Biocybernetics and Biomedical Engineering
2010, Volume 30, Number 1, pp. 41–53

Modeling of Glucose Concentration Dynamics for Predictive Control of Insulin Administration

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The compartmental models, as Hovorka's one, are usually exact but complicated. Thus, they are not suitable for direct usage in nonlinear predictive controllers because of complexity of the resulting controller and numerical problems that may occur. Thus, simplified nonlinear (neural and fuzzy) models are developed in this paper for the future use in the predictive algorithms. Training and structure selection issues are discussed in the context of neural models. The heuristic, easy to obtain, Takagi-Sugeno fuzzy model composed of the control plant step responses is also designed. It is shown that in case of the considered biological process both nonlinear models have significantly better approximation abilities than linear ones.

K e y w o r d s: insulin administration, neural networks, fuzzy models

1. Introduction

Epidemiological data indicate that diabetes is one of common lifestyle diseases. Long-term consequences of decompensated glucose concentration lead to severe decreasing of health status and dramatically increasing costs of rehabilitation. Thus, large efforts are undertaken in pharmacology and biomedical engineering to control glucose concentration by proper insulin dosing. Significant intra- and interpersonal variability cause that it is difficult to determine insulin dose for a particular subject. For example, the variability of overnight insulin requirement may result from decreasing of peripheral insulin sensitivity caused by elevated levels of growth hormone, cortisol and catecholamine which are antagonistic to insulin. This phenomenon is known as "dawn phenomenon" [1]. Other possible causes of intrapersonal variability

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Received 07 November 2008; accepted 28 July 2009

of an insulin dose may be rebound hyperglycemia after nocturnal hypoglycemia (Somogyi phenomenon [1]), day-to-day variability of subcutaneous absorption of insulin preparations [2] or defective glucose counterregulation [3]. Therefore, the closed loop control techniques are developed to maintain physiological glucose level [4].

The study performed by Hernjak and Doyle showed that model-free control algorithms e.g. PID were unstable and ineffective for the considered control problem [5]. Therefore the model based algorithms were recommended. Selection of an adequate process model is a pivotal problem. Some of the published control strategies, especially predictive control algorithms were designed on basis of a black box, linear model of insulin-glucose dynamics [4]. However, the physiological studies confirm that nonlinear models are more suitable for the control purpose. Several such models are published in the literature [6]. All of them can be arranged hierarchically driven by physiological details included in the model. The source model for the more comprehensive models was the Bergman's minimal model [6]. It represents dynamics of insulin and glucose concentrations as well as dynamics of insulin actions. However, this model has some physiological and mathematical drawbacks. The model has been developed on the basis of assumption stating that the plasma glucose and insulin compartments are independent and can be identified independently. Moreover, the model contains an "artificial" non-observable variable to model a delay in the insulin action. The equation associated with the introduced variable makes the model identification difficult. From the mathematical point of view the minimal model can produce physiologically unreliable results (e.g. problems of positive equilibrium and unbounded solutions) [6].

Numerous models published in literature are the extended version of the minimal model. Examples of such extensions compose models were proposed by Fabiatti et al. and Havorka et al. [7, 8] .These models have similar structures consisting of a model of insulin kinetics and dynamics and a model of glucose kinetics and dynamic. The mathematical descriptions of common submodels are similar in these two models.

Additionally, the model introduced by Fabiatti et al. takes hepatic balance into account. It enables for modeling of glucose absorption from a meal or OGTT. Moreover, a model of circadian glucose variability is added. However, the form of this part is doubtful from physiological point of view.

In the presented study simplified neural and fuzzy models for numerically efficient nonlinear predictive control of insulin dosage are developed. The Hovorka's model is treated as a reference one. This model represents the input-output relationship between subcutaneous insulin infusion and intravenous glucose concentration [8]. Meal ingestion is an additional input which can be treated as a disturbance. The model consists of a glucose subsystem (modeling glucose absorption, distribution and disposal), an insulin subsystem (modeling insulin absorption, distribution and disposal) and an insulin action subsystem (modeling insulin action on glucose transport, disposal and endogenous production). The mathematical formulas of the model

are presented in details in [8]. Because the model contains some nonlinearities the model dynamic is highly nonlinear. It can be easily observed analyzing steady–state characteristics and step responses of the Hovorka's model (Fig. 1). The step responses were collected for six positive changes of the insulin dose 0.01 U/L each and six negative changes–0.01U/L each. In the following part of the paper *y* denotes glucose concentration and *u* insulin dose. From the perspective of control algorithm, the insulin dose is the input (the manipulated variable) of the whole dynamic system, the glucose concentration is the output (the controlled variable) of the system.

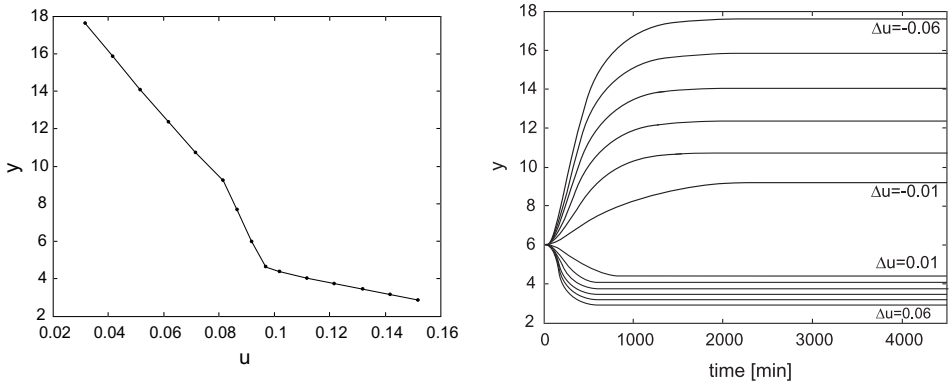

Fig. 1. The steady-state characteristic (left) and step responses of the process (right) of the Hovorka's model, *u* – insulin dose (U/L), *y* – glucose concentration (mmol/L)

2. Models for Predictive Control of Insulin Administration

Model Predictive Control (MPC) is an advanced control technique which is successful in practice [9, 10, 11]. In comparison with classical control techniques (e.g. the PID approach), MPC algorithms can take into account constraints imposed on both process inputs (manipulated variables) and outputs (controlled variables), which usually decide on quality, economic efficiency and safety. Moreover, MPC techniques are very efficient in multivariable process control and in case of processes which dynamic properties make control difficult (e.g. processes with time-delays or with inverse step-responses).

The compartmental models, as Hovorka's one, are usually exact but complicated. In theory, it is possible to use such models directly in nonlinear predictive controllers. Unfortunately, such control algorithms must solve a set of nonlinear differential equations comprising the model at each sampling instant on-line. It is computationally inefficient and numerical problems are unavoidable.

On the one hand, the model used by a predictive control algorithm should be as exact as possible. On the other hand, some model inaccuracies are compensated in

the feedback control system. Thus, simplified nonlinear (neural and fuzzy) models are designed for the future use in the predictive algorithms. Then these models can be used in such a way that numerically efficient predictive algorithms will be obtained.

Neural and fuzzy nonlinear models can be used to model highly nonlinear control plants. They are able to approximate precisely nonlinear behaviour of technological dynamic processes [12–15]. These models have relatively simple and regular structures. Well designed models have relatively small number of parameters. Identification process of such models is also simple. Neural models can be easy trained using recorded sets of input and output process data and learning algorithms. Fuzzy models may be designed using heuristic approach and expert knowledge. These types of models are usually input-output models which do not demand solving of differential or algebraic equations. Therefore they can be easier used in the predictive algorithms. It is necessary to mention one main disadvantage of approximate neural and fuzzy models. Unlike the fundamental compartmental model, approximate models do not have any clear interpretation, they are black-box-models.

Predictive control algorithms based on neural or fuzzy models can be formulated in such a way that they demand solving of only quadratic optimization problem at each iteration. Thus, they are much more numerically efficient than algorithms which use full nonlinear optimization. Despite their relative simplicity they make possible improvement of control system operation comparing to algorithms based on linear models.

2.1. Multi Layer Perceptron (MLP) Neural Network

The single-input single-output (SISO) neural model of the process is described by the following nonlinear discrete-time equation:

$$\begin{aligned} y(k) = f(&u(k-\tau),\ldots,u(k-n_B),\\ &y(k-1),\ldots,y(k-n_A)) \end{aligned} \tag{1}$$

where $f:\Re^{n_A+n_B-\tau+1}\to\Re$, $\tau \le n_B$. A feedforward MLP neural network (Multi Layer Perceptron) with one hidden layer and a linear output [12] is used as the function f in (1). The structure of the neural model is depicted in Fig. 2. The output of the model can be expressed as:

$$y(k) = w_0^2 + \sum_{i=1}^{K} w_i^2 \varphi(z_i(k)) \tag{2}$$

where $z_i(k)$ are sums of inputs of the i^{th} hidden node, $\varphi:\Re\to\Re$ is the nonlinear transfer function (e.g. the hyperbolic tangent), and K is the number of hidden nodes. Recalling input arguments of the general neural model (1) one has:

$$z_i(k) = w_{i,0}^1 + \sum_{j=1}^{I_u} w_{i,j}^1 u(k-\tau+1-j) + \sum_{j=1}^{n_A} w_{i,I_u+j}^1 y(k-j) \tag{3}$$

where $I_u = n_B - \tau + 1$. Weights of the network are denoted by $w_{i,j}^1$, $i = 1,...,K$, $j = 0,...,n_A + n_B - \tau + 1$, and w_i^2, $i = 0,...,K$, for the first and the second layer, respectively. Combining equations (2) and (3) one obtains:

$$y(k) = w_0^2 + \sum_{i=1}^{K} w_i^2 \varphi(w_{i,0}^1 + \sum_{j=1}^{I_u} w_{i,j}^1 u(k-\tau+1-j) + \sum_{j=1}^{n_A} w_{i,I_u+j}^1 y(k-j)) \tag{4}$$

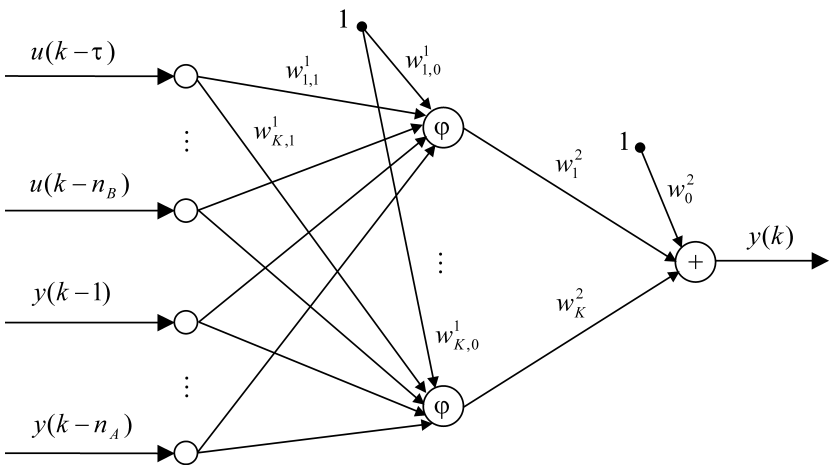

Fig. 2. The structure of the neural model

For the identification experiment the reference model [8] is used as the real process, in order to obtain two sets of data, namely training and test data sets depicted in Fig. 3 open-loop off-line operation is simulated). As the input sequence pseudorandom step changes are used. Both sets contain 2000 samples, the sampling time is 15 min. The output signal contains a small measurement noise.
Second-order dynamic neural models:

$$y(k) = f(u(k-1), u(k-2), y(k-1), y(k-2)) \tag{5}$$

are considered. Because input and output process variables have different order of magnitude, they are scaled as $u := 10(u - u_0)$, $y := 0.1(G - G_0)$ where

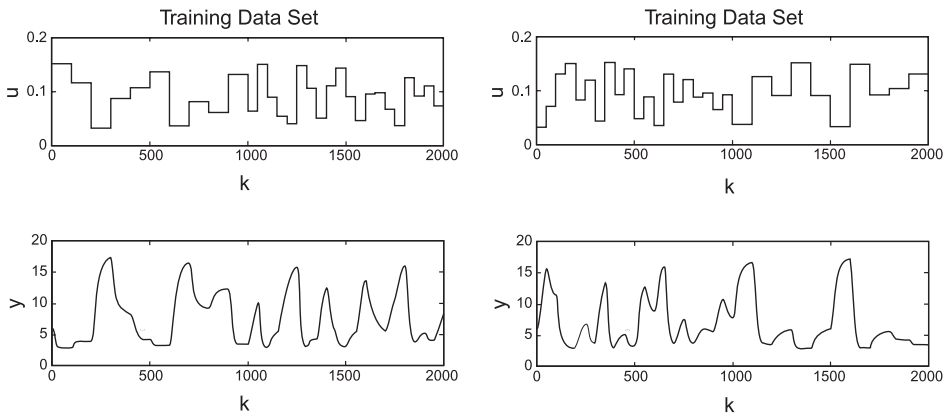

Fig. 3. Training and test data sets, u – insulin dose (U/L), y – glucose concentration (mmol/L)

$u_0 = 0.09183771738300$ and $G_0 = 6$ correspond to the nominal operating conditions of the process. All compared neural models have the same arguments determined by $\tau = 1$, $n_A = n_B = 2$, the difference is in the number of hidden nodes K. Hyperbolic tangent transfer function is used in the hidden layer. During the training the following Sum of Squared Errors cost function is minimized:

$$SSE = \sum_{k \in \text{data set}} (y(k \mid k-1) - y(k))^2 \tag{6}$$

where $y(k \mid k-1)$ denotes the output of the model for the sampling instant k calculated from the neural model at the sampling instant $k-1$, $y(k)$ is the real value of the process output variable collected during the identification experiment.

For training purposes, different unconstrained optimisation algorithms have been tested: the rudimentary backpropagation scheme (i.e. the steepest descent), the conjugate gradient methods (Polak-Ribiere, Fletcher-Reeves) and the quasi-Newton algorithms (the David-Fletcher-Powell algorithm or the Broyden–Fletcher–Goldfarb–Shanno known as BFGS method) [16]. Finally, all neural models are trained using the BFGS algorithm, which outperforms all the aforementioned competitors in terms of learning time. As the number of model parameters (weights) influences the prediction accuracy, neural networks with different numbers of hidden nodes are considered ($K = 3, 4, 5, 6, 7, 8$).

Accuracy of the neural models in terms of Sum of Squared Errors for training and test data sets is compared in Table 1. For each neural model structure the identification experiment is repeated 10 times, weights of neural networks are initialised randomly. The results presented are the best obtained. The influence of the number of hidden nodes K on accuracy of the neural models for training and test data sets is also depicted in Fig. 4.

Table 1. Accuracy of neural models in terms of Sum of Squared Errors

K	Training	Test
3	2.550950e–1	3.147607e–1
4	1.958348e–1	4.072323e–1
5	1.502756e–1	3.496883e–1
6	1.013348e–1	1.506407e–1
7	1.005943e–1	3.885861e–1
8	9.040062e–2	5.518186e–1

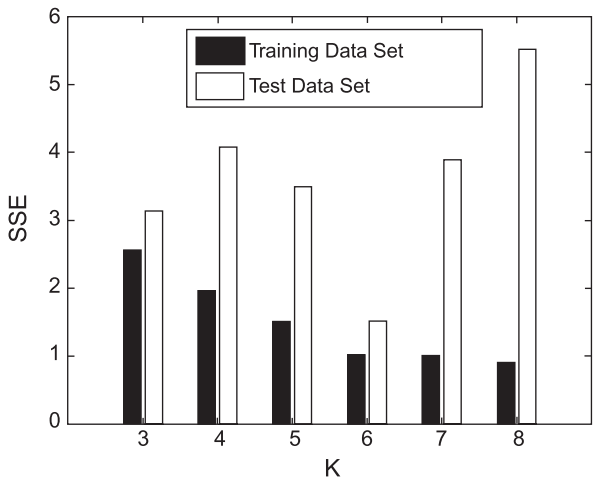

Fig. 4. The influence of the number of hidden nodes K on accuracy of the neural models for training and test data sets

On the one hand, increasing the number of hidden nodes leads to reducing the *SSE* performance index for the training data set. On the other hand, it is a well-known fact that neural networks with too many parameters have poor generalisation abilities (overfitting). It is easily observed in the case of neural models of the considered process. For the test data set the value of the *SSE* performance index rapidly increases when $K > 6$. That is why, the neural model with $K = 6$ hidden nodes is chosen as it gives small prediction errors for both training and data set. The output of the process and the output the neural model are shown in Fig. 5. Weights of the neural model are given in Table 2.

Although in this paper only second-order dynamic models are described, during the research carried out first-order ($\tau = n_A = n_B = 1$) and third-order ($\tau = 1$, $n_A = n_B = 3$) models were also considered. On the one hand, the first-order models turn out to be insufficiently accurate when compared to the second-order ones. On the other hand, the third-order models, are unable to give any significant reduction

of the SSE performance index when compared to the second-order models. As a result, second-order dynamics is chosen as a good compromise between accuracy and complexity.

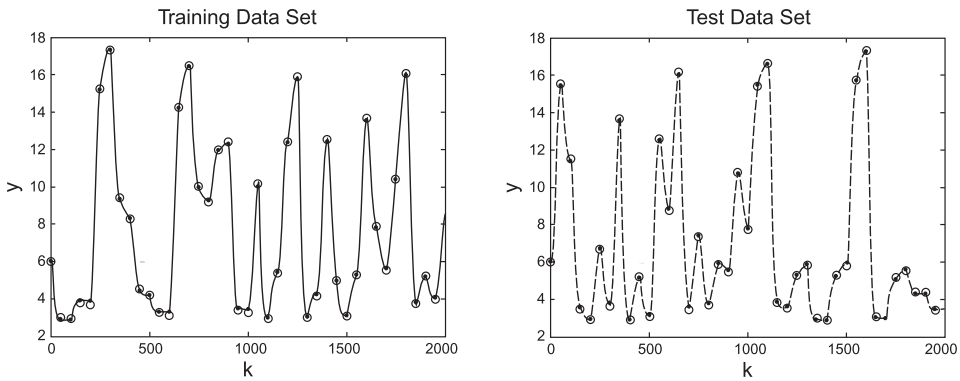

Fig. 5. The process (solid line with dots) vs. the neural model (dashed line with circles) for training and test data sets, y – glucose concentration (mmol/L)

Table 2. Weights of the chosen neural model with K=6 hidden nodes

$w^1_{1,0} = 2.472\text{e}-1$	$w^1_{1,1} = 8.260\text{e}-2$	$w^1_{1,2} = -1.052\text{e}-1$	$w^1_{1,3} = 1.194\text{e}+0$	$w^1_{1,4} = 2.548\text{e}-1$
$w^1_{2,0} = -1.788\text{e}+0$	$w^1_{2,1} = -1.566\text{e}-1$	$w^1_{2,2} = -4.390\text{e}-1$	$w^1_{2,3} = 1.331\text{e}+0$	$w^1_{2,4} = 1.038\text{e}+0$
$w^1_{3,0} = 9.152\text{e}-1$	$w^1_{3,1} = -1.586\text{e}-2$	$w^1_{3,2} = 2.364\text{e}-2$	$w^1_{3,3} = -1.355\text{e}+0$	$w^1_{3,4} = 6.540\text{e}-1$
$w^1_{4,0} = -5.115\text{e}-1$	$w^1_{4,1} = -5.748\text{e}-1$	$w^1_{4,2} = -5.943\text{e}-1$	$w^1_{4,3} = 5.174\text{e}-1$	$w^1_{4,4} = 5.566\text{e}-1$
$w^1_{5,0} = 5.136\text{e}-1$	$w^1_{5,1} = 4.0606\text{e}-1$	$w^1_{5,2} = 1.452\text{e}+0$	$w^1_{5,3} = 6.083\text{e}-1$	$w^1_{5,4} = -3.978\text{e}-1$
$w^1_{6,0} = -1.623\text{e}-1$	$w^1_{6,1} = -2.357\text{e}-1$	$w^1_{6,2} = 2.955\text{e}-1$	$w^1_{6,3} = 5.848\text{e}-1$	$w^1_{6,4} = -2.410\text{e}+0$
$w^2_0 = 8.187\text{e}-1$	$w^2_1 = 7.612\text{e}-1$	$w^2_2 = 3.113\text{e}-3$	$w^2_3 = -1.320\text{e}+0$	
$w^2_4 = 2.490\text{e}-3$	$w^2_5 = 3.910\text{e}-4$	$w^2_6 = 2.721\text{e}-1$		

The neural network is able to model the process with a very high accuracy. It is an interesting question if a linear model with constant parameters would lead to similar modelling accuracy. The linear second-order dynamic model:

$$y(k) = b_1u(k-1) + b_2u(k-2) - a_1y(k-1) - a_2y(k-2) \tag{7}$$

is found by means of the standard least-squares algorithm. The linear model has the same input arguments as the neural one (5). In Figure 6 the output of the process and the output of the linear model for both training and test data sets are compared. Output Samples (solid line) are the same as in Fig. 3 and Fig. 5. For the training data

set *SSE* = 1.026402e+004, for the test data set *SSE* = 1.220843e+004. Unfortunately, because the steady-state characteristic and step-responses of the process are significantly nonlinear as shown in Fig. 1, accuracy of the linear model is also low. Output of the linear model gives negative values which have no physiological meaning.

One can easily see that the neural model, unlike the linear one, is able to very precisely predict behaviour of the process. Hence, the neural model with $K=6$ hidden nodes is recommended to be next used in MPC algorithms.

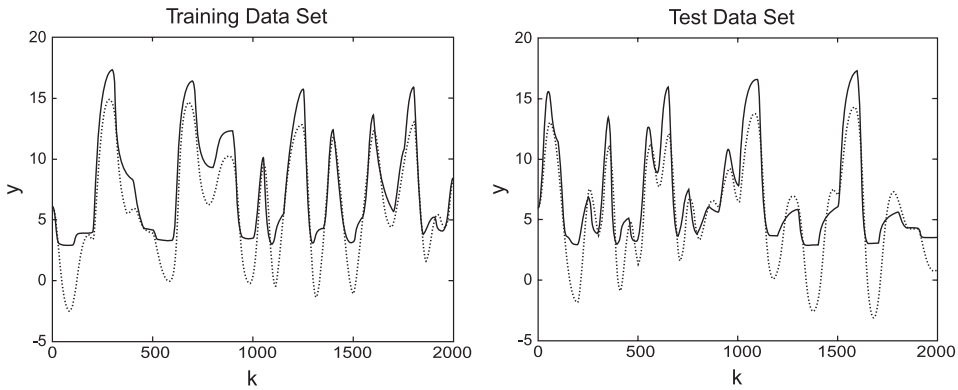

Fig. 6. The process (solid line) vs. the linear model (dashed line) for training and test data sets, y – glucose concentration (mmol/L)

2.2. Takagi–Sugeno Fuzzy Model

During research the Takagi–Sugeno (TS) fuzzy process model with local models in the form of step responses is considered [17]. Such a model is relatively easy to obtain. It is sufficient to collect a few step responses of the control plant near a few operating points (three in the case under consideration). The membership functions can be chosen using expert knowledge, simulation experiments or fuzzy neural networks. Thus the discussed model is described by the following rules:

$$\begin{aligned} &\text{If } \; y_k^{j_y} \text{ is } B_1^{f,j_y} \text{ and } \ldots \text{ and } y_{k-n_P+1}^{j_y} \text{ is } B_{n_P}^{f,j_y} \text{ and } \ldots \text{ and } u_k^{j_u} \text{ is } C_1^{f,j_u} \\ &\qquad \text{and } \ldots \text{ and } u_{k-m_P+1}^{j_u} \text{ is } C_{m_P}^{f,j_u} \\ &\text{then} \quad \tilde{y}_{k+1}^{j,f} = \sum_{m=1}^{n_u} \sum_{i=1}^{p_d-1} a_i^{j,m,f} \cdot \Delta u_{k-i}^m + a_{p_d}^{j,m,f} \cdot u_{k-p_d}^m + c^{j,f} \end{aligned} \tag{8}$$

where $y_k^{j_y}$ is a value of the j_y^{th} output variable at the k^{th} sampling instant, $u_k^{j_u}$ is a value of the j_u^{th} manipulated variable at the k^{th} sampling instant, $B_1^{f,j_y},\ldots, B_{n_P}^{f,j_y}$, C_1^{f,j_u} ,…, $C_{m_P}^{f,j_u}$ are fuzzy sets, $a_i^{j,m,f}$ ($i = 1,\ldots, p_d$) are the coefficients of step responses

in the f^{th} local model describing influence of the m^{th} input on the j^{th} output, p_d is equal to the number of sampling instants after which the coefficients of the step responses can be assumed as settled, $c^{j,f}$ are constant values, $j_y = 1,\ldots, n_y, j_u = 1,\ldots, n_u$, $f = 1,\ldots, l$, l is number of rules.

For current sampling instant using: current values of process variables, the TS model (8) and fuzzy reasoning, the following model is obtained (it is in fact the step response control plant model valid for current values of process variables):

$$\tilde{y}_k^j = \sum_{m=1}^{n_u} \sum_{i=1}^{p_d-1} \tilde{a}_i^{j,m} \cdot \Delta u_{k-i}^m + \tilde{a}_{p_d}^{j,m} \cdot u_{k-p_d}^m + \tilde{c}^j \tag{9}$$

where $\tilde{y}_k^j$ is the j^{th} output of the control plant model at the k^{th} sampling instant, $\tilde{a}_i^{j,m} = \sum_{f=1}^{l} \tilde{w}_f \cdot a_i^{j,m,f}$, $\tilde{c}^j = \sum_{f=1}^{l} \tilde{w}_f \cdot c^{j,f}$, and $\tilde{w}_f$ are the normalized weights; see e.g. [13, 14].

For the control plant under consideration three step responses were obtained from environs of the following operation points: $u = 0.092$, $y = 6$; $u = 0.077$, $y = 9.95$; $u = 0.112$, $y = 4.043$. These points were chosen after analysis of the steady–state characteristic of the reference model (one local model per one linear region). The membership functions shown in Fig. 7 were assumed.

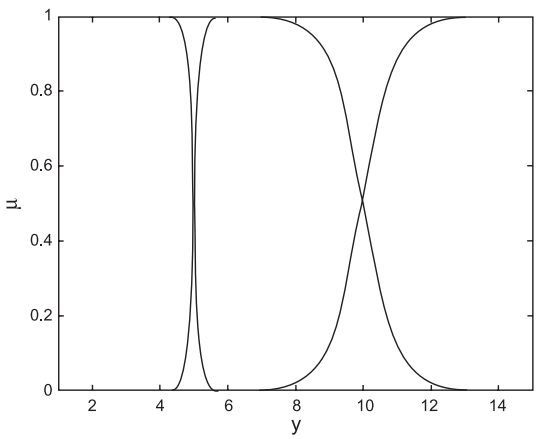

Fig. 7. Membership functions of the TS fuzzy model; μ – membership value, y – glucose concentration (mmol/L)

2.3. Comparison of Models

In case of the linear model (Fig. 8) the step responses differ significantly from the responses of the Hovorka's model. During the experiment the step responses for

four positive changes of the insulin dose: Δu = 0.01 U/L, Δu = 0.02 U/L, Δu = 0.03 U/L and Δu=0.04 U/L and four negative changes Δu = –0.01 U/L, Δu = –0.02 U/L, Δu = –0.03 U/L and Δu = –0.04 U/L were obtained. In the case of changes towards small values of glucose concentration (negative values have actually none biological meaning). On the other hand, responses generated by the fuzzy TS model are much better (Fig. 9 right), despite relative simplicity of the TS model. There are some differences but the model is sufficient for control purposes.

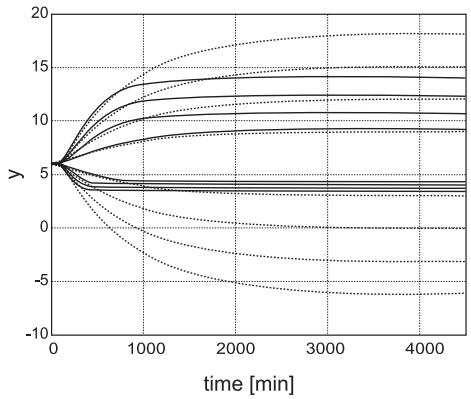

Fig. 8. Step responses of the Hovorka's model (solid lines) and the linear model (dashed lines), y – glucose concentration (mmol/L)

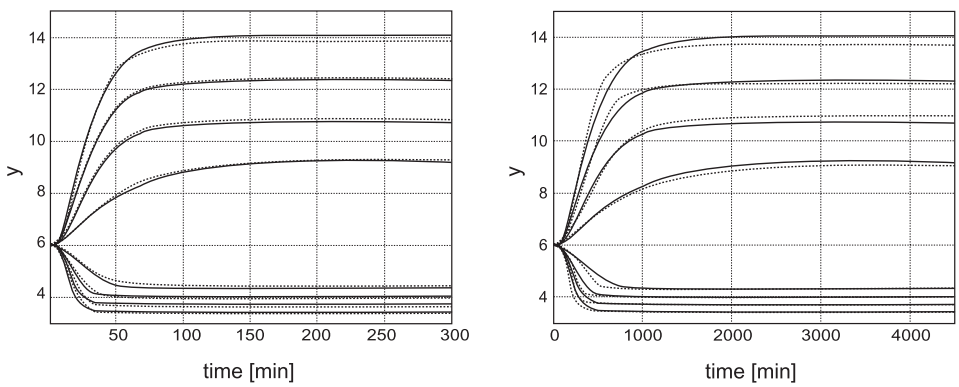

Fig. 9. Step responses of the Hovorka's model (solid lines) and the designed models (dashed lines): left – the neural model, right – the TS fuzzy model, y – glucose concentration (mmol/L)

For comparison, also step responses obtained using the neural model are drawn (Fig. 9 left). Both nonlinear models are much better than the linear model thus the predictive algorithms based on them should be better than those based on linear models, like proposed, e.g. in [18]. The neural model is slightly better tuned than the fuzzy

one. However, in case of the TS fuzzy model much simpler identification procedure was used. Moreover, if needed, the TS model may be easily extended introducing next local model(s) (next step response collected and added to the model).

3. Conclusions and Future Work

The process of glucose concentration changes is highly nonlinear. To model this process both: neural and fuzzy models are used. On the one hand, in comparison with the linear model both classes of models have high accuracy. On the other hand, there are some differences between neural and fuzzy models. Neural models (in this work Multi Layer Perceptron networks are used) are universal approximators which means that a network with at least one hidden layer can approximate any smooth function to an arbitrary degree of accuracy. However, from the practical point of view, good models should be both relatively accurate and moderately complex. That is why topology selection of neural network model is discussed in this paper. Although the RBF (Radial Basis Function) can be also employed for modeling of glucose concentration dynamics as described in [19]. Unfortunately, the RBF networks usually need much more parameters (weights) than the MLP structures of comparable accuracy.

Neural network training is in fact an unconstrained nonlinear optimisation problem. During model structure selection many candidate networks are usually trained. In contrast, the fuzzy model can be designed in relatively easy way by collection of a few step responses of the process and by using expert knowledge to shape membership functions.

As the future work authors plan to use both classes of models in computationally efficient predictive control algorithms in which neural and fuzzy models are successively linearized on-line. These algorithms offer much better control performance than the algorithms based on linear models [17, 20, 11]. Moreover, their closed-loop accuracy is similar to that obtained in predictive control algorithms with full nonlinear optimization repeated on-line. Though simple, such algorithms offer advantages resulting from its prediction capabilities and therefore, if well tuned, outperform non–predictive controllers like e.g. one described in [21].

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