A WAY FOR PREDICTING AND MANAGING THE GLYCAEMIC INSTABILITY OF THE DIABETIC PATIENT

Farida Benmakrouha, Christiane Hespel
IRISA-INSA,20 Avenue des Buttes de Coesmes, 35043 Rennes cedex, France

Mikhail V. Foursov
IRISA-Universite de Rennes-1, 35042 Rennes cedex, France

Jean-Pierre Hespel
Centre Hospitalier Universitaire de Rennes, 35000 Rennes, France

Keywords: Dynamical system, Bilinear model, Regulation, Stability, Insulin perfusion.

Abstract: We study the Bounded-Input-Bounded-Output (BIBO) stability of the system modeling the behavior “insulin delivery/glycaemia” of the diabetic patient, under continuous insulin infusion, continuous glucose monitoring, in order to point out that the patient is entering in a period of stable/unstable equilibrium.
The model is a bilinear dynamical system predicting for an interval of 15 minutes, with an average error of 15%. 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.
The BIBO stability is studied by computing the generating series G of the model. This series, generalization of the transfer fuction, is a 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. We propose a stabilizing constant input η by studying the univariate series G_η.

1 INTRODUCTION

Among the different medical possibilities to administer insulin, 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 be the most physiological one.
In order to carry out a glycaemic regulation by an intraperitonal infusion of insulin, it is necessary to predict the glycaemia as a function of the insulin infusion rate, for a given patient and a given insulin. The first closed-loop regulation method was developed by A. Albisser back in 1974 (A. M. Albisser,). Among other methods, we can mention (J. L. Selam, 1992).
But, in spite of many positive aspects of these methods, none of them was unanimously accepted by the medical community. This is partly due 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) which allows one to measure the glycaemia every 3 minutes. A first regulation system based on the CGMS was developed in 2001 by E. Renard of CHU of Montpellier in collaboration with Medtronic Minimed (Renard, 2003). In 2006, E. Renard (E. Renard, 2006), analyzes the implantation of three components: a pump for peritoneal insulin delivery, a central intravenous glucose sensor and a controller. Meals are preceded by a handheld programmed bolus calculed for pre-meals. A problem remains in case of unstability of the glycaemia close to a meal, a stress, a physical effort.

Benmakrouha F., Hespel C., Foursov M. and Hespel J. (2009).
A WAY FOR PREDICTING AND MANAGING THE GLYCAEMIC INSTABILITY OF THE DIABETIC PATIENT.
In *Proceedings of the International Conference on Biomedical Electronics and Devices*, pages 335-338
DOI: 10.5220/0001121003350338

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 (C. Hespel, 2000).
Once the model is known, the regulation consists in inverting the input/output behavior of the system (M. V. Foursov, 2003; M. V. Foursov, 2004). One has to calculate the input in terms of the output function one wishes to obtain (Fig.1). This regulation is partially closed-loop because the glycaemic values are only used every 15 minutes in order to compute the insulin delivery. On constant intervals of time $[t_i, t_{i+1}]_i$, we compute some model M_i and function insulin delivery $u_i(t)$ in order 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 and the true trajectory.

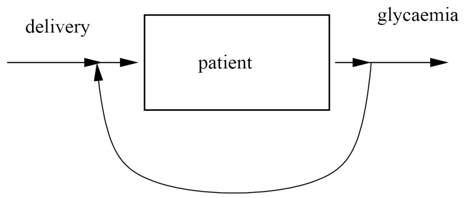

Figure 1: Regulation.

The crucial point consists in determining the size of the time intervals, i.e. 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.

2 PRELIMINARIES: MODELING, REGULATION

Two techniques are used to achieve this goal:
Phenomenological modeling requires a knowledge of the equations governing the evolution of the process. Such models of the glycaemic behavior of diabetics were developed (Albisser,).
In the behavioral modeling, the system is regarded as a black box (J. Sjoberg, 1995). The goal is to construct a model that approximates the system with a desired precision (Chen and Chen,). The parameters involved in the obtained system of equations have no practical significance, but their number depends on the required precision.
A commonly-used class of models is formed by linear dynamical systems. Linear-model-based regulation is simple to implement and it gives quite satisfactory results in many cases. It did not seem to be sufficient for regulating the glycaemia of diabetics.
Another class of models consists of bilinear systems. A bilinear system is quite similar to a linear one: it is additionally linear as a function of the input. One has thus more leeway to approximate the real system with a better precision. We choose to model the system by a bilinear system whose dimension is not fixed.
Since a diabetic does not respond in the same way to equal doses of insulin at different times of the day, we suppose that she is described by different systems at different time instants. So we construct a collection of models that describe the behavior of the glycaemia under certain conditions. Each model is thus valid only for a certain period of time (at least 15 minutes).
Mathematically, the problem is to identify locally (near t_0) up to a given order k, a single input system with drift considered as a black box, when only a sample of the input/output data is known. 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 k.
An advantage of this method is the possibility to provide, in terms of the 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 k. The problem of identification of dynamical systems in a neighborhood of t_0 is the following: to 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 identification involves the following 3 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 are identified by solving another system of linear equations.
A bilinear system corresponding to a rational series of minimal rank is constructed providing a local model.

2.1 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

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

$x(t) \in$ an $R-$vector space Q, 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 Z, by noting w a word $\in Z^*$, is $G = \sum_{w \in Z^*} \langle G|w \rangle w$.

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

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

We compute the rational expression associated with (2), by generalizing the Schutzenberger's method (Schutzenberger, 1961).

By "evaluating" the expression of G, we obtain a formal expression of the output (Fliess, 1981)

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

where the iterated integrals are recursively defined by:

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

And we compute the iterated integral $\int_0^t \delta(G)$.

2.2 The Regulation Method

Once the model is known, the regulation consists in inverting the input/output behavior. One has to calculate the input in terms of the output function one wishes to obtain. This regulation is partially closed-loop, since the glycaemic values are used to recalculate the insulin infusion rates every 15 minutes.

In a previous paper (M. V. Foursov, 2002) 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 sufficient to regulate the glycaemia. But since our bilinear model is an approximation of the actual one, the glycaemic behavior will eventually deviate from the chosen trajectory. Then, 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 (C. Hespel, 2000) showed that we can predict the glycaemia over 15-minute intervals with an error of about 10% or 15%. We need to provide a new data to the pump every 15 minutes.

3 STUDY OF 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. This evaluation consists in integrating every term of this series and in summing. We use the theorem of Hoang (Hoang, 1990) :

Theorem 1. *$\forall k$, let us suppose that G_k is exchangeable and let us denote $\varepsilon(G_k)$ by $g_k(\xi(t))$*

$$g_k(\xi(t)) = g_k(t, \xi_1(t), \cdots, \xi_m(t)) \quad (5)$$

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

$$S_k = G_0 z_{i_1} G_1 \cdots z_{i_k} G_k \quad (6)$$

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

$$\begin{array}{c} \varepsilon(S_k) = y(t) = \\ \int_0^t \int_0^{\tau_k} \cdots \int_0^{\tau_2} g_0(\xi(\tau_1)) g_1(\xi(\tau_2) - \xi(\tau_1)) \cdots \\ g_k(\xi(t) - \xi(\tau_k)) d\xi_{z_{i_1}}(\tau_1) \cdots d\xi_{z_{i_k}}(\tau_k) \end{array} \quad (7)$$

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 (F. Benmakrouha, 2007) 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*

3.1 Example 1

For an insulin delivery $u(t)$, a glycaemia $y(t)$, the state equations of the system (B_2) are

$$\begin{cases} x^{(1)}(t) &= (\begin{pmatrix} 0 & 0 \\ a & b \end{pmatrix} + u(t) \begin{pmatrix} 0 & 0 \\ 1 & 0 \end{pmatrix}) x(t) \\ y(t) &= (1.5 \quad 1) \quad x(t) \end{cases} \quad (8)$$

The generating series is :

$$G_2 = (z_1 + a z_0)(b z_0)^* + 1.5 \quad (9)$$

$G_2 = G_{21} + G_{22} + 1.5$ and $y(t) = \varepsilon(G_2)$
with $G_{21} = z_1 (b z_0)^*$, $\quad G_{22} = a z_0 (b z_0)^*$

We obtain an explicit expression of $y(t)$:
$\varepsilon(G_{21}) = e^{bt}\int_0^t e^{-b\tau_1} d\xi_1(\tau_1)$

$$\varepsilon(G_{22}) = ae^{bt}\int_0^t e^{-b\tau_1} d\tau_1 \quad (10)$$

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 $b > 0$.
This system is BIBO for $b < 0$ (if $M_1 \leq u(t) \leq M_2$ then $y(t)$ is bounded)
For instance, for $a > 0,\ b < 0,\ 0 \leq u(t) \leq M$, then $y(t) \leq x(0) + \frac{M+a}{-b}$

3.2 Example 2

The state equations of the bilinear system (B_3) are

$$\left\{ \begin{array}{lcl} x^{(1)}(t) & = & (\begin{pmatrix} 0 & 0 & 0 \\ a & b & c \\ 0 & a & 0 \end{pmatrix} \\ & & +u(t)\begin{pmatrix} 0 & 0 & 0 \\ 1 & 0 & 0 \\ 0 & 1 & 0 \end{pmatrix})x(t) \\ y(t) & = & (1.5 \quad 1 \quad 0) \quad x(t) \end{array} \right. \quad (11)$$

The generating series is

$$G_3 = (z_1 + az_0)(bz_0 + (z_1 + az_0)cz_0)^* + 1.5 \quad (12)$$

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 $\eta \neq -a$ then we decompose $G_{3,\eta}$ in partial fractions for studying the constant stabilizing inputs
$u(t) = \eta$ depending on the parameters a, b, c.

4 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 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.

REFERENCES

A. M. Albisser, B. S. Leibel, T. G. E. e. a. An artificial endocrine pancreas. *Diabetes*, 23:389–396.

Albisser, A. M. Intelligent instrumentation in diabetes management. *CRC Crit. Rev. Biomed. Eng.*, 17:1–24.

C. Hespel, J. P. Hespel, E. M. G. J. G. F. B. (2000). Algebraic identification: Application to insulin infusion. *ISGIID'2000 Evian*.

Chen, T. and Chen, H. *IEEE T.Neur.Net.*

E. Renard, G. Costalat, H. C. J. B. (2006). Artificial beta-cell: clinical experience toward an implantable closed-loop insulin delivery system. *Diabetes Metabolism*, pages 497–502.

F. Benmakrouha, C. H. (2007). Generating formal power series and stability of bilinear systems. *8th Hellenic European Conference on Computer Mathematics and its Applications (HERCMA 2007)*.

Fliess, M. (1981). Fonctionnelles causales non linéaires et indéterminées non commutatives. *Bull . Soc . Math. France*, 109:3–40.

Hoang, N. M. (1990). Contribution au développement d'outils informatiques pour résoudre des problèmes d'automatique non linéaire. Master's thesis, Université de LilleI.

J. L. Selam, P. Micossi, F. L. D. e. a. (1992). Clinical trial of programmable implantable insulin pump for type i diabetes. *Diabetes Care*, 15:877–885.

J. Sjoberg, Q. Zhang, L. L. e. a. (1995). Nonlinear black-box modeling in system identification: a unified overview. *Automatica*, 31:1691–1724.

M. V. Foursov, C. H. (2002). On formal invertibility of the input/output behavior of dynamical systems. *preprint IRISA*, 1439.

M. V. Foursov, C. H. (2003). On algebraic modeling and regulation of the behavior of diabetics. *Innovative Technologies for Insulin Delivery and Glucose Sensing*.

M. V. Foursov, C. Hespel, D. B. J. H. (2004). Nouvelle méthode de modélisation algébrique et de régulation de la glycémie. *Infu-Systèmes 21*, 3:22–24.

Renard, E. (2003). Closed-loop system with implantable pump and iv sensor. *proceedings of the symposium "Looking to the future"*, pages 78–79.

Schutzenberger, M. P. (1961). On the definition of a family of automata. *Inform. Contr.*, 4:245–270.