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Model Reference Adaptive Control of Glucose in Type 1 Diabetics: A Simulation Study ⋆

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Abstract: Paper presents the model reference adaptive control applied for the glucose concentration control in Type 1 diabetes mellitus (T1DM) subject. The adaptive controller structure allows to present the commanded insulin infusion by means of the basal infusion rate and the bolus insulin doses. T1DM simulation model is adjusted so that the simulated output corresponds to the particular data logged in a diabetic diary. These facts have allowed to compare the obtained results with the data logged in the diary.

Keywords: model reference adaptive control, type one diabetes mellitus, diabetic diary

1. INTRODUCTION

System for an automated insulin administration for a Type 1 Diabetes Mellitus (T1DM) subject is currently under intense research. One of the sections at the 18th World Congress of the International Federation of Automatic Control (IFAC) was entitled *Modeling and control for the artificial pancreas: A new era in glucose regulation of people with type 1 diabetes mellitus*. Also this fact indicates that the research intensity of control algorithms of the blood glucose concentration control has grown in recent years.

The Artificial Pancreas is a closed-loop system for maintaining normoglycemia in type one diabetic subjects Magni et al. (2007). It is called so due to its potential to regulate the blood glucose levels similarly as a pancreas in a healthy subjects De Nicolao et al. (2011). Such a system consists of several main parts.

Continuous Glucose Monitoring (CGM) system have became commercially available in recent years. These systems are based on the minimally invasive subcutaneous measurement. This has opened the way to the automated treatment of type one diabetes mellitus, which is suitable for everyday's life De Nicolao et al. (2011). In the closed-loop system the subcutaneous CGM device plays the role of sensor. A subcutaneous insulin delivery systems or an insulin pumps have been used in the everyday practice even longer time. The insulin pump serves as an actuator of the artificial pancreas.

The third integral part of the artificial pancreas is the control algorithm itself. In recent years the *in silico* trials and simulations play an important role in the development and evaluation of different control algorithms for the artificial pancreas Herrero et al. (2013). Such the simulations are based on a large-scale T1DM model, the description of which may be found for instance in Man et al. (2006); Lehmann et al. (2011); Wilinska and Hovorka (2008); Eren-Oruklu et al. (2009), and their references. On the other hand, the control algorithm design itself is usually based on the less complex model, for example see Ben Abbes et al. (2011).

In this paper, the model by Chara Dalla Man and coworkers is considered, see De Nicolao et al. (2011), and used as a T1DM simulator. T1DM simulator is adjusted so that the simulated output corresponds to the particular data logged in a diabetic diary by the T1DM subject. Consequently, the adaptive controller, based on a Model Reference Adaptive Control (MRAC) theory, for example see Tárník and Murgaš (2011), as a part of the simulated closed-loop system is evaluated by means of the adjusted T1DM simulator. The same meal protocol as logged in the diabetic diary is considered in the closed-loop system simulation. This allows to compare the insulin administration provided by the T1DM subject itself with the insulin infusion commanded by the adaptive controller.

2. DIABETIC DIARY

This section summarizes the data logged in the diabetic diary which are consequently used for the T1DM simulator adjustment.

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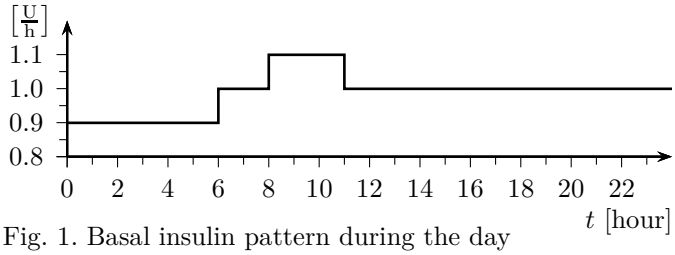

Fig. 1. Basal insulin pattern during the day

The body weight $BW = 75$ [kg] is considered. The subject uses the insulin pump with the Actrapid type insulin. Total amount of the basal insulin per day is approximately 24 [U] which implies the mean rate of the basal insulin 1 [U/h]. However the basal insulin rate is not constant during the day. The so-called *basal pattern* reflects the insulin demand during the day which is also related to the insulin sensitivity variance. The basal pattern is given in Table 1 and graphically shown in Fig. 1.

The considered diary is not a typical diabetic diary due to the number of records per day. Typically three to four records per day are taken. In this case the number of records per day is higher.

Glycemia or the concentration of glucose in the blood is measured in milimol per liter [mmol/l]. The conversion ratio between two common Glycemia units, i.e. mmol/l and mg/dl is 1 [mmol/l] = 18 [mg/dl]. The food intake is recorded in grams [g] of carbohydrates. Finally, the insulin bolus is also logged in the diary. The diabetic diary data are given in Table 2. For convenience, the data are also graphed in Fig. 2.

3. T1DM SIMULATOR ADJUSTMENT

There are two primary information in the diabetic diary that can be directly used for the model adjustment. First the body weight of the subject. In this case the subjects' body weight is close to the model default value (78 kg) Man et al. (2006). Nevertheless, $BW = 75$ [kg] is used in the adjusted T1DM model.

Further the Actrapid type insulin is used as mentioned above. Therefore the corresponding subsystem of the model has to be adjusted to represent this type of insulin. Particularly the subcutaneous insulin kinetics subsystem since the time the insulin takes to reach the circulatory apparatus is given by this subsystem. The subsystem equations are in the form, see Man et al. (2007)

$$\dot{S}_1(t) = -\left(k_{a1} + k_d\right) S_1(t) + v(t) \tag{1a}$$

$$\dot{S}_2(t) = -k_{a2} S_2(t) + k_d S_1(t) \tag{1b}$$

$$S_c = k_{a1} S_1(t) + k_{a2} S_2(t) \tag{1c}$$

where $v(t)$ [pmol/kg/min] is the insulin infusion, $S_1(t)$ [pmol/kg] and $S_2(t)$ [pmol/kg] denote the amount of insulin in the compartments (see Magni et al. (2007)) and rate constants k_{a1}, k_d, k_{a2} are the subsystem parameters.

Table 1. Basal insulin pattern

time of the day	basal insulin rate [U/h]
⟨00:00 – 06:00)	0.9
⟨06:00 – 08:00)	1
⟨08:00 – 11:00)	1.1
⟨11:00 – 24:00)	1

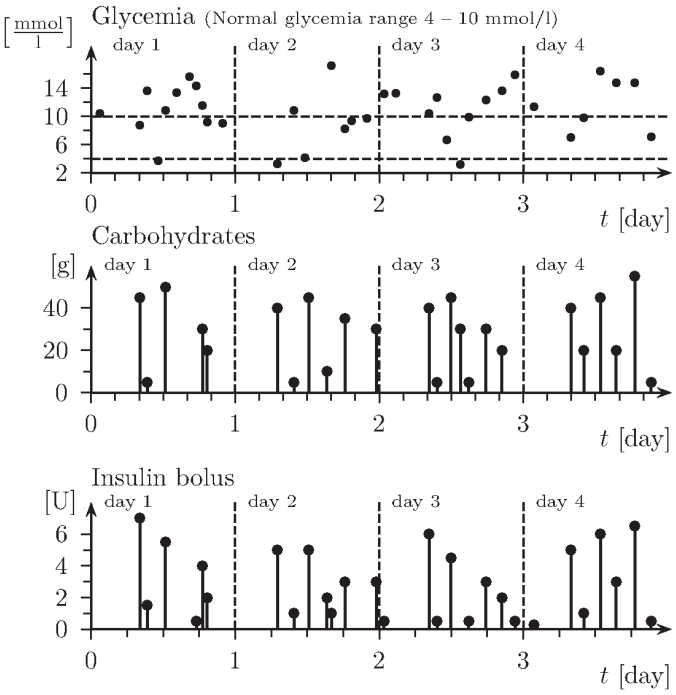

Fig. 2. Diabetic Diary — March

Insulin flow $S_c(t)$ [pmol/kg/min] is leaving the subsystem. Nevertheless, the structure of the subsystem remains unchanged. Only the parameters are adjusted.

The pharmacokinetic profile of Actrapid insulin is reported in European Medicines Agency (2006), Fig 5. The pharmacokinetics has been studied in three studies. Insulin were given subcutaneously at 0.1 U/kg in one study and at 0.2 U/kg in two studies. In this section we consider the dose of 0.2 U/kg. The time evolution of the mean serum insulin concentration [mU/l] is reported in European Medicines Agency (2006). Data are shown in Fig. 3.

Table 2. Diabetic Diary. D – number of the day; T – time of the day; G – Glycemia [mmol/l]; C – Carbohydrates [g]; B – Bolus insulin [U]

D	T	G	C	B	D	T	G	C	B
	1:26	10.4				0:47	13.2		0.5
	8:07	8.8	45	7		2:45	13.3		
	9:21	13.6	5	1.5		8:19	10.4	40	6
	11:10	3.7				9:38	12.7	5	0.5
	12:23	10.9	50	5.5		11:13	6.7		
1	14:13	13.4			3	11:55		45	4.5
	16:21	15.6				13:32	3.2	30	
	17:31	14.3		0.5		14:56	9.9	5	0.5
	18:33	11.6	30	4		17:46	12.4	30	3
	19:19	9.2	20	2		20:25	13.7	20	2
	21:53	9				22:38	15.9		0.5
	7:01	3.3	40	5		1:45	11.4		0.3
	9:48	10.9	5	1		7:58	7	40	5
	11:34	4.2				10:05	9.8	20	1
	12:15		45	5	4	12:51	16.4	45	6
	15:16		10	2		15:27	14.8	20	3
2	16:02	17.2		1		18:36	14.8	55	6.5
	18:19	8.2	35	3		21:19	7.1	5	0.5
	19:24	9.4							
	21:55	9.7							
	23:30		30	3					

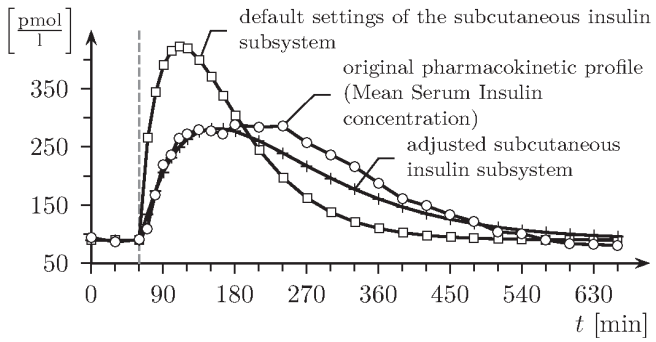

Fig. 3. Pharmacokinetic profile of Actrapid, insulin human. Comparison of the original data from European Medicines Agency (2006) with the model output.

The insulin is given at time $t = 60$ minutes. Further, the original data in insulin units [mU] are converted to picomols using the conversion ratio 1 mU = 6 pmol of insulin.

The pharmacokinetic profile corresponds to a part of model which consist of Subcutaneous Insulin Kinetics Subsystem and Insulin Subsystem. Input is the signal $v(t)$ [pmol/kg/min] and the output is the plasma insulin concentration $I(t)$ [pmol/l]. This part of the model is schematically shown in Fig. 4. However the parameters of insulin subsystem remain unchanged with model default values. As mentioned only the subcutaneous insulin parameters are adjusted.

The signal $v(t)$ [pmol/kg/min] is considered in the form

$$v(t) = v_i(t) + v_b \tag{2}$$

where v_b is the basal subcutaneous insulin infusion rate. In the view of (1), it follows that in the steady state $v_b = S_{cb}$,where S_{cb} is the steady state value of the signal $S(t)$, i.e. the subcutaneous insulin subsystem does not influence the basal concentration of the insulin.

The basal insulin concentration is $I_b = 90$ [pmol/l], see Fig. 3. It can be shown that

$$S_{cb} = I_b V_I \left(m_2 + m_4 - \frac{m_1 m_2}{m_1 + m_{3b}} \right) \tag{3}$$

where the analogous notation as in Man et al. (2007) is used. Consequently $S_{cb} = v_b = 2.178$ [pmol/kg/min]. This value is used when comparing the simulated plasma insulin concentration with the original pharmacokinetic profile.

Signal $v_i(t)$ in the equation (2) represents the insulin administration other than the basal insulin. The signal is in the form $v_i(t) = B_i \delta(t)$, where B_i [pmol/kg] is the amount of given insulin and $\delta(t)$ is a Dirac impulse approximation. In this case 0.2 U/kg of insulin implies 15 insulin units, therefore $B_i = 1200$ [pmol/kg].

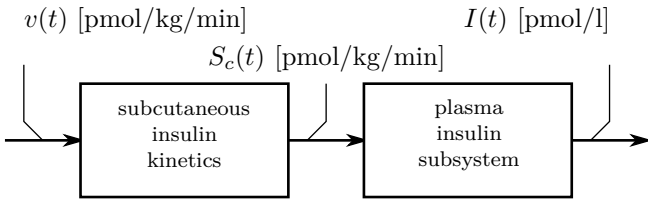

Fig. 4. Part of the considered model which corresponds to the insulin pharmacokinetic profile.

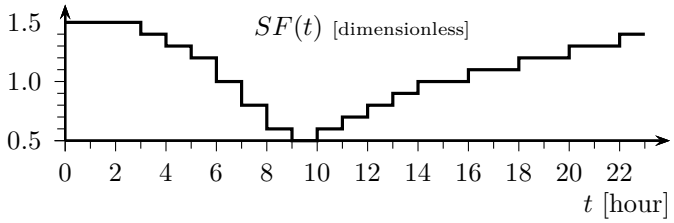

Fig. 5. Sensitivity factor $SF(t)$ which determines the time-variant peripheral insulin sensitivity.

The default model settings with $k_d = 0.0164$ [min^{-1}], $k_{a1} = 0.0018$ [min^{-1}] and $k_{a2} = 0.0182$ [min^{-1}] result in the insulin concentration as shown in Fig. 3.

To adjust the parameters the nonlinear least-squares problem solver as implemented in MATLAB™ has been used. The error function has been simply the difference between the original data-vector and the model output at exactly the same time instants. The optimization result is shown in Fig. 3 and the obtained parameter values are $k_d = 0.0104$ [min^{-1}], $k_{a1} = 0.00015$ [min^{-1}] and $k_{a2} = 0.0105$ [min^{-1}].

For the simulation the T1DM simulator basal values, similarly as in Man et al. (2007), i.e. I_b, G_b and EGP_b have to be chosen. In this step the constant basal insulin is considered, the information on the basal pattern is partially neglected. From the Table 1 it follows that the total basal insulin dose is 23.7 U per day, thus 0.9875 U/h. This corresponds to $v_b = 1.3167$ [pmol/kg/min] and consequently $I_b = 54.4$ [pmol/l].

Further, the basal glucose concentration value G_b has to be chosen. Since during a night the subject is considered in the steady state, the morning glycemia measurements have been used to determine the basal glucose concentration. In this case $G_b = 162$ [mg/dl] ($G_b = 9$ [mmol/l]) is considered.

Finally, since there is no way how to determine the basal endogenous glucose production EGP_b from the diary data, the value proposed in the original articles Man et al. (2007, 2006), i.e. $EGP_b = 2.4$ [mg/kg/min] is used. This choice is supported by the fact that the other two basal values are close to the values considered in the original articles.

A further adjustment concerns an insulin sensitivity. There are two types of the insulin sensitivities, which are referred as a peripheral insulin sensitivity V_{mx} and a hepatic insulin sensitivity k_{p3}, see Man et al. (2007, 2006). These parameters can be set as a percentage of the normal (or mean) values similarly as in Man et al. (2007). The adjustment of the sensitivity parameters is done in two steps. In the first step the percentage of the both sensitivities is chosen. In the second step the so-called VMX-profile is chosen. The VMX-profile assigns the percentage of the V_{mx} constant value to each hour of the day.

In order to find the sensitivity values a fit-function as a sum of squared errors between the blood glucose measurements and the model output has been considered. However, the records where the glucose concentration is equal to or lower than 7 mmol/l have been neglected since the T1DM model has found to be unable to reflect the short hypoglycemic periods logged in the diary.

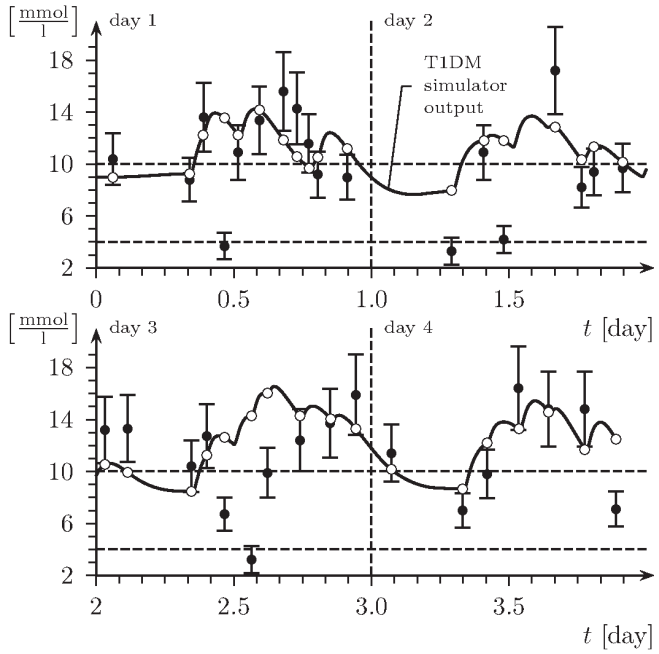

Fig. 6. Comparison of the glycemia data from the diabetic diary with the adjusted T1DM simulator output.

As a result the T1DM model is adjusted so that the 65% of V_{mx} normal value and 65% of k_{p3} normal value is chosen for the subsequent simulations. Further a sensitivity factor $SF(t)$, which is graphed in Fig. 5 is considered. Therefore the resulting peripheral insulin sensitivity is time-variant in the form 0.65 V_{mx} $SF(t)$ where V_{mx} is the normal value of this parameter as reported in Man et al. (2006). The resulting VMX-profile is given by the $SF(t)$ as shown in Fig. 5, which is chosen as an approximate inverse of the (normalized) insulin basal rate pattern.

To be able to compare the measured glycemia with the simulation the measurement accuracy has to be taken into account. A Standards organizations and a professional societies differ on accuracy acceptability criteria, as discussed in Tonyushkina and Nichols (2009). In this work the International Organization for Standardization and the U.S. Food and Drug Administration performance criteria are considered. Both are the same. The accuracy criteria is set to ± 1.11 mmol/l (± 20 mg/dl) for levels < 5.6 mmol/l (< 100 mg/dl) or $\pm 20\%$ for glucose levels ≥ 5.6 mmol/l (≥ 100 mg/dl) for at least 95% of results, see Tonyushkina and Nichols (2009).

The simulation results of the adjusted T1DM simulator are shown in Fig. 6. The diary data, particularly the carbohydrates and the insulin bolus serve as the part of the model input. Further, the basal insulin pattern is considered and the insulin sensitivity parameters are adjusted as mentioned above.

4. ADAPTIVE CONTROLLER

In this section, the adaptive controller based on the principles of the model reference adaptive control is briefly presented.

The controller design is based on the simplified T1DM subject model. The subject is modeled as a time-delay system with two inputs and one output, see Ludwig et al. (2013); Tarnik et al. (2013). The controlled system is considered in the form of transfer function, which can be identified in the operating point given by the steady-state rate of the insulin infusion, see Ludwig et al. (2013).

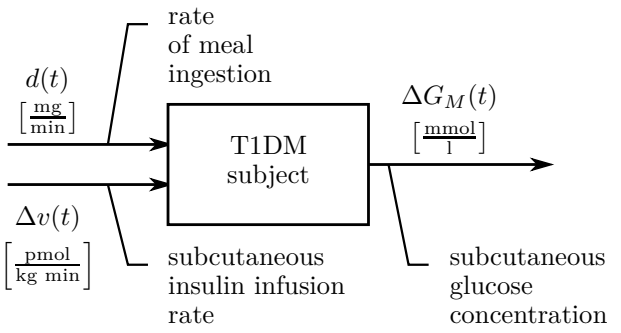

Fig. 7. Controlled system

The transfer function is in the form

$$\Delta G_M(s) = \frac{b_0}{s^2 + a_1 s + a_0} e^{-\tau s} \left(\Delta v(t) + \Psi^{\star\mathsf{T}} w(t) \right) \quad (4)$$

where a_0, a_1, b_0 and $\Psi^\star \in \mathbb{R}^3$ are in general the unknown system parameters. The time-delay τ is assumed to be known, Tarnik et al. (2013). Further, the signal $\Delta G_M(t)$ [mmol/l] is the deviation of the subcutaneous glucose concentration from the steady-state value and $\Delta v(t)$ [pmol/kg/min] is the deviation of the steady-state insulin infusion rate. The signal $w^\mathsf{T}(t) = [d(t+\tau)\ d(t-\tau_1+\tau)\ d(t-\tau_2+\tau)]$ where the signal $d(t)$ [mg/min] is a meal ingestion rate and the time-delays τ_1 and τ_2 are assumed to be known. The meal announcement information availability is assumed as common in the conventional diabetes therapy. Finally the system order $n = 2$ and the relative degree $n^\star = 2$ are known and the sign of the parameter b_0 is also known. The controlled system is schematically shown in Fig. 7.

In general, the control objective is given by the reference model in the form $y_m(s) = W_m(s) r(s)$, where $W_m(s)$ is the reference model transfer function, $y_m(t)$ is the reference model output and $r(t)$ is the reference signal.

The proposed adaptive controller consists of two parts. The first, a classical MRAC based controller and the second an adaptive disturbance rejection controller.

The control law of the MRAC based part can be written in the form

$$u(t) = \Theta^\mathsf{T}(t)\omega(t) \quad (5)$$

where $\Theta(t) \in \mathbb{R}^{2n-1}$ is the vector of adapted parameters. The signal vector $\omega(t)$ has the form $\omega^\mathsf{T}(t) = \left[\nu_1^\mathsf{T}(t)\ \nu_2^\mathsf{T}(t)\ \Delta G_M(t)\ r(t)\right]$ where the auxiliary signals $\nu_1(t),\ \nu_2(t) \in \mathbb{R}^{n-1}$ are given in the form

$$\dot{\nu}_1(t) = \Lambda \nu_1(t) + q u(t-\tau) \quad (6a)$$

$$\dot{\nu}_2(t) = \Lambda \nu_2(t) + q \Delta G_M(t) \quad (6b)$$

where $q \in \mathbb{R}^{n-1}$, $q^\mathsf{T} = [0\ \cdots\ 0\ 1]$ and $\Lambda \in \mathbb{R}^{n-1 \times n-1}$ is an arbitrary stable matrix.

An adaptation law has the form

$$\dot{\Theta}(t) = \mathrm{sgn}(b_0)\sigma_\Theta \Theta(t) - \mathrm{sgn}(b_0)\Gamma_1 e_{a1}(t)\omega_f(t) \quad (7)$$

where

$$\sigma_\Theta = \begin{cases} 0 & \text{if } |\Theta(t)| \leq \Theta_{\max} \\ \sigma_{\Theta 0} & \text{otherwise} \end{cases} \quad (8)$$

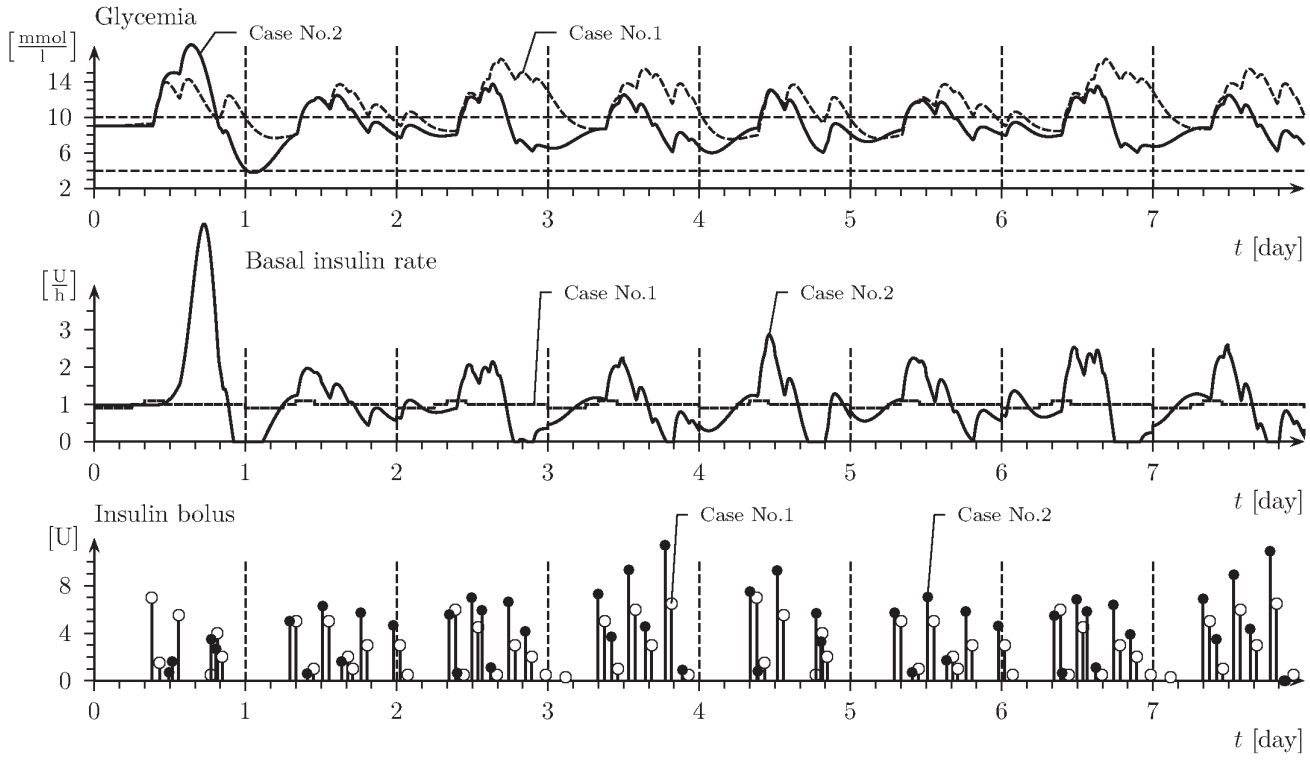

Fig. 8. Simulation results. Case No.1: Results for the insulin administration as logged in the diabetic diary. Case No.2: Results for the insulin infusion commanded by the closed-loop adaptive control system.

and $\Theta_{\max}$ and $\sigma_{\Theta 0}$ are the design constants. Further the matrix $\Gamma_1 = \Gamma_1^{\mathsf{T}} > 0$ is an adaptation gain, the signal $\omega_f(t) = \left[L^{-1}(s)\right]\omega(t)$ with $L(s) = (s+\varrho)$ and $\varrho > 0$ is chosen so that $W_m(s)L(s)$ is strictly positive real transfer function.

An augmented error signal is given in the form

$$\begin{aligned} e_{a1}(t) = &(\Delta G_M(t) + y_a(t)) - y_m(t) \\ &- \left[W_m(s)L(s)\right]\left(\left[L^{-1}(s)\right]\Theta_n^{\mathsf{T}}(t)\omega_n(t)\right. \\ &\left.-\Theta_n^{\mathsf{T}}(t)\left[L^{-1}(s)\right]\omega_n(t)\right) \end{aligned} \tag{9}$$

where the signal $y_a(t)$ is the output of the Smith-predictor-like filter in the form

$$y_a(t) = \left[W_m(s)\right]\rho(t)\left(u(t) - u(t-\tau)\right) \tag{10}$$

where $\rho(t)$ is the adapted parameter given by the adaptation law in the form

$$\dot{\rho}(t) = \sigma_\rho \rho(t) - \gamma_2 e_{a1}(t) u_{\tau f}(t) \tag{11}$$

where

$$\sigma_\rho = \begin{cases} 0 & \text{if } |\rho(t)| \le \rho_{\max} \\ \sigma_{\rho 0} & \text{otherwise} \end{cases} \tag{12}$$

and $\rho_{\max}$, $\sigma_{\rho 0}$ are the design parameters, $u_{\tau f}(t) = \left[L^{-1}(s)\right](u(t) - u(t-\tau))$. Further $\Theta_n^{\mathsf{T}}(t) = \left[\text{sign}(b_0)\Theta^{\mathsf{T}}(t)\ \ \rho(t)\right]$ and $\omega_n^{\mathsf{T}}(t) = \left[\omega^{\mathsf{T}}(t)\ \ u(t) - u(t-\tau)\right]$.

The adaptive disturbance rejection is based on the meal ingestion rate signal, i.e. on the disturbance signal $d(t)$, as follows. In order to compensate the disturbance the signal $\Delta v(t)$ is in the form $\Delta v(t) = u(t) - u_d(t)$, where

$$u_d(t) = \Psi^{\mathsf{T}}(t) w(t) \tag{13}$$

The adapted parameters $\Psi(t) \in \mathbb{R}^3$ are given by the adaptation law

$$\dot{\Psi}(t) = \sigma_\Psi \Psi(t) - \gamma_d \left(\Delta G_M(t) - y_m(t)\right) w(t) \tag{14}$$

where $\gamma_d \in \mathbb{R}, \gamma_d > 0$ and

$$\sigma_\Psi = \begin{cases} 0 & \text{if } |\Psi(t)| \le \Psi_{\max} \\ \sigma_{\Psi 0} & \text{otherwise} \end{cases} \tag{15}$$

where $\Psi_{\max}$ and $\sigma_{\Psi 0}$ are the design constants. This adaptation law can be considered as a gradient based with a switching σ-modification.

5. CLOSED-LOOP SYSTEM SIMULATION

The aim of this section is to compare the insulin administration logged in the diabetic diary with the insulin infusion commanded by the adaptive controller.

The known parameters of the controlled system are as follows: $\tau = 60$ [min], $\tau_1 = 15$ [min] and $\tau_2 = 30$ [min]. Further $\text{sign}(b_0) = -1$, which is obvious since the insulin dose increasing causes decreasing of the glucose concentration. The rest of the controlled system parameters are unknown in the adaptive controller design.

First the following scenario is simulated. The time period of eight days is considered, therefore the meal protocol and the insulin protocol logged in the diabetic diary is repeated two times. The meal data and the insulin data from the diabetic diary serve as the input to the adjusted T1DM simulator. Same basal insulin pattern as in Fig. 1 is considered and the insulin sensitivity as depicted in Fig. 5 is used. The simulation results are shown in Fig. 8. The dashed line shows the results for the case when the insulin is administered as given in the diabetic diary.

The time period of eight days is also considered in the closed-loop system simulation. The general settings of the controller for this case have found to be as follows.

The reference model in the MRAC based part is chosen in the form

$$y_m(s) = \frac{1.6 \times 10^{-5}}{s^2 + 0.008s + 1.6 \times 10^{-5}} r(s) \qquad (16)$$

i.e. two poles at -0.004 [min^{-1}]. As the reference signal $r(t)$ a periodic square signal is used, with an amplitude 0.5 [mmol/l] (around the chosen operating point) and with the period one day.

The values of the design constants in the adaptation law (7) have been chosen as

$$\Gamma_1 = 10^{-6} \begin{bmatrix} 0,2 & 0 & 0 & 0 \\ 0 & 0,2 & 0 & 0 \\ 0 & 0 & 0,2 & 0 \\ 0 & 0 & 0 & 0,2 \end{bmatrix} \quad \text{and} \quad \gamma_2 = 5 \times 10^{-6}$$

Further $\sigma_{\Theta 0} = 100$, $\Theta_{\max} = 0.2$, $\sigma_{\rho 0} = -10$ and $\rho_{\max} = 3$. The values of the disturbance rejection adaptation law have been chosen as follows: $\gamma_d = 10^{-9}$, $\sigma_{\Psi 0} = -0.0001$ and $\Psi_{\max} = 0.004$.

Finally, the adapted parameter initial values in all adaptation laws equal zero.

Simulation results for the case when the insulin administration is given by the adaptive control algorithm are shown in Fig. 8 (solid line).

6. CONCLUSION

From the diabetes compensation point of view, the control objective is to keep the glucose concentration in the normal glycemia range (4 – 10 mmol/l) for the most of the time. For the simulation results, where the insulin is given by the diabetic diary, 64% of the time the simulated glycemia has been higher than 10 mmol/l and 36% of the time lower or equal than 10 mmol/l.

As Fig. 8 indicates, in the case No.2, where the insulin has been commanded by the adaptive controller, better results have been obtained. The glycemia has been higher than 10 mmol/l only for 31% of the simulation time. The rest of the time the glycemia has been equal to or lower than 10 mmol/l including 1% of the time for which the glycemia has been lower than 4 mmol/l. However the observed hypoglycemic period in the first simulated day can be attributed to the controller adaptation process. Therefore such a insignificant hypoglycemic event can be avoided by an appropriate choice of the adapted parameter initial values (not reported in the paper).

Besides the achieved tight glucose control a significant variability of the basal insulin rate in comparison with the basal insulin pattern logged in the diabetic diary has been observed as well as the bigger bolus doses. Also this illustrates the use of the *in-silico* experiment in the control algorithm design.

REFERENCES

Ben Abbes, I., Lefebvre, M., Cormerais, H. and Richard, P. (2011), A new model for closed-loop control in type 1 diabetes, *in* 'Proceedings of the 18th IFAC World Congress'.

De Nicolao, G., Magni, L., Dalla Man, C. and Cobelli, C. (2011), Modeling and control of diabetes: Towards the artificial pancreas, *in* 'Proceedings of the 18th IFAC World Congress'.

Eren-Oruklu, M., Cinar, A., Quinn, L. and Smith, D. (2009), 'Adaptive control strategy for regulation of blood glucose levels in patients with type 1 diabetes', *Journal of Process Control* **19**(8), 1333 – 1346. Special Section on Hybrid Systems: Modeling, Simulation and Optimization.

European Medicines Agency (2006), 'Initial scientific discussion for the approval of actrapid'. Accessed in July 2013: `http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Scientific_Discussion/human/000424/WC500021655.pdf`.

Herrero, P., Georgiou, P., Oliver, N., Reddy, M., Johnston, D. and Toumazou, C. (2013), 'A composite model of glucagon-glucose dynamics for in silico testing of bihormonal glucose controllers.', *Journal of diabetes science and technology* **7**(4), 941 – 951.

Lehmann, E. D., Tarín, C., Bondia, J., Teufel, E. and Deutsch, T. (2011), 'Development of aida v4.3b diabetes simulator: Technical upgrade to support incorporation of lispro, aspart, and glargine insulin analogues', *Journal of Electrical and Computer Engineering* .

Ludwig, T., Ottinger, I., Tárník, M. and Miklovičová, E. (2013), T1DM subject as a time-delay system: Modeling and adaptive control, *in* 'International Conference on Process Control (PC) June 18-21, 2013, Štrbské Pleso, Slovakia'.

Magni, L., Raimondo, D., Bossi, L., Man, C., Nicolao, G., Kovatchev, B. and Cobelli, C. (2007), 'Model predictive control of type 1 diabetes: An in silico trial', *Journal of Diabetes Science and Technology* **1**(6).

Man, C., Raimondo, D., Rizza, R. and Cobelli, C. (2007), 'Gim, simulation software of meal glucose-insulin model', *Journal of Diabetes Science and Technology* **1**(3).

Man, C., Rizza, R. and Cobelli, C. (2006), Mixed meal simulation model of glucose-insulin system, *in* 'Engineering in Medicine and Biology Society, 2006. EMBS '06. 28th Annual International Conference of the IEEE', pp. 307 – 310.

Tarnik, M., Murgas, J., Miklovicova, E. and Farkas, L. (2013), Adaptive control of time-delayed systems with application for control of glucose concentration in type 1 diabetic patients, *in* F. Giri and V. Van Assche, eds, '11th IFAC International Workshop on Adaptation and Learning in Control and Signal Processing - July 3-5 2013, Caen, France', Vol. 11.

Tárník, M. and Murgaš, J. (2011), Additional adaptive controller for mutual torque ripple minimization in PMSM drive systems, *in* 'Proceedings of the 18th IFAC world congress 2011, Milano, Italy, August 28 - September 2', pp. 4119–4124.

Tonyushkina, K. and Nichols, J. H. (2009), 'Glucose meters: A review of technical challenges to obtaining accurate results', *Journal of Diabetes Science and Technology* **3**(4).

Wilinska, M. E. and Hovorka, R. (2008), 'Simulation models for in silico testing of closed-loop glucose controllers in type 1 diabetes', *Drug Discovery Today: Disease Models* **5**(4), 289 – 298.