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

- ✓ $x(t, \mathbf{p}) \in \mathbb{R}^n$: state variables at time t ,
- ✓ $y(t, \mathbf{p}) \in \mathbb{R}^m$: 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),
- ✓ $\mathbf{p} \in \mathcal{U}_{\mathcal{P}}$: vector of parameters, $\mathcal{U}_{\mathcal{P}} \subset \mathbb{R}^{\mathcal{P}}$: an a priori known set of admissible parameters.

Question

From measurements of the output(s) of the system, is it possible to estimate uniquely the parameter vector \mathbf{p} ?

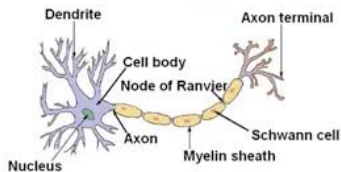
If the answer is YES, then the model is said identifiable.

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, CRISAL) and based on differential algebra approach (Kolchin and al., 1973)

- ✓ Microscopic worm *Caenorhabditis elegans* ($\approx 1\text{ mm}$ 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
- ✓ Nerve information passes from neurons to neurons, up to

A neuron is a nerve cell, that is an electrically excitable cell that receives, processes, and transmits information through electrical and chemical signals.

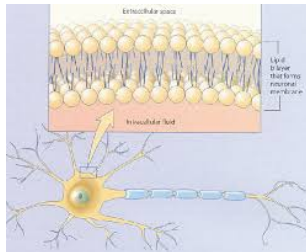


REPRESENTATION OF A NEURON

Membrane

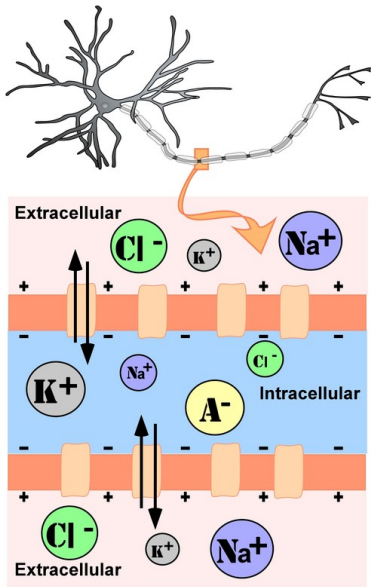
A lipid membrane

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

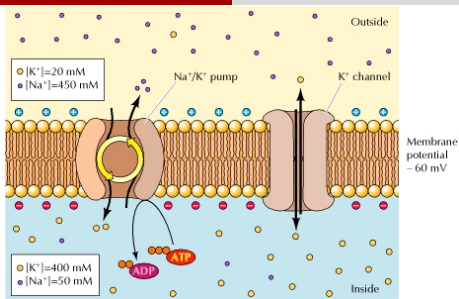
each ion through which the ions cross

the membrane.

Channels can be:

- ✓ open or close
- ✓ active or inactive.

However there is electroneutrality!

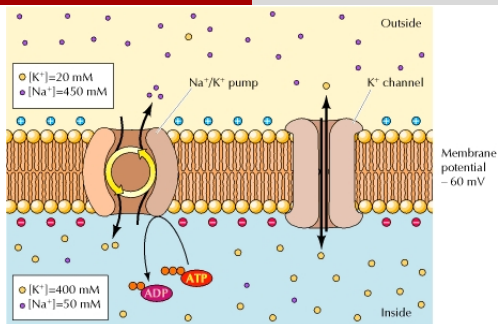


Some mechanisms permit to regulate ionic concentrations and to maintain them constant. Two types of transport:

✓ passive transport:

- **concentration gradient**: ions go from the most concentrated milieu to the least concentrated milieu
 extracellular \rightarrow intracellular: Cl^- , Na^+ , Ca^{2+}
 intracellular \rightarrow extracellular: K^+
- **electrical gradient**: the membrane is electrically charged: negatively inside, positively outside
 extracellular \rightarrow intracellular: K^+ , Na^+ and Ca^{2+}
 intracellular \rightarrow extracellular: Cl^-

✓ active transport (NA/K pump) 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:

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

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

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.

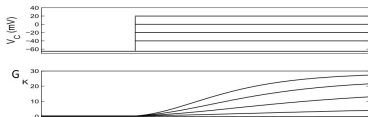
What can we measure?

The *voltage-clamp protocol*

- characterizes the activation or inactivation properties of the ionic canal
- necessitates to treat the membrane of the neuron (tetrodotoxine)
- 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 ($= x$)

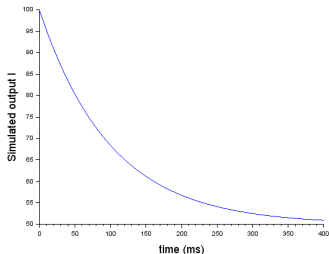
Example 1

The equation of one ion channel with one activation variable:

$$\begin{cases} \frac{dm}{dt} = \frac{m_\infty - m}{\tau}, m_0 = m(0) \\ I(t) = g m \tau (V - E) \end{cases} \Leftrightarrow \begin{cases} m(t) = m_\infty + (m(0) - m_\infty) e^{-\frac{t}{\tau}} \\ y(t) = g m u \end{cases} \quad (2)$$

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

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

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

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

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:

$$I(t) = g m (V - E) \quad (4)$$

where

$$\frac{dm}{dt} = \frac{m_{\infty} - m}{\tau}. \quad (5)$$

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

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

Proposition

If V is a constant input and I is an output of the model then the model is identifiable, in particular τ and m_∞ .

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:

$\frac{y(t)}{m_\infty g u} = \frac{m_0}{m_\infty} e^{-t/\tau} + 1 - e^{-t/\tau}$. Since the product $g m_\infty$ is identifiable, $\frac{y(t)}{m_\infty g u}$ can be estimated and the model is identifiable with respect to m_∞ . □

Example 1: WITH initial condition

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

Proposition

If V is a constant input and I is an output of the model then the model is identifiable, in particular τ and m_∞ .

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:

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

1 Rewrite (7) :

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

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

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

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

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

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

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 $\bar{p} \in \mathcal{U}_p$

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

Remark

- ✓ If $\phi(p) = (\gamma_k(p))_{k=1, \dots, q}$, (10) consists in verifying that ϕ is injective.
- ✓ The functions $(m_k(y, u))_{k=1, \dots, q}$ 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 (ϕ_1, \dots, ϕ_s) is defined by:

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

The identifiability when initial conditions are considered:

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

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 independent then the model is globally identifiable at p if for all $\bar{p} \in \bar{U}_p$

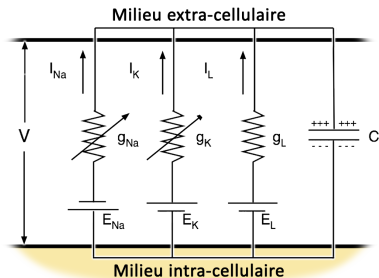
$$\begin{cases} \forall k = 1, \dots, q, \gamma_k(\bar{p}) = \gamma_k(p) \\ 1 \leq s \leq l-1, y^{(s)}(0^+, p) = y^{(s)}(0^+, \bar{p}) \end{cases} \Rightarrow p = \bar{p} \quad (13)$$

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.
- ✓ 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



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

$$\text{Model HH} \left\{ \begin{array}{l} -C\dot{V} = m^3 h \bar{g}_{Na}(V - E_{Na}) + n^4 \bar{g}_K(V - E_K) + \bar{g}_L(V - E_L) - I \\ \dot{n} = \frac{n_\infty - n}{\tau_n} \\ \dot{m} = \frac{m_\infty - m}{\tau_m} \\ \dot{h} = \frac{h_\infty - h}{\tau_h} \end{array} \right. \quad (14)$$

- ✓ 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:

$$\left\{ \begin{array}{l} \frac{dx_1}{dt} = a(x_2 - f(x_1) + I) \quad f \text{ cubic function} \\ \frac{dx_2}{dt} = b(g(x_1) - x_2) \quad g \text{ linear function} \end{array} \right.$$

x_1 : potential.

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

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

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:

$$i := [-y + x_1, -cy^3 + 3cx_2 + 3cy - 3\dot{y}, \\ bcy^3 + 3c^2y^2\dot{y} - 3bcy - 3c^2\dot{y} - 3ac + 3b\dot{y} + 3cy + 3c\ddot{y}].$$

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

- ✓ $\det(1, y^3, \dot{y}y^2, y, \dot{y})$ 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.

$$\left\{ \begin{array}{l} I \\ \frac{dm}{dt} \\ \frac{dh}{dt} \\ y \end{array} \right. = \begin{array}{l} gmh(V_0 - E) = gmh(u - E), \\ \frac{m_\infty - m}{\tau_m}, \\ \frac{h_\infty - h}{\tau_h}, \\ I, u = V_0 = cst. \end{array} \quad (16)$$

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

$$\left\{ \begin{array}{l} \frac{dx_1}{dt} \\ \frac{dx_2}{dt} \\ y \end{array} \right. = \begin{array}{l} p_1(p_2 - x_1), \\ p_3(p_4 - x_2), \\ k_1 p_5 x_1 x_2. \end{array} \quad (17)$$

Study the identifiability of model (17).

2 types of algorithms:

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

- $y = (y(t_1), \dots, y(t_n))^T$ = vector coming from experimental results.
- Given a model, $y_m(t, p)$: $(y_m(t_1), \dots, y_m(t_n))^T$ = 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:

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

Problem

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

Solution

Define the differentiable cost function

$$j(p) = \frac{1}{2} \| e(t, p) \|_2^2 = \frac{1}{2} \| y_m(t, p) - y(t) \|_2^2, \quad \text{où } p \in \mathcal{U}_{ad} \quad (18)$$

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, \dots, t_M ($y_k := y(t_k)$, $u_k := u(t_k)$).

- ✓ The input-output polynomial:

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

- ✓ Rectangular linear system ($\gamma = (\gamma_1(\mathbf{p}), \dots, \gamma_q(\mathbf{p}))^T$):

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

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

Example 2

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

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

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

✓ 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

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- ✓ Rectangular linear system $A_\gamma = b$ such that $(A)_k = (1, y_k^3, \dot{y}_k y_k^2, y_k, \dot{y}_k)$, $b_k = -\ddot{y}_k$.
- ✗ Problem: Estimation of derivatives of order 2
- ✗ Solution: Integrate twice the IO polynomial (over a sliding time window of fixed length):

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

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

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.

Neurophysiologie

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