Type 1 Diabetes Regulated by ANFIS at Molecular Levels

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Abstract—**Soft computing based controller is designed for Type 1 diabetes modeled at molecular levels. Rough rule base is generated with subtractive clustering which is followed by its refinement by parameter tuning. As a result, an Adaptive Neuro-Fuzzy Inference System (ANFIS) is created. Simulation results are in accordance with the behavior of the healthy human blood glucose system.**

Keywords—**diabetes, molecular model, subtractive clustering, ANFIS.**

I. Introduction

In many biomedical systems external controller provides the necessary input because the human body could not ensure it. Giving an example, diabetes is one of the most serious diseases that need to be artificially regulated.

The newest statistics of the World Health Organization (WHO) predate more than 1% increase of the number of diabetic patients from 2000 to 2025 and predestinate that 5.4% of the adult society will suffer from it by the year 2025 [1]. This warns that due to stress and unhealthy lifestyle diabetes could be the "disease of the future" (especially in developing countries).

The normal blood glucose concentration in the human body varies in a narrow range (70 - 110 mg/dL). Diabetes appears if for some reason the human body is unable to control the normal glucose-insulin interaction (e.g. blood glucose level is constantly out of the above mentioned range). To design an appropriate control, an adequate model is necessary. In the last decades several models appeared for Type 1 diabetic patients [2]. The most often used are the simplest minimal model of Bergman [3] and the most complex 19th order Sorensen's model [4]. Regarding the applied control strategies for diabetes mellitus, the palette is very wide [5].

The current paper focuses on a newly appeared and promising model [6] that describes the human blood glucose system in general at molecular level. Our aim was to analyze the model's possibilities from control theory point of view. First, the model is presented in Section II, then mathematical background is described in Section III which is followed by the controller design and its simulation results in Section IV.

II. Molecular model

The considered model [6] is approximately halfway from the model of Bergman [3], to the model of Sorensen [4]. It contains eight state variables and the new molecular approach provides more plausible explanations because of biochemical principles. The model can be naturally divided into three subsystems that are presented below and model constants can be found in [6].

A. Transition Subsystem of Glucagon and Insulin

$$\dot{x}_1 = -\left(k_{11}^p + k_{12}^p\right)x_1 + w_1 \tag{1}$$

$$\dot{x}_2 = -\left(k_{21}^p + k_{22}^p\right)x_2 + w_2 + u_1 \tag{2}$$

$$w_1(x_8) = \frac{G_m}{1 + b_1 e^{a_1(x_8 - C_5)}} \tag{3}$$

$$w_2(x_8) = \frac{R_m}{1 + b_2 e^{a_2(C_1 - x_8)}} \tag{4}$$

x_1 and x_2 stand for the concentration of glucagon and insulin in the plasma, respectively. w_1 and w_2 denote glucagon infusion rate and insulin infusion rate of pancreas, whereas u_1 is the concentration of intravenous insulin injected. k_{j1}^p are transitional rates, k_{j2}^p are degradation rates (j = 1,2).

B. Receptor Binding Subsystem of Glucagon and Insulin

$$\dot{x}_3 = -k_{11}^s x_3\left(R_1^0 - x_5\right) - k_{12}^s x_3 + k_{11}^p x_1 V_p V^{-1} \tag{5}$$

$$\dot{x}_4 = -k_{21}^s x_4\left(R_2^0 - x_6\right) - k_{22}^s x_4 + k_{21}^p x_2 V_p V^{-1} \tag{6}$$

$$\dot{x}_5 = k_{11}^s x_3\left(R_1^0 - x_5\right) - k_1^r x_5 \tag{7}$$

$$\dot{x}_6 = k_{21}^s x_4\left(R_2^0 - x_6\right) - k_2^r x_6 \tag{8}$$

x_3 and x_4 denote the concentration of intracellular glucagon and insulin, x_5 and x_6 are the concentrations of glucagon- and insulin-bound receptors, respectively. R_1^0 and R_2^0

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are total concentrations of specific receptors. k_{j1}^{s} stand for association rates for glucagon and insulin to bind their receptors, whereas k_{j2}^{s} are degradation and k_{j}^{r} are inactivation rates (j = 1,2). Plasma insulin volume is V_p, cellular insulin volume is V.

C. Glucose Production and Utilization Subsystem

Plasma glucose production can be classified into two classes: exogenous glucose taken from food and endogenous hepatic glucose by converting glycogen into glucose in liver. To model the endogenous conversion part, the Michaelis-Menten equation is used (see Equation 12 and 13).

- Insulin-independent glucose utilization (brain and nerve cells):

$$f_1(x_8) = U_b\left(1 - e^{-\frac{x_8}{C_2}}\right), \tag{9}$$

where x_8 denotes plasma glucose concentration and U_b stands for maximum velocity of insulin-independent glucose utilization, C_2 is constant.

- Insulin-dependent glucose utilization (fat cells and muscle):

$$f_2(x_8) = \frac{x_8}{C_3}, \tag{10}$$

$$f_3(x_4) = U_0 + (U_m - U_0)\left(\frac{x_4}{C_4}\right)^{\beta}\left[1 + \left(\frac{x_4}{C_4}\right)^{\beta}\right]^{-1}, \tag{11}$$

where U_0 and U_m denote minimum and maximum velocity of insulin-dependent glucose utilization, β, C_3 and C_4 are constants.

The glucose subsystem can be formulated as follows:

$$f_4 = \frac{k_1 x_6}{1 + k_2 x_5}\frac{V_{\max}^{gs} x_8}{K_m^{gs} + x_8}, \tag{12}$$

$$f_5 = k_3 x_5 \frac{V_{\max}^{gp} x_7}{K_m^{g1} + x_7}, \tag{13}$$

$$\dot{x}_7 = f_4 - f_5, \tag{14}$$

$$\dot{x}_8 = -f_4 + f_5 - f_1 - f_2 f_3 + u_2, \tag{15}$$

where x_7 is the concentration of glycogen, v^{gp} and v^{gs} denote the reaction velocities of glycogen phosphorilase and glycogen synthase. $V_{\max}^{gp}$, $V_{\max}^{gs}$, K_m^{gp} and K_m^{gs} are the maximum velocities and Michaelis-Menten constants of glycogen phosphorilase and glycogen synthase, respectively. u_2 denotes exogenous glucose input, f_4 and f_5 stand for conversion of glucose into glycogen and conversion of glycogen into glucose, respectively. k_1, k_2 and k_3 are feedback gains.

III. Methods

In this section main principles of the applied soft computing based controller design are presented. Rough rule base is generated with subtractive clustering [7] which is followed by its refinement by parameter tuning [7], so the final controller is an Adaptive Neuro-Fuzzy Inference System (ANFIS).

In order to simplify the notation we consider simple systems with only one input and one output. The method can be easily generalized for multivariable systems.

The rule base has the form of

$$R_i : \textit{if } x \textit{ is } A_i \textit{ then } \hat{y}_i \textit{ is } B_i \quad i = 1, 2, \ldots, m. \tag{16}$$

D. Subtractive Clustering

Sample points are given in the form (x_i, y_i), $i = 1, 2, \ldots, N$, while raster centers are chosen in the intersection of grid lines in a hypercube containing the teaching data. The subtractive clustering algorithm can be realized as follows:

1. quantization of the variables to the raster centers,
2. initialization (α, β, δ),
3. approximation of the density of sample points based on a potential function M using Euclidean distance and parameter α,
4. cycle:
   - determining the maximum of the potential function with $(\bar{x}_i^*, \bar{y}_i^*)$ center and M_m^* height,
   - updating the potential function by subtracting a Gaussian bell with $(\bar{x}_i^*, \bar{y}_i^*)$ center, M_m^* height and spread determined by parameter β,
   - jump to step 4 if $M_m^* \geq \delta$, otherwise stop.

The generated cluster centers are $N_i^* = (\bar{x}_i^*, \bar{y}_i^*)$ for $i = 1, 2, \ldots, m$ and the rules are

$$R_i : \textit{if } x \textit{ is near } \bar{x}_i^* \textit{ then } \hat{y}_i \textit{ is near } \bar{y}_i^*. \tag{17}$$

In order to characterize "near" Gaussian membership function $\mu_{A_i}(x)$ are defined with $\bar{x}_i^*$ center and $\sigma_i = (2\beta)^{-0.5}$ spread.

After determining the number of the rules (m) and the antecedent membership functions ($\bar{x}_i^*$ and σ_i) with subtractive clustering, consequent membership functions are determined by linear least squares estimation hence $\hat{y}_i = c_{i,1}x + c_{i,0}$ (first order Takagi-Sugeno-Kong fuzzy inference system).

E. Parameter Tuning

In the refinement phase parameters $\bar{x}_i^*$, σ_i, $c_{i,1}$ and $c_{i,0}$ are tuned by optimum seeking methods based on the teach data. With a first order Takagi-Sugeno-Kong fuzzy inference system the approximated output after defuzzyfication can be calculated by

$$\hat{y}(x) = \frac{\sum_{i=1}^{m} \mu_{A_i}(x)\hat{y}_i(x)}{\sum_{i=1}^{m} \mu_{A_i}(x)} = \sum_{i=1}^{m} \tau_i^*(x)\hat{y}_i(x), \qquad (18)$$

so the total error is

$$E_{total} = \sum_{k=1}^{N} \frac{1}{2}[y_k - \hat{y}(x_k)]^2 . \qquad (19)$$

If p is a parameter to be tuned then

$$\frac{\partial E_{total}}{\partial p} = -\sum_{k=1}^{N} e_k \frac{\partial \hat{y}(x_k)}{\partial p}, \qquad (20)$$

where $e_k = y_k - \hat{y}(x_k)$. Regarding Equation 20 only the following gradient vectors have to be determined:

$$\frac{\partial \hat{y}(x_k)}{\partial \bar{x}_i^*} = [\hat{y}_i(x_k) - \hat{y}(x_k)]\tau_i^*(x_k)\frac{x_k - \bar{x}_i^*}{\sigma_i^2}, \qquad (21)$$

$$\frac{\partial \hat{y}(x_k)}{\partial \sigma_i} = [\hat{y}_i(x_k) - \hat{y}(x_k)]\tau_i^*(x_k)\frac{(x_k - \bar{x}_i^*)^2}{\sigma_i^3}, \qquad (22)$$

$$\frac{\partial \hat{y}(x_k)}{\partial c_{i,1}} = \tau_i^*(x_k)x_k, \qquad (23)$$

$$\frac{\partial \hat{y}(x_k)}{\partial c_{i,0}} = \tau_i^*(x_k). \qquad (24)$$

With step length ζ the on-line sequential tuning is performed in the direction of the negative gradient:

$$p^{new} = p + \zeta e_k \frac{\partial \hat{y}(x_k)}{\partial p}. \qquad (25)$$

IV. Results

In this section a fuzzy based controller is presented that can successfully regulate blood glucose in case of Type 1 diabetes mellitus.

Regarding Equation 4 it can be seen that $R_m = 0$ represents failure of pancreatic insulin secretion that characterizes Type 1 diabetes mellitus. Our goal is to learn the function of pancreas and mimic it with an external controller so the blood glucose level of the patient stays in the healthy region.

Concerning diagnostic limitations, only blood glucose level can be easily measured. Consequently, the control algorithm can only use these data as input, and its output is the amount of intravenous insulin to be injected.

Since blood glucose regulation is based on its trend physiologically, more efficient control algorithm can be designed by using a series of input: in our case it is the measured blood glucose level of the previous 10 minutes.

In terms of an ANFIS structure the generated controller has 10 inputs and one output, and teaching resulted in two Gaussian membership functions for the antecedent part for each input variable and two linear membership functions for the consequent part. Only two rules are necessary to learn the function (see Fig. 1), so it can be remarked that the controller is extremely simple.

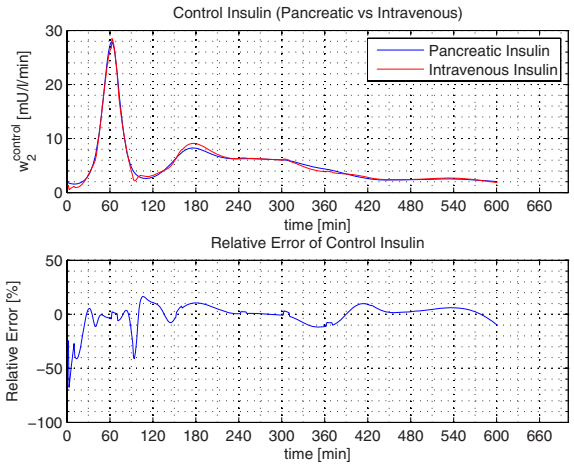

Fig. 1 Insulin secretion of the pancreas and the output of the ANFIS based controller

Since the relative error of the controller output is 50% at some places, completely rightful question is its real performance when using as a regulator of a Type 1 diabetic patient. In order to execute this examination a time threshold is applied: if $t \leq TimeThreshold$ no insulin is injected (neither by the pancreas nor by the controller), after that the controller is switched on. If we do this, we can observe the reliability of the controller, since the test data totally differs from the teach data: the system is different (healthy vs. Type 1 diabetic) and the conditions are completely else (blood glucose level is far out of the range of the teach region).

Simulation results can be seen in Fig. 2 (with *TimeThreshold*=200min), where control insulin and blood glucose level are shown for input adapted from [8]. It can be seen that the controller produces a small plateau and a high peak right after switching on, when the blood glucose level and consequently the error is high. This short and very intense phase is followed by the long and fine control period where smaller amount of insulin is injected. As a result of regulation blood glucose stabilizes at 1000mg/l (normoglycaemic state of the molecular model).

From the aspect of human physiology the results are correct, since healthy regulation contains two significantly different phases: a short and intense period (preparation phase) which is followed by a long-drawn-out tranquility phase. The normal range of blood glucose level after feeding (600-1800mg/l) is reached in less than 80 minutes which is acceptable regarding the fact that the initial value was more than 9400mg/l, which is lethal.

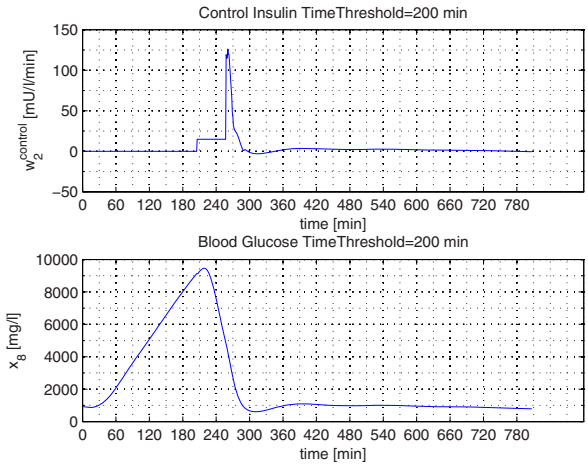

Fig. 2 Output of the controller and blood glucose level

V. Conclusions

In this paper, we examined a new molecular model from the aspect of control theory to regulate the pathologic human blood glucose system in case of Type 1 diabetes. The model is more plausible than its predecessors because of biochemical principles. The mathematical methods of ANFIS were presented and a soft computing based controller was designed for Type 1 diabetic patients. The created controller is simple and efficient since simulation results are in accordance with the behavior of the healthy human blood glucose system.

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