Feedback Control with Delay in Biological Problems: a new approach.

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We present a suitable algorithm, based on special Lie series, for the representation of the solution of an initial value problem, which has a delay term and refers itself to the behavior, for example, of a biological system controlled by a feedback signal. Classical representation of protein synthesis can furnish a case-study for this approach. We foresee non linear oscillations in concentrations of the involved substances in similar models . We also present, as a further example in which oscillations are foreseen, a simple model of the ovarian cycle in mammalian. This procedure, based on Lie series, is general in principle and could be useful in many different fields of applied research.

Keywords: Feedback control, delay, Lie Series - Dedicated to the memory of Prof. Pietro Boni.

I. INTRODUCTION

Sometimes, the investigation of biomedical problems needs peculiar mathematical approaches, with suitable algorithms, in order to give an answer to systems with complex patterns. In particular, those ones in which the control is provided by feedback signals to the system and/or nonlinear behavior is involved. Such problems are often initial-value problems assigned to a nonlinear differential system whose integration can be performed by numerical methods or, e.g. by the classical method of Lie series [1-3]. When a delay is present, one needs a further improvement of the general analytical method, because nonlinearity requires Lie series of a more general type in the representation of the components of the solution [4-13].

So, let us consider the classical mathematical approach, in protein synthesis control formulated in Goodwin's works, e.g. in [14] where a single negative feedback signal is involved. In these last years, starting from the Goodwin's, a lot of biological models have been proposed and discussed, involving more signals, of positive and negative type, acting in coupled circuits. We refer to this important historical work, because it is very well known by scientists and applied mathematicians, and fits well the problem furnishing the most simple example of a general tool for solving delay problems: the aim of this paper. Furthermore it is a simple model.

But many other examples are possible which lead to similar representative differential equations describing the behavior of a system, even more simple than the above biological system. In fact, more in general, we may think of a biological phenomenon as resulting by a chain of events in which a lower locus answers, by means of a feedback signal, to a chemical stimulus (a hormone). This arrives in situ with a time delay travelling from a higher locus, or alternatively we can even think that the hormone's target is a developing cellular structure which becomes capable to decode the stimulus after a fixed time T, becoming able to answer to the feedback signal only with a time delay.

Then, if an initial-value problem, assigned to a differential system like that we are going to recall, describing e.g. the behavior of three substances (e.g. messenger, enzyme, metabolite), it will get a unique **periodic** solution provided that the equations for any meaning of symbols preserve structure we describe in what follows.

That is all the equations are (partially) linear, the first one w.r.t. Y, the substance produced by the locus receiving the feedback signal; the second one w.r.t. Z, the equation of balance of the intermediate substance, which in the Goodwin's model contains the delay term, and the last one w.r.t. M, the substance responsible of the feedback signal.

This situation, in a more complex context, emerges also in the equations describing mammalian female cycle. So we are going to briefly discuss the model pertaining to it and describe the foreseen **oscillatory** behavior.

The validity of the method we are going to assess is not related to the periodicity properties of the solution, which could be absent in different type of equations but, rather, concerns the strategy to be adopted in the search of an explicit solution to a problem with delay. This approach, therefore, provide a suitable algorithm capable to solve similar initial-value problems with delay, representing the feedback signal controlled behavior of phenomena (not only of biological nature) that we can meet in several fields of Science and Engineering.

Our starting point is:

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$$\begin{aligned}\frac{dY}{dt} &= \frac{\gamma}{\alpha+\beta M} - kY \qquad (1)\\ \frac{dZ}{dt} &= \lambda Y_{t-T} - \mu Z\\ \frac{dM}{dt} &= \rho Z - \sigma M\end{aligned}$$

where e.g.:
the *Greek letters* are constants,
Y is the nuclear concentration of messenger,
Z is the enzyme cytoplasmic concentration,
M is e.g. the metabolite concentration, which as the final product produces the feedback signal on the genetic locus, expressed by the first term in the first equation,
Y_{t-T} is the delay term due e.g. to time of molecules transfer from the nucleus to the ribosome locus.
In each equation the negative terms express the loss rate of molecules assumed to be proportional to their concentrations.
Then:

$$Y_{t-T} = Y(t-T)$$

means e.g. that the synthesis rate of the enzyme is depending on messenger concentration in the nucleus, T units of time in the past. Computer simulation of (1) shows a periodic solution [14].

How this paper is organized?

In the next paragraph we answer the question: under which conditions does the delay presence ensure the possibility of oscillations?

Then, as principal aim, we utilize the improved algorithm of Lie series in order to solve the problem, writing explicitly the solution, observing that a finite differential system with delay is equivalent to a system without delay but comprehending an infinite sequence of differential equations. That observation is peculiar to the method.

Finally we discuss a more complex control circuit in which two feedback signals with opposite actions are involved, describing the ovarian cycle, in order to stress that nonlinear oscillations could be foreseen when the representative equations are partially linear as above mentioned.

Elsewhere we provide more detailed proofs concerning the algorithm of integration [4-13]. Here we want just to emphasize the algorithm and its intrinsic interest for expert people in delay equations.

II. PERIODIC SOLUTION

Theorem 1 *The solution to problem (1) is periodic with period T.*

Proof. In fact, how it is well known, since the second equation is linear, if a periodic solution

$$Z = Z(t-T)$$

exists, it implies analogue solutions in other equations which are linear in M and Y respectively:

$$\begin{aligned} M &= M(t-T),\\ Y &= Y(t-T).\end{aligned}$$

In order to recover this statement, let us consider the following linear problem in which y is a delayed function, which we suppose as assigned:

$$\begin{aligned}\frac{dz}{dt} &= -\mu z + \lambda y(t-\tau), t \geq 0,\\ \frac{dz}{dt} &= -\mu z, t \leq 0, \tau = delay,\\ z(0) &= z(\tau); \qquad (2)\\ y(t-\tau) &= y(t) \qquad if\ t \in [0,\tau].\end{aligned}$$

We are coming to prove that the condition (2), i.e. to have the same value at the end points $0, \tau$, ensures the periodicity of the solution with period τ.

Easily we can write the solution as:

$$z(t) = e^{-\mu t} z(0) + \lambda e^{-\mu t}\int_0^t e^{\mu s} y(s-\tau)ds.$$

Therefore, if $t \in [0,\tau]$:

$$z(t+\tau) = e^{-\mu t} e^{-\mu\tau} z(0) +$$

$$e^{-(t+\tau)\mu}\int_0^{t+\tau} e^{\mu s} y(s-\tau)ds \Longrightarrow z(t+\tau) =$$

$$e^{-\mu t}\left(\begin{array}{c} e^{-\mu\tau}z(0)+ \\ e^{-\tau\mu}\int_0^{\tau} e^{\mu s} y(s-\tau)ds\end{array}\right) +$$

$$+e^{-(t+\tau)\mu}\int_\tau^{t+\tau} e^{\mu s} y(s-\tau)ds \Longrightarrow$$

$$z(t+\tau) = e^{-\mu t} z(\tau) +$$

$$e^{-t\mu}\int_\tau^{t+\tau} e^{\mu(s-\tau)} y(s-\tau)ds \Longrightarrow$$

$$if \quad v = s-\tau,$$

$$z(t+\tau) = e^{-\mu t} z(0) + e^{-t\mu}\int_0^t e^{\mu v} y(v)dv,$$

$$then:$$

$$z(t+\tau) = e^{-\mu t} z(0) + e^{-t\mu}\int_0^t e^{\mu v} y(v-\tau)dz$$

$$= z(t).$$

Q.E.D. ■

III. LIE SERIES AS A SUITABLE ALGORITHM

Theorem 2 *Problem (1) is equivalent to an initial-value problem assigned to a non finite sequence of differential equations.*

Proof. Let us introduce the translation operator:

$$\begin{aligned} Y_{t-T} &= Y(t-T) = e^{-TD_t} Y(t) \\ D_t &= \frac{d}{dt} \\ e^{-TD_t} &= \sum_{n=0}^{+\infty} (-1)^n \frac{T^n}{n!} D_t \end{aligned}$$

and rewrite the system (1) in the following symbolic form:

$$\begin{aligned} \frac{dY}{dt} &= \Theta_1(M, Y) \\ \frac{dZ}{dt} &= \Theta_Z(e^{-TD_t} Y, Z) \\ \frac{dM}{dt} &= \Theta_M(Z, M) \\ Y(t_0) &= Y_0; Z(t_0) = Z_0; M_0(t_0) = M_0 \end{aligned}$$

where the last row represents initial values.

If we introduce the sequence of derivatives:

$$\frac{d^n}{dt^n} Y = Y_{n+1}; n \in \{0, 1, 2, ...\}$$

we can write, if $Y_1 \equiv Y$, the above initial-value problem as:

$$\begin{aligned} \frac{dY_1}{dt} &= \Theta_1(M, Y_1) = Y_2 \\ \frac{dY_2}{dt} &= \frac{d^2 Y_1}{dt^2} = \Theta_2 = Y_3 \\ &\ldots \\ \frac{dY_k}{dt} &= \Theta_k = Y_{k+1} \\ &\ldots \\ \frac{dZ}{dt} &= \Theta_Z\left(Y_1, Y_2, ..., Y_k, ...Z\right) \\ \frac{dM}{dt} &= \Theta_M(Z, M) \\ Y_1\left(t_0\right) &= Y_0; ...; Y_k\left(t_0\right) = \left[\frac{d^{k-1}}{dt^{k-1}} \Theta_1\right]_{t=t_0}; ... \\ Z(t_0) &= Z_0; M(t_0) = M_0 \end{aligned} \tag{3}$$

Where it is not difficult to prove that every derivative $\left[\frac{d^{k-1}}{dt^{k-1}} \Theta_1\right]_{t=t_0}$ depends on initial values:

$$Y(t_0) = Y_0; Z\left(t_0\right) = Z_0; M\left(t_0\right) = M_0. \tag{4}$$

E.G.:

$$\begin{aligned} Y_2(t_0) &= \left[\Theta_1\right]_{t=t_0} \\ Y_3(t_0) &= \left[\frac{\partial \Theta_1}{\partial M} \frac{dM}{dt} + \frac{\partial \Theta_1}{\partial Y} \frac{dY}{dt}\right]_{t=t_0} \\ &\ldots \end{aligned}$$

Q.E.D. ■

To solve the above initial value problem (3), which concerns a non finite number of differential first order equations, we extended [4-13] the Gröbner's method, which utilizes Lie series and concerns similar but finite problems.

Let us consider the following differential operator (generalized Lie operator):

$$D = \Theta_Z \frac{\partial}{\partial z} + \Theta_M \frac{\partial}{\partial m} + \Theta_1 \frac{\partial}{\partial y_1} + ... + \Theta_k \frac{\partial}{\partial y_k} + ...$$

where all Θ are the same functions with the same name in the above system (3), but now depending on parametric variables like those of sequence:

$$y_1, ..., y_k, ..., \quad z, \ m,$$

which replace the analogue ones indicated with capital letters.

Then let us introduce the exponential Lie operator:

$$e^{(t-t_0)D} = \sum_{v=0}^{+\infty} \frac{(t-t_0)^v}{v!} D^v$$

which is a generalization of the Gröbner's [1-3], and has the same very important properties:

i) linearity;

ii) conservation of products;

iii) "exchange" property for an analytical function. Namely the image by $e^{(t-t_0)D}$ of an analytical function is the value which the function assumes on the transformed variables.

Elsewhere, e.g. [4-13], we proved that a unique solution exists if the right-hand members of (3) are analytical functions in their arguments. Then, we can write the solution to the assigned initial-value problem in the following way:

$$\begin{aligned} Y &= \left(e^{(t-t_0)D} y_1\right)_{y_1 = Y_0; ... y_k = \left[\frac{d^{k-1}}{dt^{k-1}} \Theta_1\right]_{t-t_0}; ... z = Z_0; m = M_0}, \\ Z &= \left(e^{(t-t_0)D} z\right)_{y_1 = Y_0; ... y_k = \left[\frac{d^{k-1}}{dt^{k-1}} \Theta_1\right]_{t-t_0}; ... z = Z_0; m = M_0}, \\ M &= \left(e^{(t-t_0)D} m\right)_{y_1 = Y_0; ... y_k = \left[\frac{d^{k-1}}{dt^{k-1}} \Theta_1\right]_{t-t_0}; ... z = Z_0; m = M_0}, \end{aligned}$$

In fact it is not difficult to verify, by means of property iii) of the exponential Lie operator, that the above special functions are the components of the effective solution of (3) of (1).

This method is equivalent to solve firstly the problem with parametric initial conditions and then to particularize them with initial conditions of the assigned problem. But it needs to be remarked that we can operate the substitutions of parameters with the initial values only at the end, after the action of the exponential Lie operator.

IV. THE OVARIAN CYCLE: A SHORT REMARK

As already anticipated, finally we consider a more complex control circuit in which two feedback signals with opposite action are involved describing the ovarian cycle. This is the case of the presence of nonlinear oscillations when the representative equations are partially linear, as above mentioned.

During the post ovulatory phase of the reproductive cycle, the ovary in females answers to hormonal stimuli with a behavior that can be modelled with the following initial-value problem:

$$\begin{aligned}
\frac{dR}{dt} &= \gamma + \frac{\alpha E}{h' + h'kP + E} - \beta R; \\
\frac{dL}{dt} &= \gamma_o + \alpha_o R - \beta_o L; \\
\frac{dP}{dt} &= \gamma_1 + \alpha_1 L_{t-\tau} - \beta_1 P; \\
\frac{dE}{dt} &= \gamma_2 + \alpha_2 L_{t-\tau} - \beta_2 E; \\
R(t_o) &= R_o; L(t_o) = L_o; \\
P(t_o) &= P_o = 0; E(t_o) = E_o = 0.
\end{aligned} \tag{4}$$

where:

$$\begin{aligned}
& R \text{ is (blood concentration of) the} \\
& \text{ hypothalamic realese hormone;} \\
& L \text{ is the pituitary luteinizing hormone;} \\
P &= \sigma_1 \left(\Pi - \Pi_{pool}\right) \text{ is the negative feed back} \\
& \text{ signal from the ovary to hypothalamus} \\
& \text{due to progesterone} \\
& \Pi, \text{whose storage capacity is} \\
& \text{the constant } \Pi_{pool}; \\
E &= \sigma_2 \left(\varepsilon - \varepsilon_{pool}\right) \text{is the positive feed back} \\
& \text{signal upon hypothalamus} \\
& \text{due to estrogen } \varepsilon, \text{whose storage capacity} \\
& \text{in ovary is the constant } \varepsilon_{pool}; \\
\sigma_1, \sigma_2 &= \text{constants;} \Pi(t_o) = \Pi_{pool}; \varepsilon(t_o) = \varepsilon_{pool}; \\
& \text{all } \gamma \text{ symbol indicates the basal} \\
& \text{production velocity in stimulation absence;} \\
& L_{t-\tau} \text{ is null with its derivatives} \\
& \text{at incipient process.}
\end{aligned}$$

To write the first equation of the above system we have supposed, as an acceptable hypothesis, the competition between the feedback signals on the same hypothalamic receptor :

$$\begin{aligned}
[S]_o &= [S] + [SE] + [SP]; \\
[S]_o &= S(t_o) \text{ initial hypothalamic concentration of} \\
& \text{receptor;} \\
[S] &= \text{concentration of free receptor;} \\
[SE] &= \text{concentration of receptor linked to} \\
& \textbf{positive} \text{ feedback signal;} \\
[SP] &= \text{concentration of receptor linked to} \\
& \textbf{negative} \text{ feedback signal.}
\end{aligned}$$

At the chemical equilibrium:

$$\begin{aligned}
[SE] &= h[S][E]; [SP] = k[S][P] \\
h, k &= \text{kinetic constants;}
\end{aligned}$$

therefore:

$$[SE] = \frac{[S]_o[E]}{h' + kh'[P] + [E]}; \qquad h' = \frac{1}{h};$$

then we can suppose to be $[S]$ proportional to the production rate of hypotalamic hormone proportional to $[SE]$, whose degradation rate is proportional to the actual hormone concentration; so we write, suppressed all square brackets, the first balance equation.

To write the other equations we can assume the production rate of L proportional to R, the production rate of P and E proportional to the concentration of L at the instant $t - \tau$, τ representing the delay of the ovary response as the gland becomes "mature" for the hormone stimulation.

We can observe that the intrinsic delay of the ovary in outset of its answer to luteinizing hormone and the linearity of the two last equations of the above differential system, implies a periodic solution with period τ to the assigned initial-value problem. In fact, the differential equation of balance of estrogen and progesterone have the same periodic term

$$L_{t-\tau} = L(t - \tau)$$

and it is sufficient for the existence of a periodic solution with the same period to each linear equation, then to the proposed differential system, because also the two first equations are linear in R and L respectively.

Naturally the solution to the above initial value problem may be written with the same algorithm of Lie series that we have described above.

V. CONCLUSIONS

We presented a suitable algorithm, based on special Lie series, for the representation of the solution of an initial value problem, which has a delay term and refers itself to the behavior, for example, of a biological system controlled by a feedback signal. Classical representation of protein synthesis can provide a case-study for this approach. We foresee nonlinear oscillations in concentrations of the involved substances in similar models . We also presented, as a further example in which oscillations are foreseen, a simple model of the ovarian cycle in mammalian. This procedure, based on Lie series, is general in principle and could be useful in many different fields of applied research.

More specifically, from a mathematical point of view, an initial-value problem with at least one delay term in a finite number of equations is equivalent to an infinite sequence of equations. In the examples presented the classical Gröbner's approach is not any more sufficient. More general Lie series are necessary in order the representation of the components of solution can be found. In this case the Gröbner-Lie operator is an infinite sum, formally defined by a series of first-order differential summands. Here we presented our improved solution dealing with a classical problem in biomathematics. A lot of similar cases arise in physiology and in pathology, as well as in economics or engineering or more in general in physics. Our approach wants to be just an initial answer.

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