ANFIS Regulated type 1diabetic model for different glucose absorption scenarios

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***Abstract*—The human blood glucose system is one of the most important systems of the human body, as energy transport is fulfilled through this complex endocrine control process. Because of its great importance, many models were published, most of them with phenomenological approach. The current paper focuses on a new molecular model published recently which is capable of describing the normal blood glucose household. Type 1 diabetes can be modeled by transforming the original model, then soft computing based controller is designed. Rough rule base is generated with subtractive clustering which is later followed by its refinement by parameter tuning. As a result, an Adaptive Neuro-Fuzzy Inference System (ANFIS) is designed. A simple absorption model is presented in order to test the designed controller for different absorption curves. Simulation results are in accordance with the behavior of the healthy human blood glucose system.**

I. INTRODUCTION

The normal blood glucose concentration level in the human body varies in a narrow range (80 - 120 mg/dL). Diabetes appears if the human body is unable to control the normal glucose-insulin interaction. Consequences of diabetes are diverse and mostly long-term, for instance increased risk of cardiovascular diseases, neuropathy and retinopathy [1].

The statistics of the World Health Organization (WHO) prognosticates a more than 1% increase of diabetic patients from 2000 to 2025 and predicts that 5.4% of the adult society will suffer from it by the year 2025 [2]. This warns that due to stress and unhealthy lifestyle diabetes could be the "disease of the future" (especially in developing countries).

A. Basic Idea

Type 1 diabetes mellitus can be characterized as the loss of insulin producing beta-cells, since they are completely destroyed. Therefore, there is no human insulin production and an artificial insulin source has to be applied. It has to be controlled by an outer loop, replacing the human glucose-insulin system. The replacement might be partially or fully automatized. Self-regulation has several strict requirements, but once it has been designed it permits not only to facilitate the patient's life suffering from the disease, but using different optimization techniques also to optimize the amount of insulin dosage to be injected.

B. Earlier Results

Blood glucose control is one of the most difficult control problems to be solved in biomedical engineering. One of the main reasons is that patients are extremely diverse in their dynamics and, in addition, their characteristics are time varying. The closed-loop glucose regulation requires three components [3]: glucose sensor; insulin pump; and control algorithm, which is able to determine the necessary insulin dosage.

Modeling the system and controlling its behavior are two tightly connected questions, hence the problems could not be discussed separately. Regarding the applied control strategies for diabetes mellitus, the palette is very wide [3], [4]. Starting from classical control strategies (PID control [5], cascade control [6]), to soft computing techniques (fuzzy methods [7], neural networks [8], neuro-fuzzy methods [9]), adaptive [10], model predictive (MPC), [11], or even robust H_∞ control were already applied, [12], [13]. Most of the applied control methods were focused on the Bergman minimal model [14] (so the applicability of the designed controllers was limited due to excessive sensitivity of the model parameters).

II. MOLECULAR MODEL

In contrast with most of the earlier models the model published in 2008 applies a different approach [15]: it considers enzyme activity of glucose-glycogen and glycogen-glucose conversion and glucose utilization dynamics, however, it is not purely a molecular model. Consequently, the cause-effect relations are more plausible and different functions and processes can be separated. The considered model is approximately halfway from the simplest model of Bergman [14] to the extremely complex model of Sorensen [16] with its 8 state variables and can be naturally divided into three subsystems: the transition subsystem of glucagon and insulin, the receptor binding subsystem and the glucose subsystem. Since the model is published recently and not widely used yet, a brief review is presented here. Parameters can be found in [15].

A. Transition Subsystem

It is assumed that plasma insulin does not act directly on glucose metabolism [15], but through cellular insulin. Let x_1 and x_2 denote concentrations of plasma glucagon and insulin, respectively. Incorporating transition delay, the subsystem can be described with:

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

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

where w_1 and w_2 stand for glucagon and insulin produced by the pancreas.

B. Receptor Binding Subsystem

Let x_3 and x_4 stand for intracellular concentrations of glucagon and insulin, whereas x_5 and x_6 denote concentrations of glucagon- and insulin-bound receptors, respectively:

$$\dot{x}_3 = -k_{11}^s x_3\left(R_1^0 - x_5\right) - k_{12}^s x_3 + k_{11}^p x_1 V_p V^{-1} \tag{3}$$

$$\dot{x}_4 = -k_{21}^s x_4\left(R_2^0 - x_6\right) - k_{22}^s x_4 + k_{21}^p x_2 V_p V^{-1} \tag{4}$$

$$\dot{x}_5 = k_{11}^s x_3\left(R_1^0 - x_5\right) - k_1^r x_5 \tag{5}$$

$$\dot{x}_6 = k_{21}^s x_4\left(R_2^0 - x_6\right) - k_2^r x_6 \tag{6}$$

where R_1^0 and R_2^0 denote total concentrations of receptors, $k_{j,1}^s$ stand for the hormone-receptor association rates, $k_{j,2}^s$ the degradation rates, k_j^r the inactivation rates (j=1,2). Plasma insulin volume is denoted by V_p is plasma volume whereas V is intracellular volume [15].

C. Glucose Subsystem

Blood glucose has two sources: endogenous hepatic production with glycogen transformation and exogenous meal intake.

Exogenous glucose intake is denoted by G_{in}. In order to describe glycogen-glucose conversion by the catalytic effect of glycogen phosphorylase and glycogen synthase Michaelis-Menten equation is used.

Glucose utilization can be divided into two groups: insulin-independent (brain and nerve cells) and insulin-dependent (muscle and adipose tissues).

Insulin-independent part [15] can be modeled by

$$f_1(x_8) = U_b\left(1 - e^{-\frac{x_8}{C_2}}\right) \tag{7}$$

where x_8 denote glucose concentration, U_b and C_2 are parameters described in [15].

Insulin-dependent glucose utilization can be calculated by the product of

$$f_2(x_8) = \frac{x_8}{C_3} \tag{8}$$

$$f_3(x_4) = U_0 + (U_m - U_0)\left(\frac{x_4}{C_4}\right)^{\beta}\left[1 + \left(\frac{x_4}{C_4}\right)^{\beta}\right]^{-1}, \tag{9}$$

where U_m, U_0, C_3, C_4 and β are parameters described in [15].

By modeling glucose-glycogen and glycogen-glucose conversions the glucose subsystem can be described with

$$f_4 = \frac{k_1 x_6}{1 + k_2 x_5}\frac{V_{\max}^{gs} x_8}{K_m^{gs} + x_8} \tag{10}$$

$$f_5 = k_3 x_5 \frac{V_{\max}^{gp} x_7}{K_m^{g1} + x_7}\,, \tag{11}$$

$$\dot{x}_7 = f_4 - f_5\,, \tag{12}$$

$$\dot{x}_8 = -f_4 + f_5 - f_1 - f_2 f_3 + u_2\,, \tag{13}$$

where x_7 denote glycogen concentration, v^{gp}, v^{gs} $V_{\max}^{gp}$, $V_{\max}^{gs}$, K_m^{gp} and K_m^{gs} are parameters described in [15]. Variable 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 [15].

D. Pancreatic Control

Hormones of the pancreas (glucagon and insulin) have a cardinal role in blood glucose regulation and homeostatic stability, since negative feedback of glucagon and insulin through blood glucose level assures controllability (in medical sense):

$$w_1(x_8) = \frac{G_m}{1 + b_1 e^{a_1(x_8 - C_5)}}\,, \tag{14}$$

$$w_2(x_8) = \frac{R_m}{1 + b_2 e^{a_2(C_1 - x_8)}}\,, \tag{15}$$

where $w_1(x_8)$ and $w_2(x_8)$ denote glucagon and insulin infusion rates (total amount of secreted hormone by the pancreas), respectively (GIR and IIR).

E. Physiologic Evaluation

In order to analyze the model in a quantitative manner, a physiologically correct exogenous glucose input has to be defined. A widely used absorption curve can be seen in Fig. 1, which was recorded under extremely strict and precise conditions [17].

It allows us to neglect gut-blood circulation transfer function since it is taken into account by the absorption curve. Since we observe healthy system by now, u_1 input of the model is constant zero (no insulin is injected).

Observing simulation results, it can be seen that the behavior of the system is in accordance with physiologic expectations: the absorption of exogenous glucose is followed by the activation of the insulin pole (Fig. 2) of the regulatory system (0-50 min). Since the main idea of the control mechanism is the dipole structure glucagon secretion of the pancreas increases (Fig. 2) after the insulin phase (50-100 min).

The "two hump" behavior of the system (Fig. 3) is widely known in medical practice and can be seen here as well: the first intense and short phase of hormone secretion is followed by a long and moderate period assuring rapid reaction and precise correction as well.

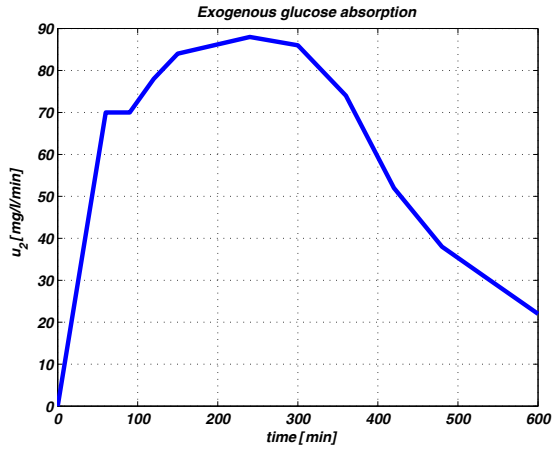

Figure 1. Glucose absorption curve adopted from [17]

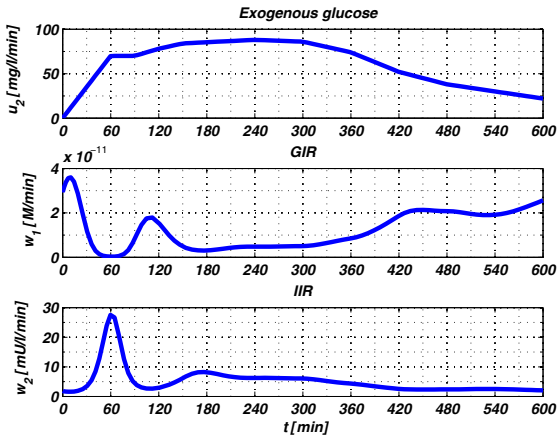

Figure 2. Pancreatic control (GIR and IIR)

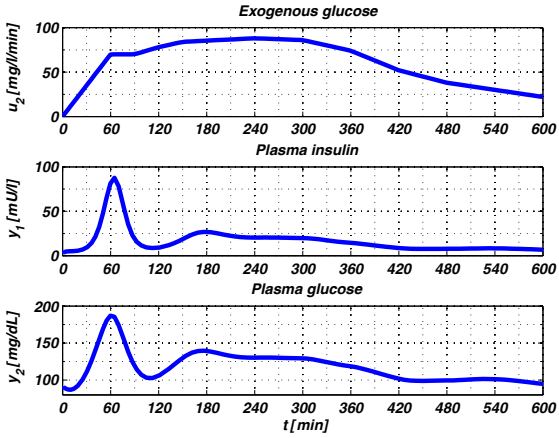

Figure 3. Plasma insulin and plasma glucose if glucose absorption is adopted from [17]

F. Model Transformation

The real purpose of the research is to regulate the pathologic system. In order to fulfill this objective, the model has to be transformed to describe type 1 diabetes mellitus.

Type 1 diabetes mellitus, also called insulin-dependent diabetes mellitus or IDDM is characterized by the loss of insulin producing beta-cells of pancreas due to an autoimmune process. The lack of insulin and unregulated glucagon production result in elevated blood glucose level.

In case of type 1 diabetes mellitus insulin secretion of the pancreas becomes insufficient to regulate blood glucose.

As $w_2(x_8)$ describes the insulin release rate (IIR) of the pancreas, R_m denotes saturation value of pancreatic insulin secretion. In order to model type 1 diabetes mellitus, R_m has to be decreased resulting in unsatisfactory pancreatic insulin secretion.

G. Open-loop Simulation

By setting $R_m = 0$, type 1 diabetes can be modeled. Applying the glucose input presented in Fig. 1 [17], open-loop simulation can be realized (Fig. 4).

Initial conditions are adapted from [1], where $x_2(0) = 2mU/l$, hence plasma insulin is present at the beginning of the simulation.

Observing Fig. 4, it can be seen that with no insulin secretion (open-loop simulation, no feedback is applied) blood glucose level elevates for about 360 minutes to 1500 mg/dL (which is lethal) then decreases as a result of the delayed effect of insulin (by this time plasma insulin is almost zero). Consequently, type 1 diabetes conditions can be created.

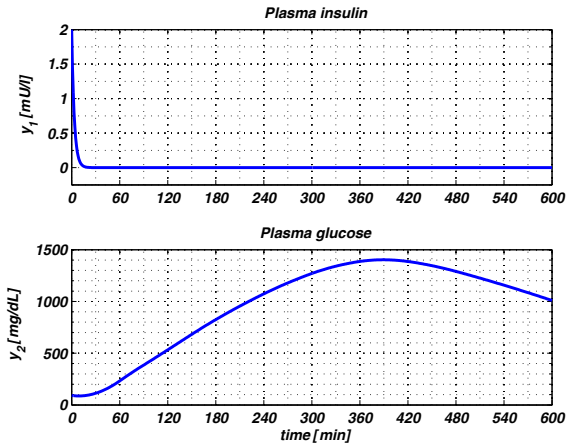

Figure 4. Plasma insulin and plasma glucose in case of type 1 diabetes if glucose absorption is adopted from

III. CONTROLLER DESIGN

Main principles of the applied Soft Computing based controller design are presented in this section [18]. Rough rule base is generated with subtractive clustering, which is followed by its refinement by parameter tuning, hence the final controller is an Adaptive Neuro-Fuzzy Inference System (ANFIS). In order to simplify the notation, methods are presented for SISO systems, but it can be easily generalized for MIMO systems.

A. Subtractive Clustering

The examined rule base is given in the form of

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

Sample points are given in the form of $S_i = (x_i, y_i)$, $i = 1, 2, \ldots, N$, while raster centers $N_{i,j} = \left(x_i^*, y_j^*\right)$ 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. approximation of the density of sample points based on potential function $M : N_{i,j} \to R$:

$$d\left(N_{i,j}, (x_k, y_k)\right) = \left(x_k - x_i^*\right)^2 + \left(y_k - y_j^*\right)^2 , \quad (16)$$

$$M\left(N_{i,j}\right) = \sum_{k=1}^{N} e^{-\alpha d\left(N_{i,j}, (x_k, y_k)\right)} . \quad (17)$$

3. Initialization: $m = 1$, $M_1 = M$ and choice of α, β, and δ,
4. Cycle:

$$M_m^* = \max_{i,j} M_m\left(N_{i,j}\right) \quad (18)$$

$$N_m^* = \arg\max_{x_i^*, y_j^*} \max_{i,j} M_m\left(N_{i,j}\right) = \left(\bar{x}_m^*, \bar{y}_m^*\right) \quad (19)$$

$$M_{m+1}\left(N_{i,j}\right) = M_m\left(N_{i,j}\right) - M_m^* e^{-\beta d\left(N_m^*, N_{i,j}\right)} \quad (20)$$

- jump to step 4 if $M_m^* \geq \delta$, otherwise stop.

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

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

In order to characterize "near" Gaussian membership functions $\mu_{A_i}(x)$ are defined with $\bar{x}_i^*$ center and

$$\sigma_i = (2\beta)^{-0.5} \quad (21)$$

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).

B. 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.:

$$\hat{y}(x) = \frac{\sum_{i=1}^{m} \tau_i(x) \hat{y}_i(x)}{\sum_{i=1}^{m} \tau_i(x)} = \sum_{i=1}^{m} \tau_i^*(x) \hat{y}_i(x) , \quad (22)$$

where firing weights are $\tau_i(x) = \mu_{A_i}(x)$, hence the total error is

$$E_{total} = \sum_{k=1}^{N} \frac{1}{2} \left[y_k - \hat{y}(x_k)\right]^2 . \quad (23)$$

If p is a parameter to be tuned then

$$\frac{\partial E_{total}}{\partial p} = \sum_{k=1}^{N} - e_k \frac{\partial \hat{y}(x_k)}{\partial p} \quad (24)$$

where $e_k = y_k - \hat{y}(x_k)$.

In order to teach the rule base, only the following gradient vectors have to be determined:

$$\frac{\partial \hat{y}(x_k)}{\partial \bar{x}_i^*} = [\hat{y}_i(x_k) - \hat{y}(x_k)]\tau_i^*(x_k)\frac{x_k - \bar{x}_i^*}{\sigma_i^2}, \quad (25)$$

$$\frac{\partial \hat{y}(x_k)}{\partial \sigma_i} = [\hat{y}_i(x_k) - \hat{y}(x_k)]\tau_i^*(x_k)\frac{(x_k - \bar{x}_i^*)^2}{\sigma_i^3}, \quad (26)$$

$$\frac{\partial \hat{y}(x_k)}{\partial c_{i,1}} = \tau_i^*(x_k)x_k, \quad (27)$$

$$\frac{\partial \hat{y}(x_k)}{\partial c_{i,0}} = \tau_i^*(x_k). \quad (28)$$

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

IV. Results

A. Glucose Absorption

In order to observe the real performance and robustness of the designed controller, several different input data should be used. Given the fact that the required input of the Liu-Fusheng model is glucose absorption, which is greatly difficult to measure, the only real input data we have is [17]. Therefore, the authors generated virtual but plausible and realistic absorption data.

Based on theoretical models of absorption [19], the concentration of glucose absorbed can be considered to follow a Weibull curve:

$$g = p_3\left(\frac{t}{p_1}\right)^{p_2}\exp\left(-\left(\frac{t}{p_1}\right)^{p_2}\right) \quad (29)$$

Observing the role of parameters p_1, p_2 and p_3, it can be seen that p_1 corresponds to the input scaling, in other words, it scales the curve along the horizontal axis. Variable p_2 determines the shape of the curve, since it can be interpreted as a time constant of the system, while p_3 scales the curve along the vertical axis. Therefore, the amount of the glucose input can be taken into account by p_3, whereas patient variability can be modeled by p_2. It has to be noted that this method is not to create the precise model of glucose absorption (e.g. the exact quantitative relation between patient variability and p_2; or meal input and p_3 is not determined, although physiological considerations were taken into account) but to generate plausible absorption curves based on [17].

Approximating the absorption curve presented in [17], the following parameters are derived: $p_1 = 344.54$, $p_2 = 1.59$ and $p_3 = 190.49$. The original absorption curve of [17] and the approximated can be seen in Fig. 5.

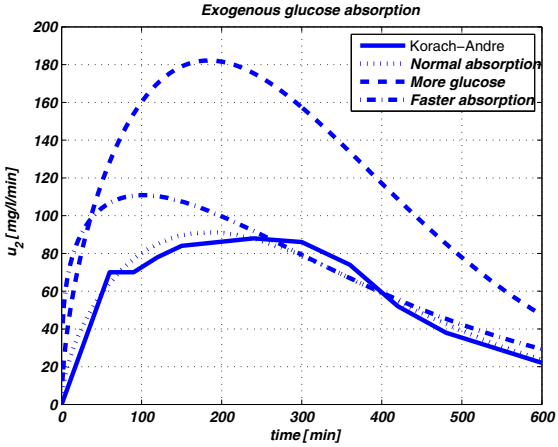

Figure 5. Different absorption curves – adopted from [17]; Weibull-absorption approximating [17], absorption in case of more glucose intake; absorption in case of faster absorption

B. Simulation results

Three different simulation scenarios are presented here:

1. original: $p = [p_1 \quad p_2 \quad p_3]$,
2. more glucose intake: $p = [p_1 \quad p_2 \quad 2p_3]$,
3. faster absorption: $p = [p_1 \quad 0.8p_2 \quad p_3]$.

In order to test the performance of the designed ANFIS controller, it is only switched on after 30 minutes. In other words, in the first 30 minutes the system is unregulated, hence blood glucose level is increasing, as it can be seen in Fig. 6-8.

Closed-loop simulation results for the three different scenarios can be seen in Fig. 6-8. Observing glucose levels, it can be seen that the controller is robust enough in terms of meal disturbance and patient variability, since blood glucose level starts almost instantly decreasing after switching on the controller and stays in the desired range.

As for control insulin, a short and intense peak is followed by a longer and moderate one, hence the "two hump" behavior of the system can be seen, as well as in case of regulated blood glucose level. Therefore, the results are plausible from a physiological aspect.

V. Conclusions

In this paper, the Liu-Fusheng model was presented which is capable of describing the healthy human blood glucose household.

By modifying the pancreatic insulin secretion, the model could be transformed to describe type 1 diabetes mellitus. In order to regulate the pathologic human blood glucose system, an Adaptive Neuro-Fuzzy Inference System was designed. By developing a simple absorption model, different simulation scenarios can be created, hence increased glucose intake and faster absorption can be modeled. The designed ANFIS controller could successfully regulate type 1 diabetes in case of all scenarios.

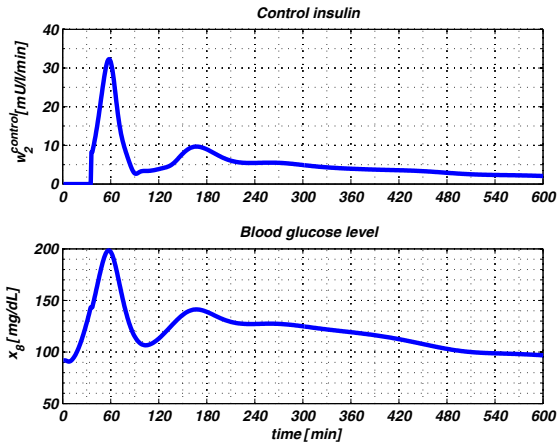

Figure 6. Control insulin and plasma glucose in case of type 1 diabetes and original glucose intake

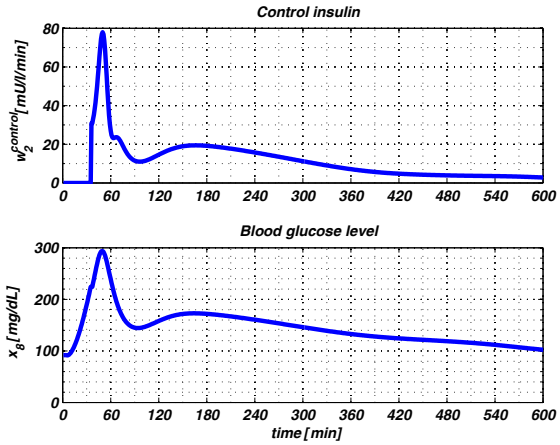

Figure 7. Control insulin and plasma glucose in case of type 1 diabetes and more glucose intake

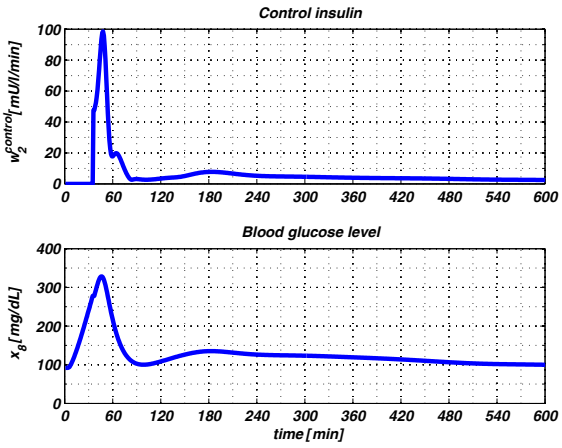

Figure 8. Control insulin and plasma glucose in case of type 1 diabetes and faster absorption

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REFERENCES

[1] A. Fonyó and E. Ligeti, "Physiology," (in Hungarian), 3rd ed., Medicina, 2008.

[2] S. Wild, G. Roglic, A. Green, R. Sicree and H. King, "Global prevalence of diabetes - Estimates for the year 2000 and projections for 2030," *Diabetes Care*, vol. 27, no. 5, pp. 1047–1053, May 2004.

[3] F. Chee and T. Fernando, "Closed-loop control of blood glucose", Springer, Berlin, 2007.

[4] R. S. Parker, F. J. Doyle III and N. A. Peppas, "The intravenous route to blood glucose control. A review of control algorithms for noninvasive monitoring and regulation in type I diabetic patients," *IEEE Engineering in Medicine and Biology*, pp. 65–73, Jan. 2001.

[5] F. Chee, T. L. Fernando, A. V. Savkin and V. van Heeden, "Expert PID control system for blood glucose control in critically ill patients," *IEEE Transactions on Information Technology in Biomedicine*, vol. 7, no. 4, pp. 419–425, Dec. 2003.

[6] M. Ortiz-Vargas and H. Puebla, "A cascade control approach for a class of biomedical systems," in *Proc. 28th IEEE EMBS Ann. Int. Conference*, New York, pp. 4420–4423, Sept. 2006.

[7] M. Ibbini, "A PI-fuzzy logic controller for the regulation of blood glucose level in diabetic patients," *Journal of Medical Engineering and Technology*, vol. 30, no. 2, pp. 83–92, Apr. 2006.

[8] S. G. Mougiakakou, A. Prountzou, D. Iliopoulou, K. S. Nikita, A. Vazeou and Ch. S. Bartsocas, "Neural network based glucose – insulin metabolism models for children with type 1 diabetes," in *Proc. 28th IEEE EMBS Ann. Int. Conference*, New York, pp. 3545–3548, Sept. 2006.

[9] D. Dazzi, F. Taddei, A. Gavarini, E. Uggeri, R. Negro and A. Pezzarossa, "The control of blood glucose in the critical diabetic patient: A neuro-fuzzy method," *Journal of Diabetes and Its Complications*, vol. 15, pp. 80–87, Mar. 2001.

[10] J. Lin, J. G. Chase, G. M. Shaw, C. V. Doran, C. E. Hann, M. B. Robertson, P. M. Browne, T. Lotz, G. C. Wake and B. Broughton, "Adaptive bolus-based set-point regulation of hyperglycemia in critical care," in *Proc. 26th IEEE EMBS Ann. Int. Conference*, San Francisco, pp. 3463–3466, Sept. 2004.

[11] R. Hovorka, V. Canonico, L. J. Chassin, U. Haueter, M. Massi-Benedetti, M. Orsini Federici, T. R. Pieber, H. C. Schaller, L. Schaupp, T. Vering and M. E. Wilinska, "Nonlinear model predictive control of glucose concentration in subjects with type 1 diabetes," *Physiological measurement*, vol. 25, pp. 905–920, Jul. 2004.

[12] L. Kovacs, B. Palancz, B. Benyo, L. Torok and Z. Benyo, "Robust blood-glucose control using *Mathematica*", in *Proc. of 28th Ann. Int. Conf. of IEEE Eng. in Biomedicine Society (EMBC'06)*, 451–454, New York, USA, Sept. 2006.

[13] L. Kovacs and B. Paláncz, "Glucose-insulin control of Type1 diabetic patients in H_2/H_∞ space via Computer Algebra", *Springer Verlag, Lecture Notes in Computer Science*, vol. 4545, pp. 95–109, Jul. 2007.

[14] B. N. Bergman, Y. Z. Ider, C. R. Bowden and C. Cobelli, "Quantitive estimation of insulin sensitivity," *American Journal of Physiology*, vol. 236, pp. 667–677, Jun. 1979.

[15] W. Liu and T Fusheng, "Modeling a simplified regulatory system of blood glucose at molecular levels", *Journal of Theoretical Biology*, vol. 252, pp. 608-620, June 2008.

[16] J. T. Sorensen, "A physiologic model of glucose metabolism in man and its use to design and assess improved insulin therapies for diabetes," PhD Thesis, Dept. of Chemical Eng. Massachusetts Institute of Technology, Cambridge, 1985.

[17] M. Korach-André, H. Roth, D. Barnoud, M. Péan, F. Péronmet and X. Leverve "Glucose appearance in the peripheral circulation and liver glucose output in men after a large 13C starch meal", American Journal of Clinical Nutrition, vol. 80, pp. 881–886, Oct. 2004.

[18] B. Lantos, "Fuzzy systems and genetic algorithms". Muegyetemi, Budapest, 2002.

[19] VK. Piotrovskii, "The use of Weibull distribution to describe the in vivo absorption kinetics", *Journal of Pharmacokinetics and Pharmacodynamics*, vol. 15 no. 6, pp. 681–686, July 1987.