Glycaemic stability of the diabetic patient and therapeutic adjustments

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***Abstract*— In previous papers, we provided a modeling of the behavior "insulin delivery/glycaemia" of the diabetic patient under continuous insulin infusion, continuous glucose monitoring and we provided a method of regulation of his glycaemia.**
This behavioral model is bilinear, predicting the behavior on an interval of 15 minutes, with an average error of 15%. And consequently, the model is adjusted for every 15 minutes.
The aim of this paper is to study the Bounded-Input-Bounded-Output (BIBO) stability of the bilinear model in order to point out that the patient is entering in a period of stable/unstable equilibrium. In case of stable equilibrium, the prediction will be valid for a longer time interval, when in case of unstable equilibrium, it will leads one to reduce the time intervals and to pilot closely the variations of insulin delivery.
The BIBO stability is studied by computing the generating series G of the model. This series, generalization of the transfer fuction, presents an usefull tool for analyzing the stability of bilinear systems. It is a rational power series in noncommutative variables and by evaluating it, a formal expression of the output in form of iterated integrals is provided. Three cases arise: firstly, the output can be explicitly computed; secondly, the output can be bounded/unbounded if the input is bounded; thirdly, no conclusion seems available about the BIBO stability by using G. In this case, we propose a stabilizing constant input η by studying the univariate series G_η.

I. INTRODUCTION

There exist many medical possibilities to administer insulin: sub-cutaneous, intravenous and intraperitoneal. The sub-cutaneous route is most secure and easy to implement, but it lacks reliability. The intravenous route is the most rapidly responding method, but it may cause vascular complications. The intraperitoneal route seems to the most physiological one. Moreover, it has almost to delay in the insulin action. Even though there is no consensus on the best way to deliver insulin, there seems to be a certain tendency to prefer the intraperitoneal route.

In order to carry out a glycaemic regulation by an intraperitonal infusion of insulin, it is necessary to be able to predict the glycaemia as a function of the insulin infusion rate, for a given patient and a given insulin type. There exist many open-loop, partially closed-loop and closed-loop techniques. The very first closed-loop regulation method was developed by A. Albisser et al. back in 1974 [1]. Among other methods, we can mention [17].

Unfortunately, in spite of many positive aspects of these methods, none of them was unanimously accepted by the medical community. This is partly due to the lack of the precision of the available data and, especially, to insufficient frequency of glycaemic sampling and the difficulty to vary rapidly the insulin infusion rates.

Recent technical progress made it possible to overcome these difficulties. In 2000 appeared the first holter glycaemic device: the CGMS (Continuous Glucose Monitoring System) of Medtronic Minimed, which allows one to measure the glycaemia every 3 minutes. Many other similar devices followed suit. This engineering breakthrough gave a new momentum to the research in the field of diabetes regulation. A first regulation system based on the CGMS was developed in 2001 by E. Renard of CHU of Montpellier in collaboration with Medtronic Minimed [15]. But in spite of the encouraging results of this work, the model used during the regulation does not seem to be precise enough to be clinically used on a wider scale.

Then we proposed a bilinear modeling giving a good approximation of the behavior "insulin delivery/glycaemia" on an interval of 15 minutes, in standard conditions [12].

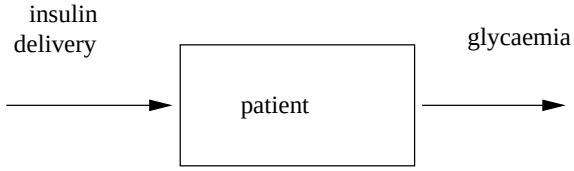

Fig. 1. Model

Once the model (Fig.1) is known, the regulation consists in inverting the input/output behavior of the system [7], [8]. In other words, one has to calculate the input (command) in terms of the output function one wishes to obtain (Fig.2).

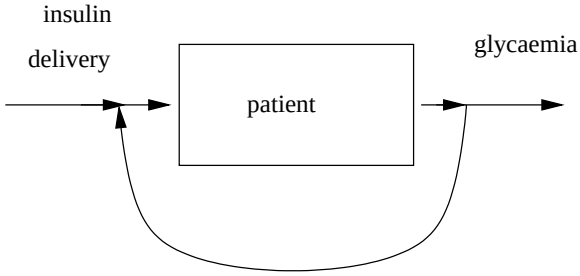

Fig. 2. Regulation

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This regulation is said to be partially closed-loop because the glycaemic values are only used every 15 minutes in order to compute the insulin delivery. More precisely, on constant intervals of time $[t_i, t_{i+1}]_i$, we compute some model M_i and some function insulin delivery $u_i(t)$ allowing us to follow an ideal trajectory $y_i(t)$ for the glycaemia. On every time interval, the trajectory is recalculed because of the variation between the ideal trajectory $y_i(t)$ and the true trajectory (Fig.3).

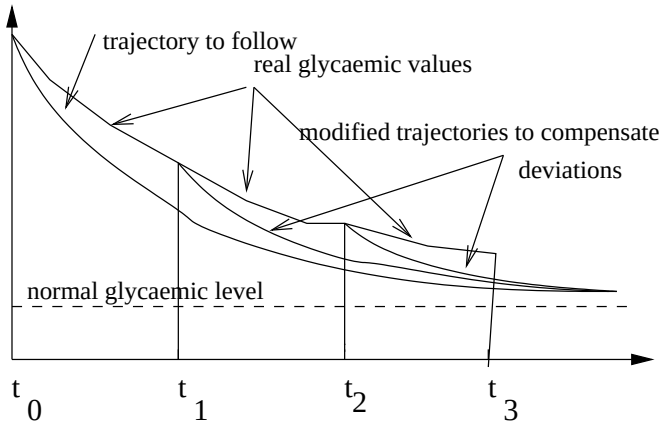


Fig. 3. Trajectory

The crucial point consists in determining the size of the time intervals, that means the frequency of the changes of the insulin delivery. The study of the stability leads us to reduce the size of the interval when the system is unstable.

II. Modeling "insulin/glycaemia" and regulation of the glycaemia

There are two general categories of techniques used to achieve this goal: phenomenological modeling and behavioral modeling.

Phenomenological modeling requires a prior knowledge of the equations governing the evolution of the considered process. Numerous phenomenological models of the glycaemic behavior of diabetics were still developed, for example see [2].

In the behavioral modeling, one does not need any prior knowledge of the phenomenon. The system is regarded as a black box [19]. The goal is to construct a model that approximates the unknown system with a desired precision [5]. The parameters involved in the obtained system of equations have no practical significance, but their number usually depends on the required precision.

A commonly-used class of models is formed by linear dynamical systems. Such models were extensively considered by the control theory specialists. Linear-model-based regulation is rather simple to implement and it gives quite satisfactory results in many different cases. However, it did not seem to be sufficient for regulating the glycaemia of diabetics.

Another class of models consists of bilinear dynamical systems. A bilinear system is quite similar to a linear one: it is simply additionally linear as a function of the input. One has thus more leeway to approximate the real system with a better precision. In our method, we choose to model the dynamical systems by bilinear systems whose dimension is not fixed in advance.

Since a diabetic does not respond in the same way to equal doses of insulin at different times of the day, it is reasonable to suppose that she is described by different dynamical systems at different time instants. The goal of our modeling method is to construct a collection of models that describe the behavior of the glycaemia under certain conditions. These conditions can be either defined in advance (for example, during the inter-prandial period, during meals or during physical effort), or determined by a learning process. Each model is thus valid only for a certain period of time. In practice, we can show that our model is valid for at least fifteen minutes. Moreover, this duration is likely to increase with the increase of the precision of the glucose sensors.

Mathematically speaking, the problem is to identify locally (near a time instant t_0) up to a given order k, a dynamical system (Σ) considered as a black box, when only a sample of the input/output data is known. The considered dynamical systems involve one input and the drift. The input is the insulin infusion rate and the drift corresponds to the fact that the system undergoes some changes even in the absence of any input.

Our method involves the identification up to order k of the generating series G of the unknown system and the construction of a bilinear system (B_k) approximating the unknown system up to order k. The generating series of a nonlinear system can be seen as a generalization of the transfer function. It is used to represent the input/output behavior of the system.

The main advantage of this method is the possibility to provide, in terms of the chosen order k, a system (B_k) approximating the unknown system. (B_k) is chosen so that its output and the output of the unknown system coincide up to order k.

The problem of identification of dynamical systems in a neighborhood of t_0 is stated in the following way: to explicitly determine the generating series of the unknown system, up to a given order k, given the Taylor series of the input and corresponding output functions.

The main tool used during the identification is the generating series of the system. A generating series can be considered as an infinite (noncommutative) polynomial that codes the relationship between the inputs and the output.

The identification involves the following three steps. During the first step, one obtains a system of linear equations that express the relationship between the derivatives of the input and the output. The unknown parameters are certain linear combinations of the coefficients of the generating series. On the next step, these linear combinations of the coefficients are identified from the available data, by choosing appropriate input/output sets. Finally, the coefficients themselves are identified by solving another system of linear equations.

This algorithm is programmed in MAPLE and presented in [13]. A polynomial generating series G_k is thus identified, and it is equal to the generating series G of the system (Σ) truncated at degree k.

Once a truncated generating series G_k is identified, it remains to construct a model therefrom. We construct a bilinear system, approximating the dynamical system (Σ), by prolonging G_k to a rational series R_k whose generating series is of minimal rank among all the series coinciding with G_k up to order k (see [10]). Rational series are generalizations of rational functions and the dynamical systems representing them are bilinear. A bilinear system corresponding to this rational series of minimal rank R_k is finally constructed. This system provides a local model of the black box.

A. The bilinear model

A bilinear system (B) with a single input $u_1(t)$ and a drift $u_0(t) \equiv 1$ is given by its state equations

$$(B)\left\{\begin{array}{lcl} x^{(1)}(t) & = & (M_0 + u_1(t)M_1)x(t) \\ y(t) & = & \lambda.x(t) \end{array}\right. \quad (1)$$

where $x(t) \in Q$, $R-$vector space, M_0, M_1, λ are $R-$linear. We consider the alphabet $Z = \{z_0, z_1\}$, where z_0 codes the drift and z_1 codes the input. The expansion of the generating series G built on the alphabet Z, by noting w a word $\in Z^*$, is the following:

$$G = \sum_{w \in Z^*} \langle G|w\rangle w$$

G is a rational series defined from (1) by:

$$G = \lambda.x(0) + \sum_{\nu \geq 0} \sum_{j_0,\cdots,j_\nu=0}^{1} \lambda.M_{j_0} \cdots M_{j_\nu} x(0) z_{j_0} \cdots z_{j_\nu} \quad (2)$$

Firstly, we compute the rational expression associated with (2), which is a digest of the expansion of G, by generalizing the Schutzenberger's method [16] for computing the rational expression describing a rational series. This rational series can be represented by a finite weighed automaton [11].
By "evaluating" the expression of G, we can obtain a formal expression of the output [6]

$$y(t) = \sum_{w \in Z^*} \langle G|w\rangle \int_0^t \delta(w) = \int_0^t \delta(G) = \varepsilon(G) \quad (3)$$

where the iterated integrals are recursively defined by:

$$\int_0^t \delta(w) = \left\{\begin{array}{ll} 1 & if \quad w = 1_Z \\ \int_0^t (\int_0^\tau \delta v) u_i(\tau) d\tau & if \quad w = v z_i \end{array}\right. \quad (4)$$

Secondly, we compute directly the iterated integral $\int_0^t \delta(G)$ where G is the rational expression that we computed previously.

B. The regulation method

Once the model is known, the regulation consists in inverting the input/output behavior of the system. In other words, one has to calculate the input (command) in terms of the output function one wishes to obtain. The regulation used in this case is called partially closed-loop, since the glycaemic values are used to recalculate the insulin infusion rates every fifteen minutes. These rates change continuously in a purely closed-loop scenario.
In a previous paper [9] we have shown that we are capable of finding the Taylor series expansion of the command from the Taylor series expansion of the desired output trajectory, using generating series techniques similar to those used during the identification and the modeling. The algorithm consists in sequential solving a system of polynomial equations. If the model of a diabetic were an exact one, this would be largely sufficient to regulate the glycaemia. But since our bilinear model is only an approximation of the actual one, the glycaemic behavior will eventually deviate from the chosen trajectory. As a consequence, from time to time the trajectory has to be recalculated in order to compensate for these deviations and the insulin infusion device has to be reprogrammed accordingly.
An important point is to determine the frequency of change of the insulin infusion rates. The first tests of our modeling method [12] showed that we can predict the glycaemia over 15-minute intervals with an error of about 10% or 15%. Therefore, we need to provide a new data to the pump approximately every fifteen minutes. As we have already remarked above, this duration is likely to increase with the increase of the precision of the glucose sensors.

III. THE BIBO STABILITY

A dynamical system is Bounded-Input-Bounded-Output (BIBO) stable if its output $y(t)$ is defined and bounded for every bounded input $u(t)$.
The output of a bilinear dynamical system can be computed in evaluating its generating series. More precisely, the evaluation of the series consists in integrating every term of this series and in summing.

We use the theorem of Hoang Minh [14] :
Theorem 1:
$\forall k$, let us suppose that G_k is exchangeable and let us denote $\varepsilon(G_k)$ by $g_k(\xi(t))$

$$g_k(\xi(t)) = g_k(t, \xi_1(t), \cdots, \xi_m(t))$$

where $\xi_j(t)$ is the primitive of the input $u_j(t)$ cancelling for $t = 0$. Then, $\forall k$, the series

$$S_k = G_0 z_{i_1} G_1 \cdots z_{i_k} G_k$$

where $z_{i_1}, \cdots, z_{i_k} \in Z$, has the following evaluation:

$$\varepsilon(S_k) = y(t) =$$
$$\int_0^t \int_0^{\tau_k} \cdots \int_0^{\tau_2} g_0(\xi(\tau_1)) g_1(\xi(\tau_2) - \xi(\tau_1)) \cdots$$
$$g_k(\xi(t) - \xi(\tau_k)) d\xi_{z_{i_1}}(\tau_1) \cdots d\xi_{z_{i_k}}(\tau_k)$$

Three cases occur: In some cases, this process is easy and $y(t)$ can be explicitly computed. In other cases, if we assume that $u(t)$ is bounded by 2 values Min, Max, then we can know if so is $y(t)$, without computing explicitly $y(t)$. Lastly, in some difficult cases, we only try to find some stabilizant constant inputs $u(t) = \eta$ such that the output remains bounded, if it is possible. We prove that the output of the bilinear system for the input $u(t) = \eta$ consists in evaluating some univariate series G_η. This series being rational, can be written as a quotient of 2 polynomials. We can then use 2 propositions [3], [4] dealing with the poles of G_η in order to decide that a stability exists for $u(t) = \eta$

Proposition 1
A necessary condition for the BIBO stability of (B), is that, for every $\eta \in R$, the real part of the poles of G_η is ≤ 0 and the imaginary poles of G_η are single.

Proposition 2
If there exists η such that every pole of G_η has a negative real part and if every imaginary pole is single, then $u(t) = \eta$ is a stabilizing input

1) Example 1: The state equations of the system (B_2) are the following, for an insulin delivery $u(t)$ and a glycaemia $y(t)$

$$\left\{ \begin{array}{rcl} x^{(1)}(t) & = & (\begin{pmatrix} 0 & 0 \\ a & b \end{pmatrix} + u(t) \begin{pmatrix} 0 & 0 \\ 1 & 0 \end{pmatrix})x(t) \\ y(t) & = & (1.5 \;\; 1) \;\; x(t) \end{array} \right.$$

The generating series is :

$$G_2 = (z_1 + az_0)(bz_0)^* + 1.5$$

Its automaton is presented in the Fig.4

We split this series in 2 parts
$G_{21} = z_1(bz_0)^*, \quad G_{22} = az_0(bz_0)^*$
with $G_2 = G_{21} + G_{22} + 1.5$.
We can compute the evaluation of G_{21} et G_{22} and we obtain an explicit expression of the output $y(t)$.
$\varepsilon(G_{21}) = e^{bt} \int_0^t e^{-b\tau_1} d\xi_1(\tau_1)$ and
$\varepsilon(G_{22}) = ae^{bt} \int_0^t e^{-b\tau_1} d\tau_1$
For $u(t) = \eta$ then $\xi_1(\tau_1) = \eta\tau_1$, we get :
$y_{2,\eta}(t) = \frac{\eta+a}{b}(e^{bt} - 1) + x(0)$
This system is not BIBO for $b > 0$ and is BIBO for $b < 0$ (if $M_1 \leq u(t) \leq M_2$ then $y(t)$ is bounded)
For instance, for $a > 0, \quad b < 0, \quad 0 \leq u(t) \leq M$, then $y(t) \leq x(0) + \frac{M+a}{-b}$

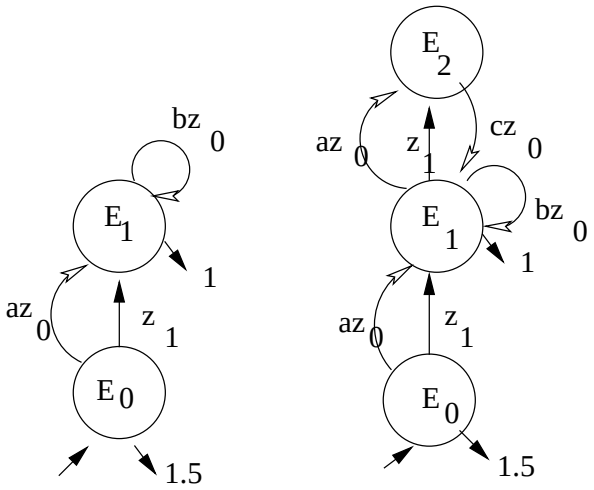
2) Example 2: The state equations of the bilinear system (B_3) are

$$\left\{ \begin{array}{rcl} x^{(1)}(t) & = & (\begin{pmatrix} 0 & 0 & 0 \\ a & b & c \\ 0 & a & 0 \end{pmatrix} + u(t) \begin{pmatrix} 0 & 0 & 0 \\ 1 & 0 & 0 \\ 0 & 1 & 0 \end{pmatrix})x(t) \\ y(t) & = & (1.5 \;\; 1 \;\; 0) \;\; x(t) \end{array} \right.$$

The generating series is

$$G_3 = (z_1 + az_0)(bz_0 + (z_1 + az_0)cz_0)^* + 1.5$$

Its automaton is presented in the Fig.4.



example 1 example 2

Fig. 4. Automata of ex 1 , ex2

We compute $G_{3,\eta}$ by substituting ηz_0 to z_1 in G_3: $G_{3,\eta} = 1.5 + \frac{(a+\eta)z_0}{1-bz_0-(a+\eta)cz_0^2}$.
If $\eta = -a$ then $y_{3,\eta}(t) = x(0)$ else we decompose $G_{3,\eta}$ in partial fractions for studying the constant stabilizing inputs $u(t) = \eta$ depending on the parameters a, b, c.

IV. CONCLUSIONS AND FUTURE WORKS

The BIBO stability of a bilinear system cannot be generally studied by considering its state equation. In this paper, we use the "evaluation" of its generating series G. If the rational expression of G is simple or obtained by concatenating some simple rational expressions, then the use of the generating series of the system provides an answer about the stability and a bound for the output. Otherwise, we can look for a stabilizant constant input $u(t) = \eta$ by using the univariate series G_η.
By applying this method to the bilinear model approximating the behavior "insulin delivery/glycaemia", we expect an information about the stability of the (unknown) system describing really this behavior.
A specific surveillance depending on whether the system is stable/unstable will be set. Rather than take constant interval of 15 minutes for recalculate the ideal trajectory of the glycaemia, we propose that the time intervals depend on this information about the stability. In case of unstability, the varying size of the intervals of time would be defined in order to keep the glycaemia between some moderate bounds.

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