ADAPTIVE GLYCEMIA CONTROL: IMPLEMENTATION IN MATLAB

M. Rebro, M. Tárník

Institute of Robotics and Cybernetics, Faculty of Electrical Engineering and Information Technology, Slovak University of Technology in Bratislava, Ilkovičova 3, 812 19 Bratislava, Slovak Republic

Abstract

Glycemia control is subject of development of Artificial Pancreas for people with type 1 diabetes. Designed control algorithms are tested by means of simulations of insulin-glucose system. The paper presents parameter estimation of Hovorka model using measured CGM data for creating individualized simulators of two specific patients - virtual patients (VP). These simulators are then used to verify designed control algorithm.

1 Introduction

Diabetes [1] is a group of metabolic diseases connected to high blood sugar levels, which are present over prolonged time period. There are two main types of Diabetes, Type 1 Diabetes Mellitus (T1DM) can be called also as insulin-dependent diabetes because the regular administration of insulin is needed due to absolute deficiency of insulin production in pancreas. The other Type 2 Diabetes Mellitus (T2DM) can be caused either by relative deficiency of insulin production (not enough to cover the metabolic needs of cells) or by insulin resistivity of cells, this type of diabetes is often linked to obesity and unhealthy lifestyle.

Maintaining safe levels of blood sugar of T1DM patient depends on administration of right insulin dosage at right time. This can be often difficult because the change of glycemia can be caused either by meal consumption (glycemia rises) or physical activity (glycemia falls) and these changes may depend on even more unknown factors.

Insulin therapy uses subcutaneous insulin of two types to compensate different glycemia rises. Basal insulin is the slow acting one, which compensates glycemia rising caused by endogenous glucose production and its purpose is to make blood sugar levels steady, when there is no disturbance (meal intake) present. Bolus insulin is fast acting and used to compensate glycemia rise, when disturbance is present.

Artificial pancreas is the possible means to unburden T1DM patients from worrying of the right insulin administration. It is the set of devices, which forms closed loop control system of glycemia. Continuous glucose monitoring (CGM) is used to measure glycemia, providing the feedback to control system. Insulin pump provides basal and bolus insulin administration. Both of these devices are connected with microcomputer, which makes decisions of insulin dosage based on glucose measurements. To avoid hypoglycemia, when bolus causes too much decrease of glycemia or maybe when patient does physical activity, artificial pancreas [2] can administrate glucagon, which has opposite effect of insulin-this is called bihormonal artificial pancreas.

Development of control algorithms combined with dependable devices is the key to create artificial pancreas, which could partially mimic a properly functioning biologic pancreas. This paper focuses on designing control algorithm for insulin administration and its testing on individualized T1DM simulator.

2 Hovorka model

Hovorka model [3] is a nonlinear compartment model with two inputs (insulin and glucose intake) and one output (glycemia). Model (Fig. 1) is divided into four subsystems: Glucose

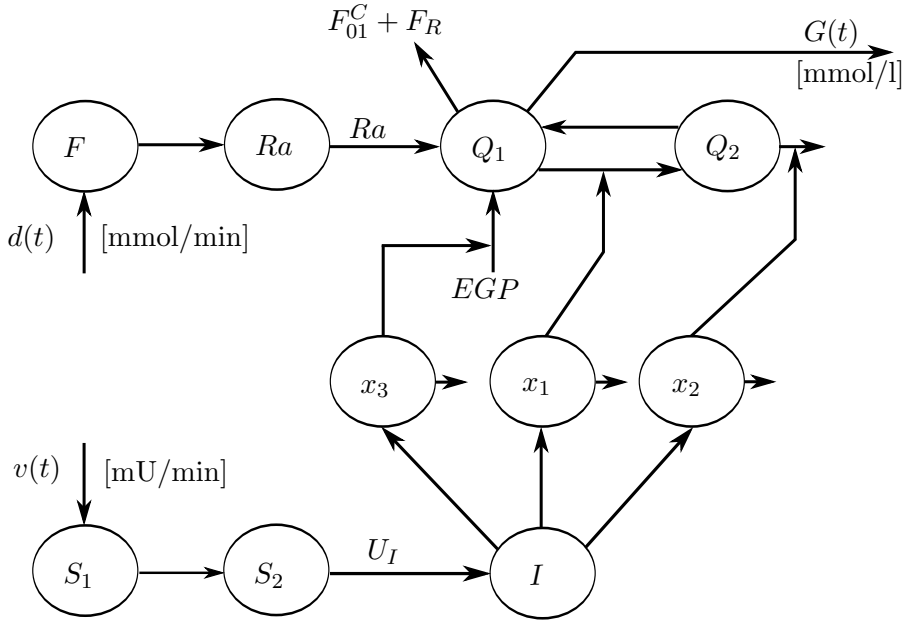


Fig. 1: Graphical representation of Hovorka model

absorption (F, Ra), Insulin absorption (S_1, S_2, I), Insulin action (x_1, x_2, x_3) and Glucose (Q_1, Q_2) subsystem.

Glucose absorption subsystem is described by differential equations:

$$\begin{aligned} \frac{dF(t)}{dt} &= A_G \frac{d(t)}{t_G} - \frac{F(t)}{t_G} \\ \frac{dRa(t)}{dt} &= \frac{F(t)}{t_G} - \frac{Ra(t)}{t_G} \end{aligned} \tag{2.0.1}$$

Where $d(t)$ [mmol/min] is rate of glucose intake - subsystem input, $F(t)$ [mmol/min] is rate of glucose absorption in first compartment, $Ra(t)$ is rate of appearance of glucose in plasma - subsystem output, A_G [-] is carbohydrate bioavailability and t_G [min] is the time constant of this subsystem. Rate of glucose intake is described: $d(t) = D \cdot \delta(t - \tau_G)$, where δ is Dirac impulse function approximation corresponding to sample rate and D [mmol] is glucose amount (1 mg=180 mmol for glucose molecule).

Equations of insulin absorption subsystem are:

$$\begin{aligned} \frac{dS_1(t)}{dt} &= v(t) - \frac{S_1(t)}{t_I} \\ \frac{dS_2(t)}{dt} &= \frac{S_1(t)}{t_I} - \frac{S_2(t)}{t_I} \\ \frac{dI(t)}{dt} &= \frac{S_2(t)}{t_I V_I} - k_I I(t) \end{aligned} \tag{2.0.2}$$

Where $v(t)$ [mU/min] is rate of insulin intake - subsystem input and it is sum of bolus and basal, $v(t) = v_{bas}(t) + v_{bol}(t)$. Bolus insulin administration is modeled same way as glucose intake (Dirac impulses). Signals S_1 and S_2 are state variables describing absorption of subcutaneously administered insulin, t_I [min] is time constant, $I(t)$ [mU/l] is the plasma insulin concentration - subsystem output, V_I [l] is the distribution volume and k_I [min^{-1}] is the fractional elimination rate.

Insulin action subsystem describes three actions of insulin on glucose kinetics:

$$\begin{aligned}\frac{dx_1(t)}{dt} &= k_{b1}I(t) - k_{a1}x_1(t)\\ \frac{dx_2(t)}{dt} &= k_{b2}I(t) - k_{a2}x_2(t)\\ \frac{dx_3(t)}{dt} &= k_{b3}I(t) - k_{a3}x_3(t)\end{aligned} \tag{2.0.3}$$

Where $x_1(t)$ [min^{-1}] is rate of remote effect of insulin on glucose transport, $x_2(t)$ [min^{-1}] elimination and $x_3(t)$ [-] endogenous glucose production. Dynamics of these effects is given by constants: k_{a1} [min^{-1}], k_{a2} [min^{-1}], k_{a3} [min^{-1}] (deactivation rate constants) a k_{b1} [$\text{min}^{-2}\text{mU}^{-1}\text{l}$], k_{b2} [$\text{min}^{-2}\text{mU}^{-1}\text{l}$], k_{b3} [$\text{min}^{-1}\text{mU}^{-1}\text{l}$] (activation rate constants).

Last subsystem is the nonlinear one and describes insulin-glucose interaction dynamics:

$$\begin{aligned}\frac{dQ_1(t)}{dt} &= -\left[\frac{F_{01}^C}{V_G G(t)} + x_1(t)\right]Q_1(t) + k_{12}Q_2(t) - F_R + Ra(t) + EGP_0[1 - x_3(t)]\\ &= -(F_{01}^C + F_R) - x_1(t)Q_1(t) + k_{12}Q_2(t) + Ra(t) + EGP_0[1 - x_3(t)]\\ \frac{dQ_2(t)}{dt} &= x_1(t)Q_1(t) - [k_{12} + x_2(t)]Q_2(t)\end{aligned} \tag{2.0.4}$$

Where Q_1, Q_2 represent the masses of glucose in the accessible (where glycemia measurements are made) and non-accessible compartments, k_{12} [min^{-1}] is the transfer rate constant from Q_2 to Q_1. Glycemia (the model output) is given by:

$$G(t) = \frac{Q_1(t)}{V_G} \tag{2.0.5}$$

Where V_G [l] is glucose distribution volume. F_{01}^C [mmol/min] represents total non-insulin dependent glucose flux.

$$F_{01}^C = \begin{cases} F_{01} & G(t) \geq 4.5 \text{ mmol/l} \\ F_{01}G(t)/4.5 & \text{otherwise} \end{cases} \tag{2.0.6}$$

F_R [mmol/min] represents renal glucose clearance above the glucose concentration threshold of 9 mmol/l:

$$F_R = \begin{cases} 0.003(G(t) - 9)V_G & G(t) \geq 9 \text{ mmol/l} \\ 0 & \text{otherwise} \end{cases} \tag{2.0.7}$$

There are 15 parameters in Hovorka model - H_p. Individualization of simulator is then estimation of these parameters, using the CGM data of specific Diabetes patients.

Estimation of whole set of parameters H_p is done by estimation of two parts of the set [4]. First part H_{p1} is set of parameters used in insulin absorption subsystem and the estimation of these parameters was done by using specific insulin - Aspart [6] pharmacokinetics (PK) data ($I_{FK}(t)$) and by solving the quadratic optimization problem:

$$\min_{H_{p1}} \; ||I_{PK} - I(H_{p1})||^2 \tag{2.0.8}$$

Insulin dosage used in PK measurement experiment was 15 U, which corresponds to subsystem input of 3 U/min over the time period of 5 minutes (sample time).

The other 12 parameters - H_{p2} were estimated as two sets on the basis of two sets of CGM data. Both datasets represents one day of T1DM patient, so this way we get two sets of

Table 1: First identified set of parameters - H_{p1}

t_I [min]	V_I [l]	k_I [l/min]
50.99	5.357	0.2383

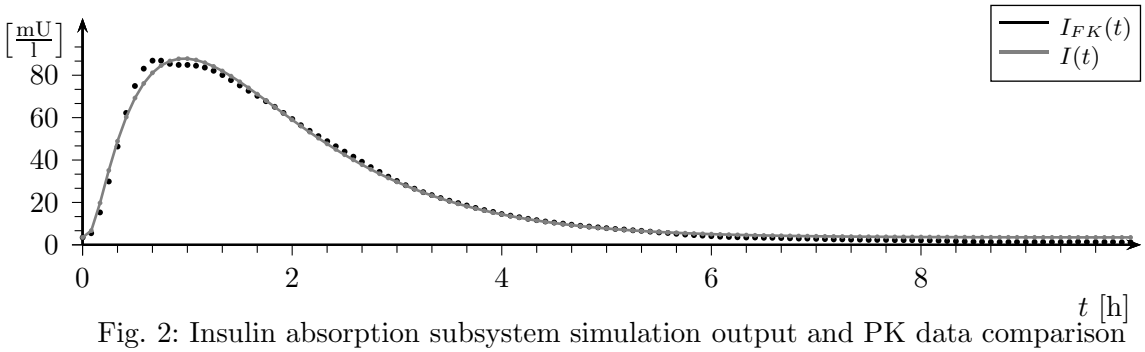


Fig. 2: Insulin absorption subsystem simulation output and PK data comparison

individualized parameters for simulator (virtual patient). Parameter identification was done by solving optimization problem:

$$\min_{H_{p2}} \; ||G_{CGM} - G(H_{p2}))||^2 + [25(G_{bCGM} - G_b(H_{p2}))]^2 + [0.8(\bar{G}_{CGM} - \bar{G}(H_{p2})]^2 \qquad (2.0.9)$$

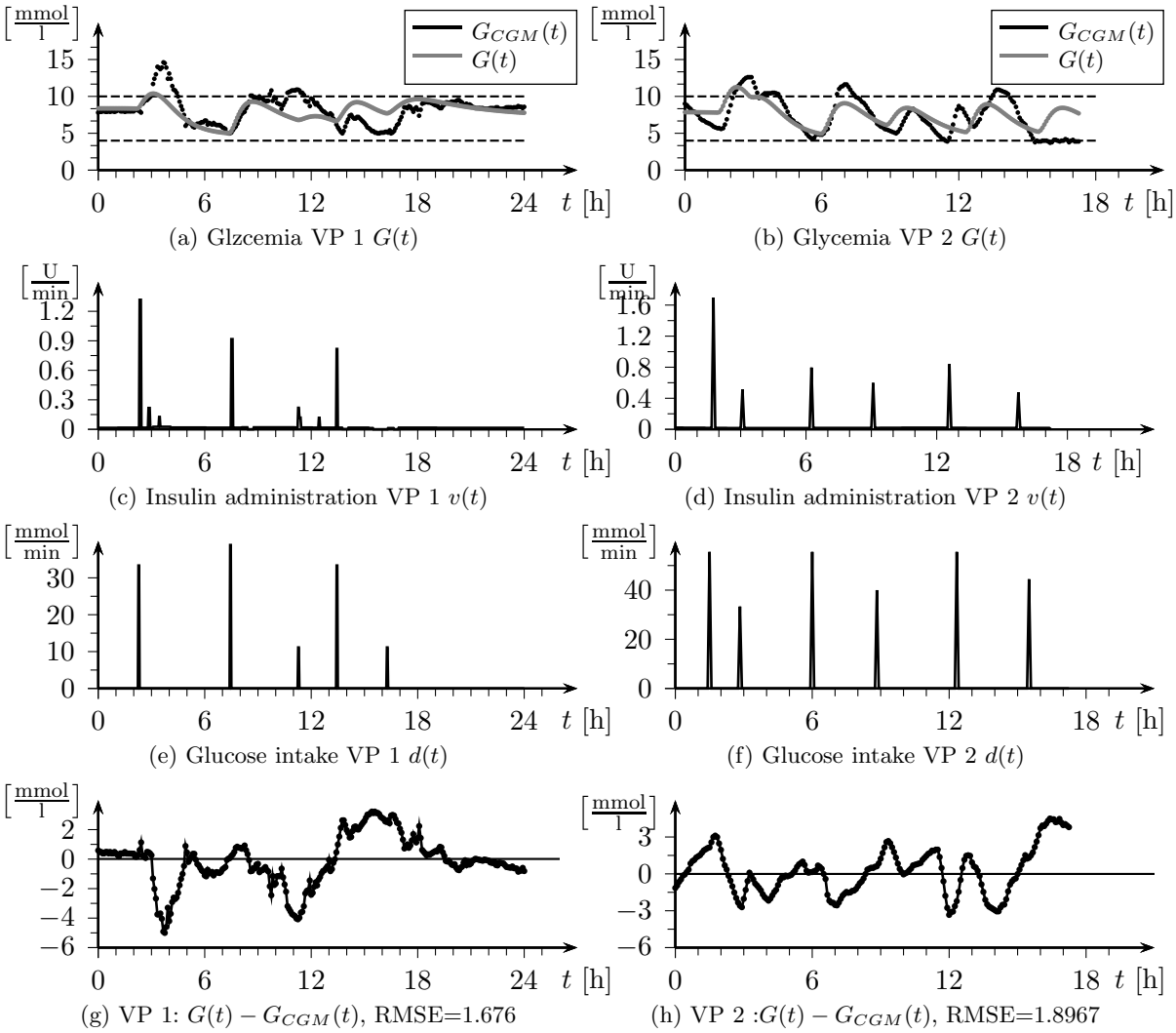
Table 2: Set of remaining identified parameters - H_{p2}

parameter [rozmer]	VP 1	VP 2
A_G [-]	0.67	0.43
t_G [min]	28.583	24.012
k_{12} [min^{-1}]	0.0815	6.651
V_G [l]	12.069	12.424
EGP_0 [mmol/min]	1.0361	1.1978
F_{01} [mmol/min]	0.8507	0.9759
k_{b1} [$\text{min}^{-2}\text{mU}^{-1}\text{l}$]	3.429×10^{-3}	9.644×10^{-3}
k_{b2} [$\text{min}^{-2}\text{mU}^{-1}\text{l}$]	7.08×10^{-6}	1.9937×10^{-5}
k_{b3} [$\text{min}^{-1}\text{mU}^{-1}\text{l}$]	5.713×10^{-4}	2.4288×10^{-4}
k_{a1} [min^{-1}]	7.372	1.4482
k_{a2} [min^{-1}]	2.145×10^{-3}	1.742×10^{-3}
k_{a3} [min^{-1}]	0.866	42.486

3 Control design

Due to possibility of variety of model parameters, model reference adaptive control (MRAC) is proposed as the control algorithm [4]. Control objectives are: closed loop stability and maintaining glycemia in range 4-10 mmol/l with emphasis on avoiding the state of hypoglycemia (<4 mmol/l). There are multiple assumptions about controlled process model in Lyapunov approach. One of them is that, process model is linear, with known relative degree and sign of gain. Therefore the linear approximation of Hovorka model, in specific operating point of basal values of insulin and glycemia (v_b,G_b) is needed. The most simple model structure with satisfying precision found, is of degree 3 and relative degree 2:

$$y(t) = \frac{B_{Cv}(s)}{A_C(s)}u(t) + \frac{B_{Cd}(s)}{A_C(s)}d(t) \qquad (3.0.1)$$



(a) Glzcemia VP 1 $G(t)$

(b) Glycemia VP 2 $G(t)$

(c) Insulin administration VP 1 $v(t)$

(d) Insulin administration VP 2 $v(t)$

(e) Glucose intake VP 1 $d(t)$

(f) Glucose intake VP 2 $d(t)$

(g) VP 1: $G(t) - G_{CGM}(t)$, RMSE=1.676

(h) VP 2 :$G(t) - G_{CGM}(t)$, RMSE=1.8967

Fig. 3: Hovorka model parameters - identification results

If degree of polynomial $B_{Cd}(s)$ is less or equal to degree of $B_{Cv}(s)$, then we can this model express as:

$$y(t) = \frac{B_{Cv}(s)}{A_C(s)} \left(u(t) + \frac{B_{Cd}(s)}{B_{Cv}(s)} d(t) \right) \tag{3.0.2}$$

Linear system, for which we can use well known output feedback MRAC with relative degree of two, will be:

$$G_{Cv}(s) = \frac{B_{Cv}(s)}{A_C(s)} \tag{3.0.3}$$

Control input is then $u(t)$ [mU/min] and term

$$u_d(t) = \frac{B_{Cd}(s)}{B_{Cv}(s)} d(t) \tag{3.0.4}$$

represents disturbance input and $d(t)$ [mmol/min] is glucose intake.

The relative degree of the controlled system is two, so the augmented error method is used. Also, to ensure robustness due to nonlinearity of actual process and possible disturbance inputs, a switching σ-modification and normalization of adaptive law is added.

As we can see from terms 3.0.1 and 3.0.2, degrees of $B_{Cd}(s)$ are $B_{Cv}(s)$ the same. Now lets assume that poles and zeros of linear disturbance model are close enough to approximate this transfer function with simple gain. The online identification of this gain then could provide us with adaptive disturbance rejection. This disturbance can be written as

$$u_d(t) = \Theta_d(t)d(t) \tag{3.0.5}$$

where $\Theta_d(t)$ is parameter to adapt. Output feedback MRAC will in this case control administration of basal insulin (because it does not count with disturbances) and adaptive disturbance rejection will control bolus administration.

Total insulin administration will then be:

$$v(t) = u(t) + v_b - u_d(t) \tag{3.0.6}$$

Using the error $y(t) - y_m(t)$, where y_m is reference model output, the proposed adaptive law for disturbance rejection is

$$\begin{aligned} \dot{\Theta}_d(t) &= -\frac{\gamma d(t)[y(t) - y_m(t)]}{1 + d^2(t)} - \sigma_d(t)\gamma\Theta_d(t) \\ \sigma_d(t) &= \begin{cases} 0 & \text{if } |\Theta_d(t)| \leq M_{0d} \\ \left(\frac{|\Theta_d(t)|}{M_{0d}} - 1\right)^{q_0} \sigma_{0d} & \text{if } M_{0d} < |\Theta_d(t)| \leq 2M_{0d} \\ \sigma_{0d} & \text{if } |\Theta_d(t)| > 2M_{0d} \end{cases} \end{aligned} \tag{3.0.7}$$

where γ, M_{0d}, σ_{0d} are adaptive law parameters. Since the signal $d(t)$ (glucose intake) is present during the day as Dirac impulses with specific area, adaptation of $\Theta_d(t)$ can take some time to have desired effect. Simulations of both virtual patients gave us mean values of this parameter. Using this value as the initial for $\Theta_d(t = 0) = -16$, gave an overall better results.

4 Simulation results

Performance of designed MRAC is evaluated by graphical comparison of simulation results and CGM data, where CGM data represent manual insulin infusion, see Fig. 4. Times spent in hypoglycemia/hyperglycemia, i.e. T_{hypo}, T_{hyper}, and minimum/maximum values of glycemia, i.e. G_{min}, G_{max}, are used for further quantification of control performance, see Tab. 3 and 4. There is also shown performance of MRAC, when used without adaptive disturbance rejection (ADR), to give us better idea of, how this addition is important for better control performance.

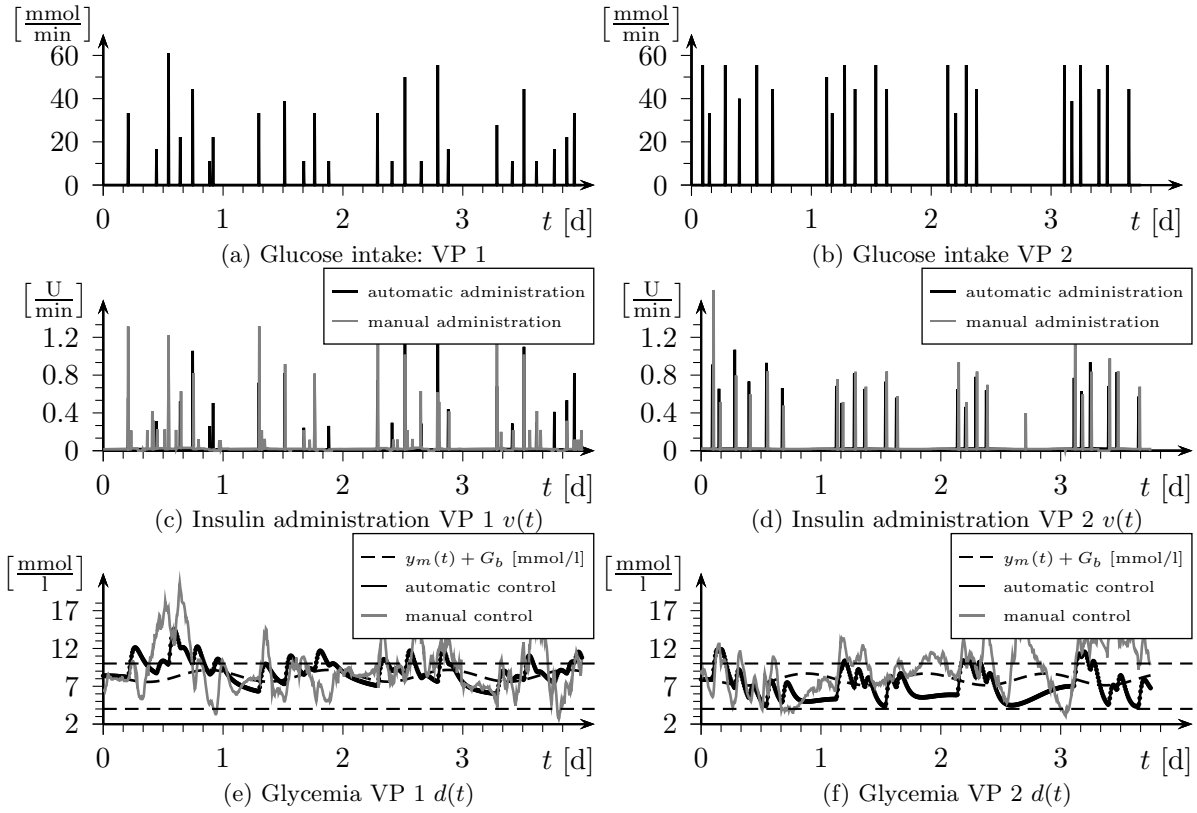
Table 3: Control performance comparison: VP 1

	manual	MRAC without ADR	MRAC with ADR
G_{min} [mmol/l]	2.7	5.46	6.0
G_{max} [mmol/l]	19.25	20.01	13.5
T_{hypo} [h]	1.42	0.0	0.0
T_{hyper} [h]	28.25	30.17	22.17

To test the robustness of designed control, the set of virtual patients is created by reasonable random changes in model parameters. Control algorithm is tested for these virtual patients and its performance is evaluated by means of error grid analysis, where the light area means the best control performance and the dark area means unsatisfactory control performance, see Fig. 5.

Table 4: Control performance comparison: VP 2

	manual	MRAC without ADR	MRAC with ADR
G_{min} [mmol/l]	3.1	3.76	4.34
G_{max} [mmol/l]	18.4	16.27	11.87
T_{hypo} [h]	2.58	1.25	0.0
T_{hyper} [h]	38.58	23.25	8.5



(a) Glucose intake: VP 1
(b) Glucose intake VP 2
(c) Insulin administration VP 1 $v(t)$
(d) Insulin administration VP 2 $v(t)$
(e) Glycemia VP 1 $d(t)$
(f) Glycemia VP 2 $d(t)$

Fig. 4: Simulation results of designed control for VP 1 and VP 2

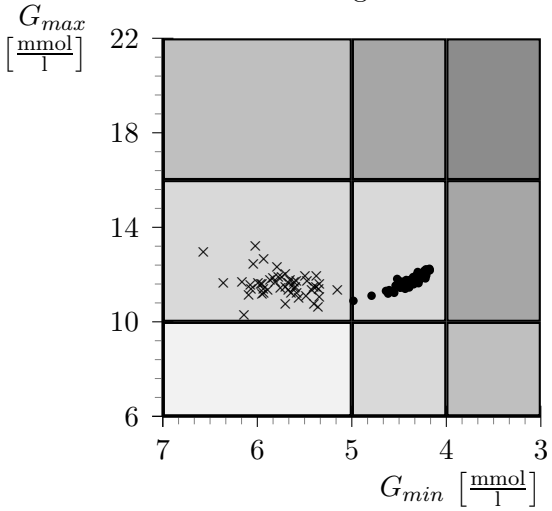


Fig. 5: Grid analysis of designed control for VP 1 (cross) and VP 2 (dot)

5 Conclusion

This paper presents the the individualization of two T1DM insulin-glucose simulators in form of Hovorka model parameters identification. This way, two virtual patients are obtained for design and testing of glycemia control. Proposed control algorithm is in form of MRAC with adaptive

disturbance rejection, using CGM measurements and information about carbohydrate amounts in meals. Simulation results are compared with measured CGM data with aim of performance evaluation. Automatic control showed better results than the manual one and was able to operate even when model parameter variation was present, showing the robustness of designed control. Since this approach is counting on patient input of meal carbohydrate information, this controller is not autonomous and thus does not unburden T1DM patient completely. The control objective of maintaining glycemia in range 4-10 mmol/l was not ultimately achieved, but the state of hypoglycemia was never reached. Adaptive control shows promising results in glycemia control and different approaches for control design could better the performance.

References

[1] WHO. (2014) Diabetes Fact sheet.
Online at `http://www.who.int/mediacentre/factsheets/fs312/en/`.

[2] Firas H. El-Khatib, Steven J. Russell, Kendra L. Magyar, Manasi Sinha, Katherine McKeon, David M. Nathan, and Edward R. Damiano. Autonomous and Continuous Adaptation of a Bihormonal Bionic Pancreas in Adults and Adolescents With Type 1 Diabetes. J Clin Endocrinol Metab, May 2014, 99(5):1701–1711.

[3] Roman Hovorka, Valentina Canonico, Ludovic J. Chassin, Ulrich Haueter, Massimo Massi-Benedetti, Marco Orsini Federici, Thomas R. Pieber, Helga C. Schaller, Lukas Schaupp, Thomas Vering and Malgorzata E. Wilinska. Nonlinear model predictive control of glucose concentration in subjects with type 1 diabetes. In Physiol. Meas. 25 905–920. 2004. doi:10.1088/0967-3334/25/4/010. Online at `http://stacks.iop.org/PM/25/905`.

[4] Matúš Rebro. 2015. Automated insulin administration, Masters Thesis, Slovak University of Technology,Faculty of Electrical Engineering and Information Technology

[5] Lalo Magni, Ph.D., Davide M. Raimondo, M.S., Chiara Dalla Man, Ph.D., Marc Breton, Ph.D., Stephen Patek, Ph.D., Giuseppe De Nicolao, Ph.D., Claudio Cobelli, Ph.D., and Boris P. Kovatchev, Ph.D.. Evaluating the Efficacy of Closed-Loop Glucose Regulation via Control-Variability Grid Analysis. Journal of Diabetes Science and Technology Volume 2, Issue 4, July 2008 © Diabetes Technology Society

[6] S R Mudaliar, F A Lindberg, M Joyce, P Beerdsen, P Strange, A Lin and R R Henry. Insulin aspart (B28 asp-insulin): a fast-acting analog of human insulin: absorption kinetics and action profile compared with regular human insulin in healthy nondiabetic subjects. doi: 10.2337/diacare.22.9.1501 Diabetes Care September 1999 vol. 22 no. 9 1501-1506

Matúš REBRO
matus.rebro@stuba.sk

Marián TÁRNÍK
marian.tarnik@stuba.sk