Modelling glycaemia of diabetics : an application.

F. Benmakrouha and C. Hespel and M.V. Foursov

***Abstract*— We present and study, in this paper, a Tagaki-Sugeno(TS) fuzzy model that consists in a family of linear models mixed together with nonlinear membership functions. We apply this method to the problem of treatment of diabetics. Taking the insulin infusion rate as the input and the blood glucose rate as the output, we consider the patient as a black box [12], [11], whose model has to be obtained from the available measures of inputs–outputs. We dispose of a glycaemia file automatically produced for every person, and an insulin file shared by several persons.**
We investigate the model's quality on two criteria : a convergence measure and the impact of datum plane covering on the outcome of a fuzzy inference system.
We emphasize on the importance of datum plane covering. Many papers propose fuzzy algorithms for extraction of knowledge from numerical data [7], [8], [9]. But few works have been developed for design of experiments and datum plane covering. We propose a measure used to pre-validate a fuzzy model. This pre-validation takes place after design of the inference system. So, when the model is not pre-validated, we do not have to carry out the next steps, optimisation and validation.

I. INTRODUCTION

There exist several methods for glycemic identification, based on mathematical, computer science and control theory techniques, 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 [2], [3], [4], [5], [6].

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 glycemic sampling. We note also that most of models proposed are :
- either linear which do not take into account the nonlinear aspects of almost real-time life problems.
- or global systems, which is not satisfactory. 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 he is described by different systems at different time instants.

The first objective of this paper is to propose a method of modeling the "insulin delivery/glycaemia" behavior of some patient, under insulin infusion, for a given type of insulin, under continuous glucose monitoring. This method belongs to the class of methods that consider the patient as a black box. We construct a collection of linear models that describe the behavior of the glycemia 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. To combine this collection of linear models and represent nonlinear aspects of our problem, we choose a Tagaki-Sugeno(TS) fuzzy model. We validate this model by computing the mean square error, performance index of system, on the totality of measures(1700 points).

The second objective is to measure the impact of datum plane covering on the outcome of a fuzzy inference system. Most of optimization methods make the assumption that datum plane is sufficiently covered. If this assumption no longer holds, we will see that these methods cannot work, since it implies that, before optimization, the fuzzy system gives acceptable results.

This work was not supported by any organization

F. Benmakrouha is with the Mathematics and Computer Science, INSA,35043 Rennes Cedex, France benma@insa-rennes.fr

C. Hespel is with Mathematics and Computer Science, INSA,35043 Rennes Cedex, France hespel@insa-rennes.fr

M.Foursov is with Mathematics and Computer Science, IFSIC-IRISA ,35042 Rennes Cedex, France foursov@irisa.fr

II. THE TAGAKI-SUGENO MODEL

The model under consideration in this section is a Tagaki-Sugeno model, which corresponds to discretized linear models of order 1, combined with nonlinear functions.

$$y(t) = \sum_{i=1}^{r} h_i(z(t))(a_1^i.y(t - idecal) + b_1^i.u(t - idecal))$$

r is the number of linear models,
$z(t)$ a vector which depends lineary or not on the state,
$h_i(z(t)) >= 0$, $i = 1, \cdots, r$ nonlinear functions verifying the convex sum property.
$idecal$ is the time lag between input and its effect, which is specially interesting in our application. We have measures about every five minutes and we admit that the effect of insulin (considered in our application)is fast and noticeable ten (idecal=2) minutes later, up to half an hour(idecal = 6). The determination of unknown parameters a_1^i and a_2^i is done by the algorithm of recursive least square.

III. Application to the insulin/glycaemia behavior of diabetics

A. The application

Diabetes is a major chronical disease affecting over 200 million people world wide, and for which no efficient treatment exists so far. Diabetes is responsible for numerous complications which cost up to 60 % of the whole diabetes management budget. Following the invention of implantable insulin pumps and continuous glucose sensors, it became possible to envisage developing an artificial pancreas, a computer program located inside the insulin pump and calculating, from the glycemic values measured by the glucose sensor, the insulin values necessary to maintain the normoglycemia.

B. The available data

The correlated data "'insulin infusion delivery/glycaemia"' has been provided by the team of Pr. Pinget, CHU of Strasbourg. They concern the same person and the same insulin.
The insulin infusion has been done by an intra-peritoneal route and the glycaemia has been checked by a subcutaneous sensor. Measures of glycaemia have been made every five minutes during 7 days, which corresponds to 1700 measures. A bolus is a dose of insulin infused manually, in addition to the basic dose, since postprandial glycemia cannot be regulated satisfactorily. The insulin file contains crude data about basic insulin doses as well as boluses. So, a pretraitement of the insulin file has been necessary to produce a file of insulin delivery for the same person every five minutes.

C. Experiments and Validation of the model

The learning set is composed of the first measures(280 points) that corresponds to insulin infusion and blood glucose concentration of a patient during a day. We take 7 ($r = 7$)linear models, considering that each model is valid about three and half hours. The mean square error(MSE)is calculated on the totality of the measures(1700 points).

We make experiments by changing the parameter $idecal$ of the model, time lag between an input and its effect.

r	idecal	MSE
7	2	0.04
7	3	0.06
7	6	0.16
7	24	1.02

TABLE I
First Table .

The test of our modeling method shows that we can predict the glycaemia over a long period (7 days), by considering glycaemia and insulin delivery 15-minute (resp 30-minute) before with an error of about 6%(resp 16%), which is a good result compared with current results.
However, we see that results obtained are not so good in the last case, when we consider slow effect insulin (with 2-hours delay). In this case, our model has to be refined, by increasing its order.

IV. Datum Plane Covering

We propose a measure used to pre-validate a fuzzy model. We suppose that there exists a learning set $\Omega = \{(\mathbf{x}_j, d_j)\}$, where $\mathbf{x}_j$ is an input vector and d_j, the corresponding output. We also assume that the desired function f is defined in

$$V = [a_1, b_1] \times [a_2, b_2] \times ... \times [a_p, b_p]$$

Usually, to validate a fuzzy inference system, the mean square error (MSE) is calculated on a test set. If the MSE exceeds a threshold, then training is done, using a gradient method. This consists in modifying C_j at each presentation of examples from the error $(y(\mathbf{x}_j) - d_j)$.
Unfortunately, in case of model invalidation, we cannot determine never learned rules that cause the gap between the model and the real system. Moreover, if there is an insufficient covering of datum plane, training and finer splitting of input space are inefficient and useless.
With the criterion proposed below, we estimate the datum plane coverage and we are able to isolate inactivated rules. Then, partial remodeling of the fuzzy inference system is possible.

When designing a fuzzy system, we attribute to each input I r modalities (or labels) noted $y_1, \cdots y_l, \cdots y_r$. We note X^I the variable for the input I of average $\bar{x}^I$ and variance $\sigma^2_{X^I}$. We note Ω^I the corresponding learning set . Each label y_l of I defines a subset Ω^I_l of Ω^I : we obtain a partition of Ω^I in m classes. We note $n^I_l = card(\Omega^I_l)$ and $n^I = card(\Omega^I)$. We have $n^I = \Sigma^m_{l=1} n^I_l$. Then, if we consider the restriction de X^I to Ω^I_l $(l = 1, \cdots, m)$, we may define the average (noted $\bar{x}^I_l$)and the variance (noted $\sigma^2_{X^I_l}$ of X^I on this subset:

$$\bar{x}^I_l = \frac{\sum_{\omega \in \Omega^I_l} X(\omega)}{n^I_l}$$

$$\sigma^2_{X^I_l} = \frac{\sum_{\omega \in \Omega^I_l} (X(\omega) - \bar{x}^I_l)^2}{n^I_l}$$

We have an index of connection between the datum plane coverage (for an input I) and the learning set defined by :

$$s^I = \sqrt{\frac{\sigma^2_E}{\sigma^2_Y}}$$

where

$$\sigma^2_{X^I} = \sigma^2_E + \sigma^2_R$$

and

$$\sigma^2_E = \frac{\sum^r_{l=1} n^I_l * (\bar{x}^I_l - \bar{x}^I)^2}{n^I}$$

and

$$\sigma_R^2 = \frac{\sum_{l=1}^{r} n_l^I * \sigma_{X_l^I}^2}{n^I}$$

and

$$\bar{x}^I = \frac{\sum_{l=1}^{r} (n_l^I * \bar{x}_l^I)}{n^I}$$

A. Experiments

The mean squarre error, performance index of the approximate system, is calculated on measures of the training set(Tr-set), before optimization step.

B. First Example

This example has been shown in [10].

$$y = \frac{sin(x)}{x}$$

We compare, using this example, output inferred by fuzzy systems :

- when datum plane is "sufficiently" covered
- when datum plane is not well-covered

n is the number of membership functions
MSE (resp $MSEA$) is the mean square error after 0 (resp 20) iterations.

The generalisation set is [0.3 8.0]. the index $\bar{x}^I$ (coverage rate) is zero when data are only on the last interval.
We note that training is useless when the model is not pre-validated.

n	Tr-set	MSE	MSEA	index
7	[0.3 8.0]	0.12	0.00001	0.61
7	[7.0 8.0]	0.12	0.13	0.0

TABLE II
FIRST TABLE .

C. Second example

This example is our application : The index for insulin delivery is 0.1 because of boluses infused at some time instants.
From these experiments, we remark that coverage rate is correct under two conditions

- (i) datum plane and test interval are not disjoined.
- (ii) the ratio number of rules / card(Tr-set) is acceptable.

Input	Card(Tr-set)	MSE	MSEA	index
1	280	0.07	0.06	0.93
2	280	0.07	0.06	0.1

TABLE III
SECOND TABLE .

V. CONCLUSION

We have proposed in this paper a method of modeling the "insulin delivery/glycaemia" behavior of some patient. The linear model does not seem to be satisfactory, our idea was to use a combined linear/nonlinear model describing the insulin-infusion-rate/glycemia behavior. Our method gives encouraging results over longer time periods (compared to current results).
However, this modeling has to be compared to other existing modeling methods.
Another prospect is to use this model in order to develop a glycemic regulator for a diabetic. The most sophisticated existing glycemic regulator is tested at the Montpellier University Hospital since 2001. This regulator uses a linear model with 2 parameters which are identified for each patient. It improves considerably the life quality of a diabetic. However, the postprandial glycemia cannot be regulated satisfactorily. We hope that our method will lead to a better glycemic regulation.
We have also proposed a measure for pre-validation of a fuzzy inference system. When the model is not pre-validated, we have not to carry out next steps, particularly optimization step.
We have shown that this criterion is a good measure for datum plane coverage.

REFERENCES

[1] A.M. Albisser, B.S. Leibel, T.G. Ewart, et al., An artificial endocrine pancreas, Diabetes, 23 (1974), pp. 389-396.

[2] J.L. Selam, P. Micossi, F.L. Dunn et al., Clinical trial of programmable implantable insulin pump for type I diabetes, Diabetes Care, 15 (1992) pp. 877-885.

[3] G. Bleckert, U.G. Oppel, and E. Salzsieder, *Mixed graphical models for simultaneous model identification and control applied to glucose-insulin metabolism* ,Comput.Methods Prog.Biomed. 56(1998), no. 2, 141-155.

[4] B. Candas and J. Radziuk, *An adaptive plasma glucose controller based on a nonlinear insulin/glucose model*, IEEE Trans. Biomed. Eng. **41** (1994), no. 2, 116–123.

[5] R.S. Parker, F.J. Doyle III, and N.A. Peppas, *A model-based algorithm for blood glucose control in Type I diabetic patients*, IEEE Trans. Biomed. Eng. **46** (1999), no. 2, 148–157.

[6] Z. Trajanoski and P. Wach, *Fuzzy filter for state estimation of a glucoregulatory system*, Comput. Methods Progr. Biomed. **50** (1996), no. 3, 265–273.

[7] T. Johansen *Fuzzy model based control: stability,robustness, and performance issues*, IEEE Trans.Fuzzy Syst. 2(3)(1994) 221-234

[8] H. Wang, K. Tanaka, M.Griffin, *An approach to fuzzy control of nonlinear systems: stability and design issues*, IEEE Trans.Fuzzy Syst. 4(1)(1996) 14-23.

[9] S. Cao, N. Rees, G. Feng, *Analysis and design for a class of complex control systems.*, Part I: Fuzzy modelling and identification, Automatica 33(6)(1997) 1017-1028.

[10] J.Gutierrez, F. Fernandez, S. Guadarrama, E. Trillas , "A step towards conceptually improving tagaki-sugeno's approximation",*IPMU'2002*, III:pp 1789-1794, July 2002.

[11] A. Juditsky, H. Hjalmarsson, A. Benveniste, B. Delyon, L. Ljung, J. Sjberg,and Q. Zhang, *Nonlinear black-box models in system identification: mathematical foundations*, Automatica J. IFAC 31 (1995), no. 12, 1725–1750.

[12] J. Sjberg, Q. Zhang, L. Ljung, A. Benveniste, B. Delyon, P.-Y. Glorennec, H. Hjalmarsson, and A. Juditsky, *Nonlinear black-box modeling insystems identification: a unified overview*, Automatica J. IFAC 31 (1995), no. 12, 1691–1724.