# Identifiability, Integro-Differential Equations and Neurobiology

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March 13, 2017

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## Journées Annuelles du GT BIOSS (Montpellier)
## Talk Afternotes

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This document was obtained by merging the slides of the talk and an "ideal" version of the speech, synthetized after the talk. Questions should be addressed to `Francois.Boulier@univ-lille1.fr`.

This talk presents an interdisciplinary research project mixing computer algebra (Lille), applied mathematics and modeling (Le Havre) and neurobiology (Rouen).

# The Keywords

## Lille / Computer Algebra

Symbolic manipulation of nonlinear differential models, to facilitate parameter estimation. Inputs and outputs of models. Integrate rather than differentiate.

## Le Havre / Applied Mathematics

Designing a differential model of the neuron/astrocyte interaction, in order to understand the outbreak of the cortical spreading depression (CSD).

## Rouen / Neurophysiology

Vascular system. Astrocytes. UII. Key phenomenon indicating CSD outbreak? Essential subset of ingredients to be introduced in the model equations? Gathering consistent data (same biological model).

**The Keywords.** The computer algebra part of the project (Lille) deals with the symbolic manipulation of nonlinear differential systems. All the manipulations mentioned in this talk somehow aim at facilitating parameter estimation. We will be concerned by inputs and outputs of models. We want to integrate rather than differentiate equations.

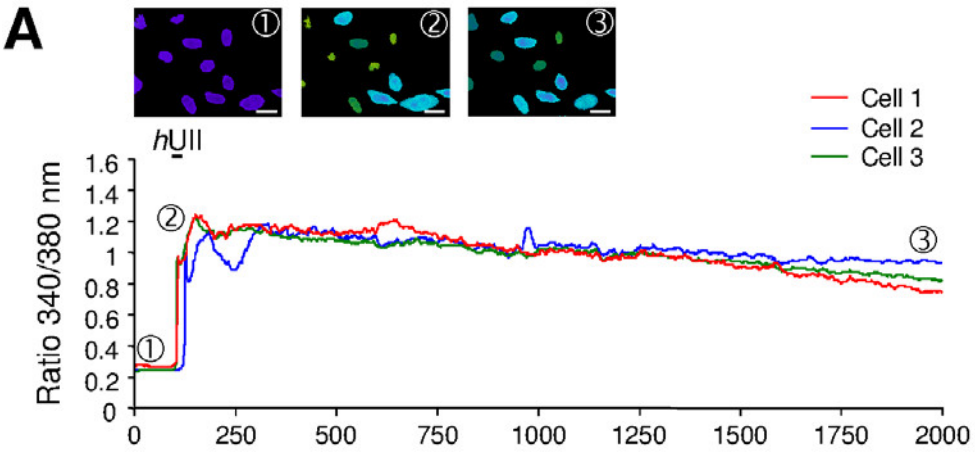
The Rouen team is interested in the vascular system of the brain, glial cells called *astrocytes* and a particular neuropeptide, the *urotensin II*. In our project, the biological question consists in determining key ingredients of the outbreak of a disease: the *cortical spreading depression*. One of the issue consists in gathering consistent data i.e. data acquired on the same biological model and in the same experimental conditions.

In between, the Le Havre team aims at designing a nonlinear differential model of the ionic activities of the neuron/astrocyte interaction, featuring these key ingredients and aiming at understanding the outbreak of the cortical spreading depression.

# Parameter Estimation

Estimating parameters is easier with integral equations than with differential ones, because numerical integration schemes are less sensitive to noise than numerical differentiation ones.

$$\dot{y}(t) = k\, y(t) \quad \text{vs} \quad y(t) - y(0) = k \int_0^t y(\tau)\, \mathrm{d}\tau\,.$$




## 1 Identifiability

**Parameter Estimation.** The bottom picture shows experimental curves obtained by Rouen [13, Fig. 5] by means of calcium imaging techniques. The picture has no relationship with the equation above but permits us to illustrate the type of data which are available to us.

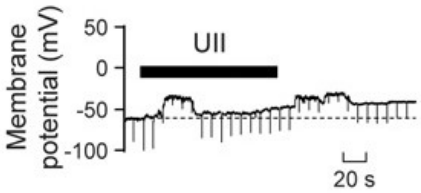
The two equations actually are two different forms of the same equation.

On the one hand, assume you want to estimate the parameter $k$ using the experimental curve and the differential form of the equation (left). You will have to evaluate $y(t)$ at many different values of $t$, but you will also have to evaluate the derivative $\dot{y}(t)$ over the curve. Obviously, the estimate of the derivative is not going to be very precise. On the other hand, if you use the integral form of the equation (right), you will avoid the problem of numerically estimating the derivative and replace it by the one of numerically estimating the integral. Intuitively, the result will be much more reliable. One often says that integration filters high frequency noise.

# Inputs and Outputs

In a more realistic case, experimental curves are not available for *all* variables of the mathematical model.

Input $u(t)$ (concent. [UII])
Output $y(t)$ (V. membrane)




Question: knowing the input, the output and the experimental curves, can we estimate the parameters $k_{12}$, $k_{21}$, $V_e$ ?

$$\begin{aligned} \dot{x}_1(t) &= -k_{12}\, x_1(t) + k_{21}\, x_2(t) - \frac{V_e\, x_1(t)}{1 + x_1(t)} + u(t)\,, \\ \dot{x}_2(t) &= k_{12}\, x_1(t) - k_{21}\, x_2(t)\,, \\ y(t) &= x_1(t)\,. \end{aligned}$$

**Inputs and Outputs.** In a more realistic situation, one cannot expect to have experimental curves for *all* variables of the dynamical system. The variables for which such curves may be available are the *outputs* (classically denoted $y(t)$) and the *inputs* (classically denoted $u(t)$) of the dynamical system.

The experimental curve corresponds to another neurophysiological experiment performed by Rouen [19, Fig. 3]. The output would be here the potential of the membrane of some astrocyte. During the experiment, the extracellular medium of the cell is temporarily enriched with some quantity of the urotensin II (denoted UII). The input would be here the concentration of UII: it would be a piecewise constant function of the time.

As in the former slide, the mathematical model [9] has strictly no relationship with the experiment. Among the unknown functions of the model, one sees an input $u(t)$ and an output, equal to the state variable $x_1(t)$. It is implicitly assumed that no experimental data will ever be available for $x_2(t)$.

A question naturally arises: is it possible to estimate the three unknown model parameters $k_{12}$, $k_{21}$ and $V_e$, with such restricted informations?

# The Input-Output Equation

Question: knowing the input, the output and the experimental curves, can we estimate the parameters $k_{12}$, $k_{21}$, $V_e$ ?

Answer: yes, from the input-output equation (obtained by elimination in differential algebra).

$$-\theta_1\, u(t) + \theta_2\, \frac{y(t)}{y(t)+1} + \theta_3\, \frac{\mathrm{d}}{\mathrm{d}t}\left(\frac{y(t)^2}{y(t)+1}\right) - \theta_4\, \frac{\mathrm{d}}{\mathrm{d}t}\left(\frac{1}{y(t)+1}\right) = \dot{u}(t) - \ddot{y}(t)\,,$$

where the $\theta_i$ stand for the following parameter blocks::

$$\theta_1 = k_{21}\,, \quad \theta_2 = k_{21}\, V_e\,, \quad \theta_3 = k_{12} + k_{21}\,, \quad \theta_4 = k_{12} + k_{21} + V_e\,.$$

The knowledge of the $\theta_i$ is sufficient (here) to determine the model parameters $k_{12}$, $k_{21}$ and $V_e$ ($\rightarrow$ identifiability)

**The Input-Output Equation.** The answer is yes, if you compute a differential equation which only depends on the parameters, the inputs, the outputs and some of their derivatives. This equation can actually be computed by computer algebra packages implementing elimination algorithms in differential algebra [8, 5].

In his plenary talk, Thomas Sturm presented us the state-of-the-art of quantifier elimination for polynomial systems in real variables. The idea is the same here, with these differences: variables denote functions instead of numbers; the eliminated quantifiers are existential quantifiers only.

Because of the elimination process, the parameters do not appear "as is" anymore in the input-output equation. They actually occur in more complicated expressions, called *blocks of parameters*.

By parameter estimation methods (at least in principle), one can estimate the values of the blocks. But, knowing the values of the $\theta_i$, can we deduce the values of the model parameters — which is what we want? Over this example, yes. In general, it depends on the model. The *identifiability* study of a model is a theoretical study of the model aiming at answering this question.

As far as I know, the idea of this identifiability method goes back to [22]. Many developments were undertaken afterwards by a small team of applied mathematicians [12] involving a colleague from Le Havre [31], still very active on the topic [36].

# Integro-Differential Form of the Input-Output Equation

It can be computed by software. What is the point?

- More reliable parameter estimation
- Does not involve any derivative $\dot{u}(t)$ of the input (a piecewise constant function).

$$
\begin{aligned}
&- \theta_1 \int_a^t \int_a^{\tau_1} u(\tau_2)\, \mathrm{d}\tau_2\, \mathrm{d}\tau_1 \\
&+ \theta_2 \int_a^t \int_a^{\tau_1} \frac{y(\tau_2)}{y(\tau_2)+1}\, \mathrm{d}\tau_2\, \mathrm{d}\tau_1 \\
&+ \theta_3 \left( \int_a^t \frac{y(\tau)^2}{y(\tau)+1}\, \mathrm{d}\tau - \frac{y(a)^2}{y(a)+1}\,(t-a) \right) \\
&- \theta_4 \left( \int_a^t \frac{1}{y(\tau)+1}\, \mathrm{d}\tau - \frac{1}{y(a)+1}\,(t-a) \right) \\
&- \dot{y}(a)\,(t-a) \\
&= \int_a^t u(\tau)\, \mathrm{d}\tau - u(a)\,(t-a) - y(t) + y(a)
\end{aligned}
$$

## 2 Integro-Differential Equations

**Integro-Differential Form of the Input-Output Equation.** As stressed on the first slide, parameter estimation techniques are more reliable using integral equations than differential ones.

In general, the transformation process needs not succeed and may end up with an incompletely transformed formula, where the same unknown function may occur both in differentiated form and under some integral sign. Such formulae are said to be *integro-differential*.

Our colleague at Le Havre and her coauthors have become expert in performing this transform using their mathematical skills [24, 32].

Partly because of this need, a quite complicated computer algebra transformation algorithm was recently developed at Lille [4, 6, 7]. This algorithm actually computed the integral form on the slide of the former input-output equation.

Another advantage of this formulation, with respect to the former one, is that it does not involve any derivative of the input. Since, in many cases, the input — a piecewise constant function — is not differentiable, this is quite interesting.

# A Research Program for Computer Algebra

- Can we compute the integral form without ever differentiate?
- Any sound elimination theory for integro-differential algebra?
- What about integro-differential modeling?

*Vito Volterra, who coined the term "integro-differential equations", searched their applications in biology. The Volterra-Kostitzin equation models a population intoxicated by its own metabolic production. The kernel $K(t-\tau)$ is typical of an "historical" phenomenon.*

$$\dot{y}(t) = \varepsilon\, y(t) - k\, y(t)^2 - c\, y(t) \int_{t-T}^{t} K(t-\tau)\, y(\tau)\, \mathrm{d}\tau\,.$$

**A Research Program for Computer Algebra** By lack of time, I will not even mention the three first items on the slide but, if you think about it, many fascinating computer algebra research questions are open. For details, see [9].

One may however remark that the initial motivation for integro-differential equations comes from biology [27, 33]. Classical biological books such as [3] mention the Volterra models for population dynamics but do not mention at all the integro-differential ones. However, the interesting Volterra-Kostitzin equation [21, pages 66-67], which models a population in a closed environment, intoxicated by its own metabolic product, was considered in recent biology books [26, chapter 4].

# The Cortical Spreading Depression (CSD)

A slow depolarization wave affecting neurons and glial cells (3mm/min).

The CSD has different variants:

- harmless: the increase of neuronal metabolism is matched by an increase of blood flow (vasodilatation);
- pathological: the increase of blood flow does not match the needs;
- malignant: the coupling between neuronal metabolism and blood flow is inverse (vasoconstriction, ischaemia).

*Pathological or malignant, it induces neuronal death, observed in subarachnoid haemorraghe (SAH) patients.*

## 3 Neurobiology

**The Cortical Spreading Depression (CSD).** It is well described in a series of papers cossigned by Jens Dreier such as [35] and [14] (which analyzes the cse of 13 patients, striken by subarachnoid haemorraghe!). See also the recent survey [10], which actually concludes by the fact that CSD is still an enigma!

The CSD actually is a wave of depolarization of neurons and glial cells, which progresses slowly, at the spead of $3\text{mm}/\text{min}$.

It has different forms. In its harmless form, it is accompanied with an increase of the neuronal metabolism — aiming at restoring normal polarizations — thus with an increase of blood supply, by means of a vasodilatation.

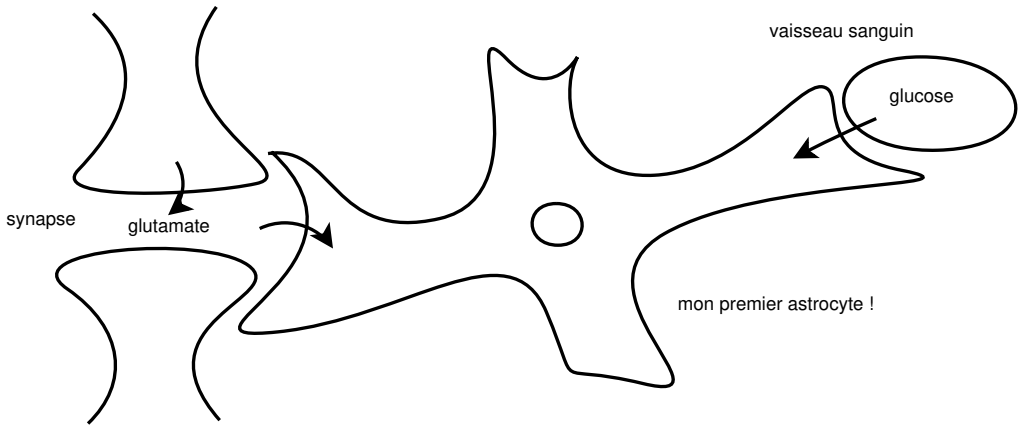
It starts becoming pathological when the increase of blood supply does not match the needs of the increase of metabolism.

There even exists a malignant form, where the coupling of the neuroglial metabolism and the vascular system is inverse: instead of a vasodilatation, one observes a vasoconstriction hence a decrease of the blood supply. The technical word for the lack of blood supply is *ischaemia*.

It is this malignant form, sometimes called *cortical spreading ischaemia*, which has attracted the attention of our colleagues from Rouen.

Pathological of malignant, the CSD may cause the death of affected neurons. This is a real issue since the CSD is developed by some patients striken by a breakage of anevrism: if the patient does not die, some of his neurons are immediately killed by the accident. For these ones, one cannot do anything. However, some of these patients develop a CSD afterwards and this CSD may kill another set of neurons. A long term idea would be to help identifying such patients arriving in hospitals, to help offering them some adapted therapeutics, in order to avoid the death of this second set of neurons.

# A Key Glial Cell: the Astrocyte




1. it transforms the glucose brought by the vascular system into lactate which van be processed by neurons ($\rightarrow$ ATP);
2. it removes glutamate from synapses hence might measure the neuronal metabolism and regulate blood flow.

Hypothesis: the pathological behaviour of astrocytes is at the core of the CSD outbreak.

**A Key Glial Cell: the Astrocyte.** It is a cell much studied by our colleagues from Rouen, who believe that its pathological behaviour may very well be at the core of the CSD outbreak: an idea not completely new [15].

Astrocytes are not even mentioned in [1] but their role is however very clearly presented in [23]. They are glial cells at the interface between the vascular system and the neurons. On the one hand, they have the important task of transforming the sugar brought by the blood into lactate, which is assimilated by neurons and converted into ATP — a major source of energy for the cells. Plain glucose cannot be directly processed by neurons. On the other hand, they are involved in the reuptake of glutamate, a neurotransmitter released in synapses, when action potentials get transmitted from one neuron to another one. Therefore, one may think that they have all the relevant information to measure the neuron activity and regulate the vascular system accordingly. The vasoconstricting capacity of astrocytes was actually established in [25].

# A Key Ion: Calcium

Many CSD-related phenomena are known to be related to abnormal increases of the cytosolic calcium $[Ca^{2+}]_c$ concentration.

- In the normal case, $[Ca^{2+}]_c \simeq 10^{-4} [Ca^{2+}]_e$ (extracellular) ;
- This homeostasy is maintained by ATP-dependent pumps.

One argument: in ischemic situation, the lack of ATP reduces the efficiency of the pumps, which cannot sufficiently regulate $[Ca^{2+}]_c$.

There are other arguments . . .

**A Key Ion: Calcium** It has long been known [29] that many pathological CSD-related processes are related to abnormal increases of cytosolic concentrations of calcium.

There are many arguments.

One of them is easy to understand: in normal conditions, the calcium cytosolic concentration is somewhat $10000$ times smaller than the extracellular one and, the main mechanisms which maintain this homeostasy are ATP-dependent pumps. In ischemic situation, blood supply does not bring enough sugar anymore, astrocytes do not produce enough lactate and ATP-dependent pumps lack of ATP.

# A Suspect Peptide: the Urotensin II (UII)

Hypothesis: UII has an aggravating role on the pathological increase of $[Ca^{2+}]_c$.

- UII is a potent vasoconstrictor hence a cause of ischaemia.
- Ischaemia increases $[Ca^{2+}]_c$ by influx of $[Ca^{2+}]_e$ (extracellular).
- However, UII activates also a metabolic pathway (Phospholipase C/IP3) which increases $[Ca^{2+}]_c$ by releasing $Ca^{2+}$ kept in intracellular stores (Rouen).

Warning: these experiments were performed on different biological models and in different experimental conditions.

**A Suspect Peptide: the Urotensin II (UII)** The urotensin II is a potent vasoconstrictor [2]. Our colleagues from Rouen would actually like to establish its toxic role in the CSD outbreak.

An intriguing question arose which has motivated a modeling task. Since it is a vasoconstrictor, the presence of UII in the extracellular space is a cause of ischaemia hence a cause of increase of $[Ca^{2+}]_c$. On the one hand, it was established that this ischaemia-induced increase is essentially due to an influx of extracellular $Ca^{2+}$ [15]. On the other hand, the colleagues from Rouen proved that UII also activates a metabolic pathway (phospholipase C/IP3) which increases $[Ca^{2+}]_c$ by releasing calcium kept in intracellular stores, such as the endoplasmic reticulum [19]. We may thus make the hypothesis that UII has an aggravating role in the increase of $[Ca^{2+}]_c$.

One must however take care: the above results were obtained from different biological models and in different experimental conditions. Consistent experimental data must still be gathered.

# Our Modeling Objective is Guided by a Biological Question

A modeling question: designing a nonlinear differential model of the action of UII over $[Ca^{2+}]_c$ in astrocytes which clarifies the relationships between the dynamics. A model with "mechanistic insight"? A submodel of the CSD outbreak.

- The modeling process suggests neurophysiological experiments (with/without ischemic conditions, with/without UII).
- The question-related parameters are the only ones which need be identifiable.
- If any "historical phenomenon", we get integro-differential variants of models.
- The theoretical integro-differential algebra questions are guided by an application and hand-processed examples. This is very important because of close indecidable problems.

**Our Modeling Objective is Guided by a Biological Question.** One thus sees a first modeling question which should lead to a submodel of some complete model: designing a nonlinear differential model of the action of UII over $[Ca^{2+}]_c$ in astrocytes which clarifies the relationships between the dynamics.

This modeling task has already suggested neurophysiological experiments: measuring the intracellular calcium dynamics with/without ischemic conditions, in the presence/absence of UII.

The model we are looking for will involve parameters related to the question it comes from and some other parameters. Observe that the question-related parameters — and only these ones — need be identifiable.

During the modeling task, some "historical" phenomena (the qualifier was coined by Volterra [34, page 300]) may be observed, leading to integro-differential variants of the models.

Last observe that many algorithmic problems in integro-differential algebra might be undecidable. It is already the case in differential algebra. See [11, 16] and the recent [30]. However, *ad hoc* derivation-free computations of input-output equations could be achieved on small examples. This stresses the importance to undertake these theoretical studies while being guided by a clear application, to avoid not so relevant theoretical pitfalls.

# A Mechanistic Model: Hodgkin-Huxley

The model is *mechanistic* for it claims that very few biological hypotheses are sufficient to explain the "action potential curve":

1. the notion of membrane capacity is well-defined,
2. the potassium current reverts when the membrane potential reaches the potassium Nernst equilibrium (the same for the sodium),
3. each potassium channel is made of four units that must be open to let the ion pass — similar statement for the sodium — both known to be wrong, today.

The differential model makes the claim precise.

$$C_{\mathrm{M}}\,\dot{V}(t) = -\overline{g}_{\mathrm{K}}\,n^4\,(V - E_{\mathrm{K}}) - \overline{g}_{\mathrm{Na}}\,m^3\,h\,(V - E_{\mathrm{Na}}) - \overline{g}_{\mathrm{L}}\,(V - E_{\mathrm{L}}) + I_{\mathrm{app}}\,,$$

The term $n^4(t)$ provides the number of open potassium channels. The parameters it depends on have no biological significance and were obtained by curve fitting.

**A Mechanistic Model: Hodgkin-Huxley.** I have written this concluding slide (not shown during the talk) while thinking to a section of Bertil Hille's book [17, Ch. 2, pages 54-56, *Do models have mechanistic implications?*], which addresses the question of the interest of the famous Hodgkin-Huxley model. The book does not take any firm position, by the way.

Hodgkin and Huxley obtained their Nobel price in 1953, because of their series of articles on the mechanisms underlying the action potential and, in particular, for their nonlinear differential model [18]. Their model is "mechanistic" in the sense of [28] for it claims that very few biological hypotheses are sufficient to explain the famous "action potential curve". Among these hypotheses:

1. the notion of membrane capacity is well-defined,
2. the potassium current reverts when the membrane potential reaches the potassium Nernst equilibrium (the same for the sodium),
3. each potassium channel is made of four units that must be open to let the ion pass — there exists a similar statement for the sodium — both claims known to be wrong, today.

The differential equation supports the claim by reproducing many observed behaviours of the action potential curve (the English text alone is not precise enough for that).

It is interesting to remark that the Hodgkin-Huxley model involves two types of parameters: parameters and variables which have a biological meaning and are related to the question which motivated the model; and other parameters and variables which are actually given numerically in [20, chapter 5, page 224]. These values were obtained by parameter estimation. The question of their identifiability was not addressed.

All proportions being kept, we are looking for models in the same spirit.

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