Journal of Cybernetics and Informatics

published by

Slovak Society for Cybernetics and Informatics

Volume 13, 2012

http://www.sski.sk/casopis/index.php (home page)

ISSN: 1336-4774

Journal of Cybernetics and Informatics 13 (2012)
http://www.sski.sk/casopis/index.php

THE STUDY ON SELECTED MODEL OF THE GLUCOSE-INSULIN SYSTEM

Marián Tárník

Slovak University of Technology, Faculty of Electrical Engineering and Information Technology,
Institute of Control and Industrial Informatics
Ilkovičova 3, 812 19 Bratislava, Slovak Republic
e-mail: marian.tarnik@stuba.sk

Abstract

In this article the selected model of the glucose-insulin system is studied. The model equations and parameters are summarized and schematically shown. The resulting implementation is graphically verified using figures from original articles.

Keywords: Glucose-insulin system, Type 1 Diabetes Mellitus Modeling

1 INTRODUCTION

At the 18th World Congress of the International Federation of Automatic Control (IFAC) one of the sections was titled *"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 blood glucose levels has grown in recent years. The availability of minimally invasive subcutaneous CGM (Continuous Glucose Measurements) has opened the way to automated treatment of type 1 diabetes mellitus, which is suitable for everyday's life [3].

The Artificial Pancreas is a closed-loop control system for maintaining normoglycemia in type 1 diabetes mellitus [9]. It is called so due to its potential to enforce glucose regulation as done by the pancreas in healthy subjects [3]. The system has two main parts. First, the innovative sensors and actuators. As mentioned above, the CGM devices are available commercially in recent years, and the subcutaneous insulin delivery systems (insulin pumps) have been used even longer. The second part of the artificial pancreas is formed by the control algorithm or controller, which in general uses the information from CGM device and generates commands to the insulin pump. We can consider an information system, which provides physicians with information on patient status as a third important part of the artificial pancreas.

Many techniques are available to design the closed-loop control system. Many of them are model based, therefore a control model of the system is necessary. During the last decade, numerous models of the glucose-insulin system have been published. Most of them are designed and verified using *in vivo* data. However, there are models which are wholly or partly designed and verified using *in silico* data, for instance see [1]. The models in this category are usually sufficiently simple to allow the computation of the control law and sufficiently accurate to represent the actual insulin-glucose system. The *in silico* data are generated using complex model, which describes the insulin-glucose system in more detail. The analysis of such a complex model is the aim of this article.

Recently, and building on the complex model developed in the healthy state [12], a type 1 diabetes simulator has been developed which has been accepted by FDA (U.S. Food and Drug Administration) as a substitute of pre-clinical animal trials for certain insulin treatments [1, 3, 6]. The individual parts of the simulator are reported in the literature in several articles [12, 10, 11, 9, 6, 2] (one comprehensive description have not been found by author).

The aim of this article is to analyze and study the type 1 diabetes model, which is used in this simulator, using data available in literature. The point of view of a control engineer is obviously considered. Similar analyzes and studies can be found in the literature and in the recent work of students. As an example we mention the Bachelor's thesis [7].

There are also other types of models reported in the literature, for instance see [4, 5, 8] and mainly its references, or survey [2]. However, these model are not discussed in this article.

2 GLUCOSE-INSULIN MODEL

Most of parts of the glucose-insulin model are reported in the article by Chiara Dalla Man and colleagues [12]. Therefore, in this section we summarize the subsystems of the model reported in article with some minor formal modifications.

The Glucose Subsystem is described as follows

$$\dot{G}_p(t) = -k_1 G_p(t) + k_2 G_t(t) + \Big(EGP(t) - U_{ii}(t) - E(t) + Ra(t)\Big) \qquad G_p(0) = G_{pb} \qquad (1)$$

$$\dot{G}_t(t) = -k_2 G_t(t) + k_1 G_p(t) - U_{id}(t) \qquad G_t(0) = G_{tb} \qquad (2)$$

$$\dot{G}_M(t) = -k_{sc} G_M(t) + k_{sc} G(t) \qquad G_M(0) = G_b \qquad (3)$$

$$G(t) = \frac{G_p}{V_G} \qquad G(0) = G_b \qquad (4)$$

where G_p and G_t (mg/kg) are glucose masses in plasma and rapidly equilibrating tissues, and in slowly equilibrating tissues, respectively; G (mg/dl) plasma glucose concentration; suffix $_b$ denotes basal state; EGP is the endogenous glucose production (mg/kg/min); Ra is the glucose rate of appearance in plasma (mg/kg/min); E is renal excretion (mg/kg/min); U_{ii} and U_{id} are the insulin-independent and -dependent glucose utilizations respectively (mg/kg/min); G_M is the subcutaneous glucose concentration (mg/dl); V_G is the distribution volume of glucose; and k_1, k_2 and k_{sc} are the rate parameters. Parameter values of V_G, k_1, k_2, k_{sc} are reported in Tab. I.

The Endogenous Glucose Production Subsystem can be described in the form

$$\ddot{I}_d(t) + 2k_i \dot{I}_d(t) + k_i^2 I_d = k_i^2 I \qquad I_d(0) = I_b;\ \dot{I}_d(0) = 0 \qquad (5)$$

$$EGP(t) = \eta\Big(k_{p1} - k_{p2} G_p(t) - k_{p3} I_d + k_{p4} I_{po}\Big) \qquad EGP(0) = EGP_b \qquad (6)$$

where $EGP(t) \geq 0$; I_{po} is the amount of insulin in the portal vein (pmol/kg); I_d (pmol/l) is a delayed insulin signal. The parameter k_{p1} is the extrapolated EGP at zero glucose and insulin, k_{p2} liver glucose effectiveness, k_{p3} parameter governing amplitude of insulin action on the liver, k_{p4} parameter governing amplitude of portal insulin action on the liver and k_i rate parameter accounting for delay between insulin signal and insulin action. Parameter values are reported in Tab. I.

The Glucose Utilization subsystem is divided into two components. The first component is insulin-independent utilization U_{ii}, which is constant, and represents glucose uptake by the brain and erythrocytes:

$$U_{ii}(t) = F_{cns} \qquad (7)$$

where the constant parameter F_{cns} is reported in Tab. I. Insulin-dependent utilization U_{id} depends nonlinearly from glucose in the tissues

$$\dot{X}(t) = -p_{2U} X(t) + p_{2U}\,(I(t) - I_b) \qquad X(0) = 0 \qquad (8)$$

$$V_m(t) = V_{mx} X(t) + V_{m0} \qquad (9)$$

$$U_{id}(t) = \frac{V_m(t)\, G_t(t)}{K_{m0} + G_t(t)} \qquad (10)$$

Table I. Parameter values of the glucose-insulin model

Parameter	Value	Unit	Parameter	Value	Unit
k_1	0.065	min^{-1}	k_{e1}	0.0005	min^{-1}
k_2	0.079	min^{-1}	k_{e2}	339	mg/kg
V_G	1.88	dl/kg	K	2.30	pmol/kg per (mg/dl)
k_{sc}	0.1	min^{-1}	α	0.05	min^{-1}
k_{p1}	2.7	mg/kg/min	β	0.11	pmol/kg/mirn per (mg/dl)
k_{p2}	0.0021	min^{-1}	γ	0.5	min^{-1}
k_{p3}	0.009	mg/kg/min per pmol/l	V_I	0.05	l/kg
k_{p4}	0.0618	mg/kg/min per pmol/kg	m_1	0.190	min^{-1}
k_i	0.0079	min^{-1}	m_2	0.484	min^{-1}
η	1	dimensionless	m_4	0.194	min^{-1}
F_{cns}	1	mg/kg/min	m_5	0.0304	min kg / pmol
V_{m0}	2.50	mg/kg/min	m_6	0.6471	dimensionless
V_{mx}	0.047	mg/kg/min per pmol/l	HE_b	0.6	dimensionless
K_{m0}	225.59	mg/kg	k_d	0.0164	min^{-1}
p_{2U}	0.0331	min^{-1}	k_{a1}	0.0018	min^{-1}
			k_{a2}	0.0182	min^{-1}

where V_m is assumed to be linearly dependent on a remote insulin X (insulin in the interstitial fluid). I is plasma insulin and p_{2u} is the rate constant of insulin action on the peripheral glucose utilization. Total glucose utilization is thus $U(t) = U_{ii}(t) + U_{id}(t)$. Parameter values are reported in Tab. I.

The Glucose Renal Excretion Subsystem can be described in the form

$$E(t) = k_{e1}\Big(G_p(t) - k_{e2}\Big) \tag{11}$$

where the glucose excretion $E \geq 0$ is constrained to be non-negative; k_{e1} is the glomerular filtration rate (min^{-1}) and k_{e2} (mg/kg) is the renal threshold of glucose. Parameter values are reported in Tab. I.

Finally, *The Insulin Subsystem* is described as follows

$$\dot{Y}(t) = \begin{cases} -\alpha Y(t) + \alpha\beta\,(G(t) - G_b) & \text{if } \beta\,(G(t) - G_b) \geq -S_b \\ -\alpha Y(t) - \alpha S_b & \text{if } \beta\,(G(t) - G_b) < -S_b \end{cases} \qquad Y(0) = 0 \tag{12}$$

$$S_{po}(t) = \begin{cases} Y(t) + K\dot{G}(t) + S_b & \text{if } \dot{G}(t) > 0 \\ Y(t) + S_b & \text{if } \dot{G}(t) \leq 0 \end{cases} \tag{13}$$

$$\dot{I}_{po}(t) = -\gamma I_{po}(t) + S_{po}(t) \qquad I_{po}(0) = I_{pob} \tag{14}$$

$$S(t) = \gamma I_{po}(t) \tag{15}$$

$$HE(t) = -m_5 S(t) + m_6 \qquad HE(0) = HE_b \tag{16}$$

$$m_3(t) = \frac{m_1 HE(t)}{1 - HE(t)} \qquad m_3(0) = m_{3b} \tag{17}$$

further

$$\dot{S}_1(t) = -(k_{a1} + k_d) S_1(t) + u(t) \qquad S_1(0) = 0 \tag{18}$$

$$\dot{S}_2(t) = -k_{a2} S_2(t) + k_d S_1(t) \qquad S_2(0) = 0 \tag{19}$$

and

$$\dot{I}_l(t) = -(m_1 + m_3(t)) I_l(t) + m_2 I_p(t) + S(t) \qquad I_l(0) = I_{lb} \tag{20}$$

$$\dot{I}_p(t) = -(m_2 + m_4) I_p(t) + m_1 I_l(t) + k_{a1} S_1(t) + k_{a2} S_2(t) \qquad I_p(0) = I_{pb} \tag{21}$$

$$I(t) = \frac{I_p(t)}{V_I} \qquad I(0) = I_b \tag{22}$$

where α (min^{-1}) is the delay between glucose signal and insulin secretion, β (pmol/kg/min per mg/dl) is the pancreatic responsivity to glucose, K (pmol/kg per mg/dl) is the pancreatic responsivity to the glucose rate of change, γ (min^{-1}) is the transfer rate constant between portal vein and liver. Further, u (pmol/kg/min) represents the administration (bolus and infusion) of insulin [9], S_1 represents the amount of nonmonomeric insulin in the subcutaneous space, which is partly transformed into monomeric insulin (second compartment) S_2 and partly enters the circulation with rate constants of insulin absorption k_{a1} and k_d, respectively; the monomeric insulin is finally absorbed with rate constant k_{a2} [9]. And finally, I_l and I_p (pmol/kg) are insulin masses in plasma and in liver, respectively; I (pmol/l) plasma insulin concentration; as mentioned suffix $_b$ denotes basal state; S insulin secretion (pmol/kg/min); V_I distribution volume of insulin (l/kg); and m_1, m_2, and m_4 (min^{-1}) rate parameters; HE hepatic extraction of insulin. The parameter values are reported in Table I.

The initial conditions of the model equations result from the computation of the basal state, when the time derivative of all the signals is zero, as follows [12]. From the equation (16) and from the equation (17) we have

$$S_b = \frac{1}{m_5}(m_6 - HE_b) \tag{23}$$

$$m_{3b} = \frac{m_1 HE_b}{1 - HE_b} \tag{24}$$

where HE_b and other parameters are given in Table I. Then from the equations (20) and (21) we have

$$I_{pb} = \frac{\frac{2}{5} S_b (1 - HE_b)}{m_4} \tag{25}$$

$$I_{lb} = \frac{1}{m_{3b}} \left(S_b - m_4 I_{pb} \right) \tag{26}$$

and $I_b = \frac{I_p}{V_I}$, which is obvious. From (15) we also have $I_{pob} = \frac{S_b}{\gamma}$. Further, we have three unknowm values G_{pb}, G_{tb} and EGP_b. If the value of G_{pb} is known, then from equation (4) we have $G_b = \frac{G_{pb}}{V_G}$. At basal steady-state endogenous production equals glucose utilization [12]: $EGP_b = U_{iib} + U_{idb} = F_{cns} + \frac{V_{m0} G_{tb}}{K_{m0} + G_{tb}}$, where we have assumed the healthy subject, therefore $E(0) = 0$. At steady-state we also assume that $Ra = 0$ in equation (1). Using these two facts and the equation (6) we have three equations with three unknowns in the form

$$0 = EGP_b + \eta \left(k_{p2} G_{pb} + k_{p3} I_b + k_{p4} I_{pob} - k_{p1} \right) \tag{27}$$

$$0 = F_{cns} - EGP_b + k_1 G_{pb} - k_{p2} G_{tb} \tag{28}$$

$$0 = (EGP_b - F_{cns})(K_{m0} + G_{tb}) - V_{m0} G_{tb} \tag{29}$$

The glucose-insulin system is schematically shown in the Fig. 1, where the function $f(G)$ is described by equations (12) and (13), $f(G_t, V_m)$ is described by (10), $f(HE)$ is described by (17) and differential equations are shown in the form of transfer functions in the s-domain.

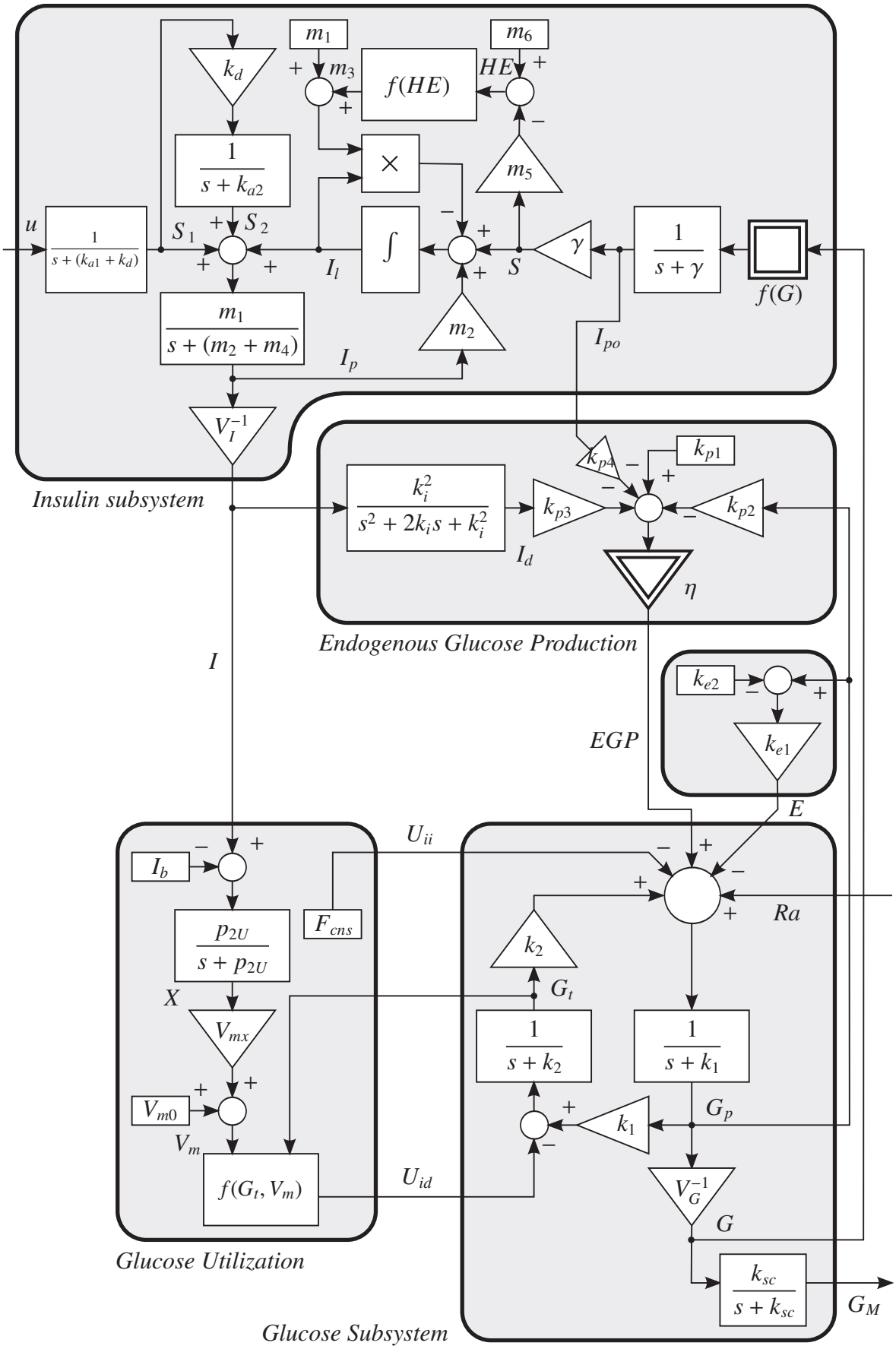


Fig. 1. Scheme of the glucose-insulin system

Table II. Parameter values of the model of glucose intestinal absorption

Parameter	Value	Unit	Parameter	Value	Unit
k_{gri}	0.0558	min^{-1}	k_{max}	0.0558	min^{-1}
k_{abs}	0.057	min^{-1}	k_{min}	0.0080	min^{-1}
f	0.90	dimensionless	a	0.00013	mg^{-1}
BW	78	kg	b	0.82	dimensionless
			c	0.00236	mg^{-1}
			d	0.010	dimensionless

3 GLUCOSE RATE OF APPEARANCE IN PLASMA

In this section we summarize a physiological model of glucose intestinal absorption as reported in [12, 10]. The output of model (subsystem) is the glucose rate of appearance in plasma which, from the control point of view, acts as a disturbance in the glucose-insulin system. Model equations are

$$\dot{Q}_{sto1}(t) = -k_{gri}Q_{sto1}(t) + D\delta(t) \qquad Q_{sto1}(0) = 0 \tag{30}$$

$$\dot{Q}_{sto2}(t) = -k_{empt}(Q_{sto})Q_{sto2}(t) + k_{gri}Q_{sto1}(t) \qquad Q_{sto2}(0) = 0 \tag{31}$$

$$\dot{Q}_{gut}(t) = -k_{abs}Q_{gut}(t) + k_{empt}(t)Q_{sto2}(t) \qquad Q_{gut}(0) = 0 \tag{32}$$

$$Q_{sto}(t) = Q_{sto1}(t) + Q_{sto2}(t) \tag{33}$$

$$Ra(t) = \frac{f\,k_{abs}\,Q_{gut}(t)}{BW} \tag{34}$$

where

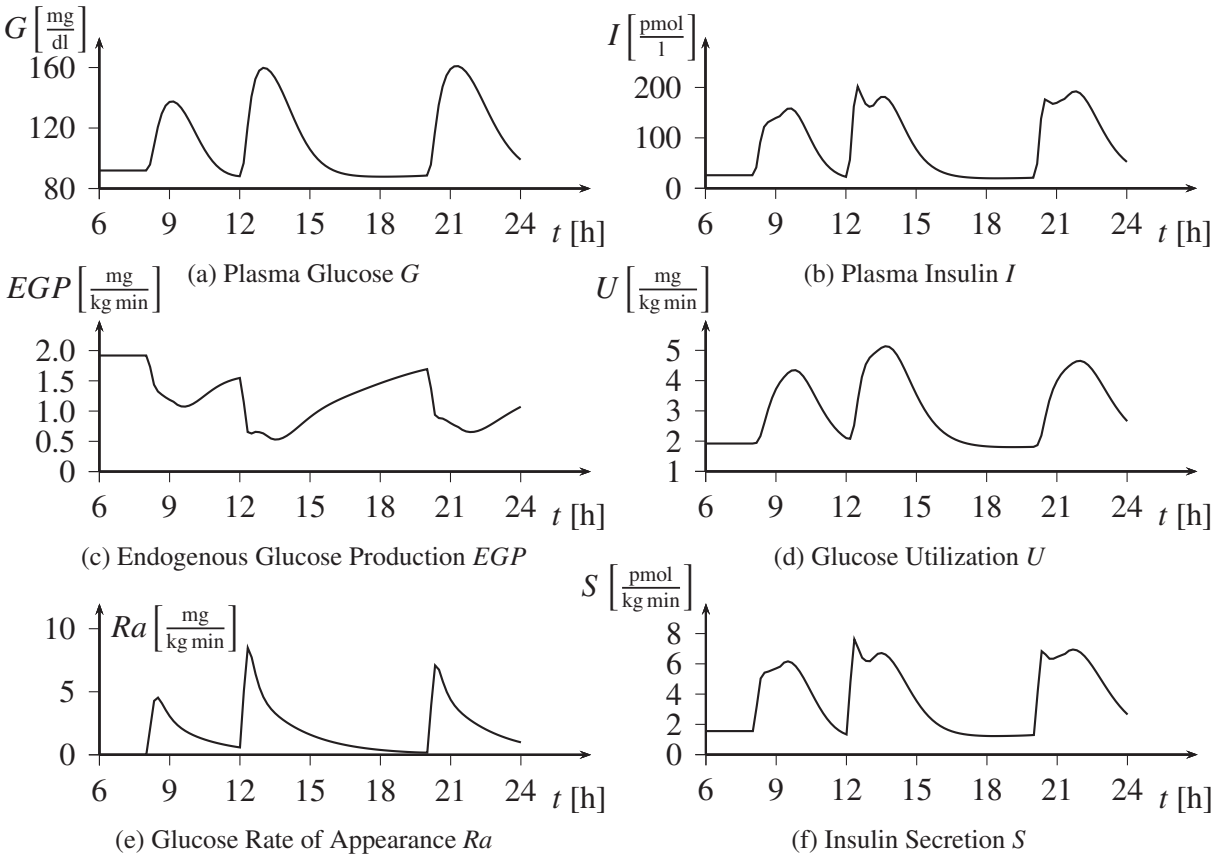
$$k_{empt}(Q_{sto}) = k_{min} + \frac{k_{max} - k_{min}}{2}\left(\tanh\left(a\,(Q_{sto}(t) - bD)\right) - \tanh\left(c\,(Q_{sto}(t) - dD)\right) + 2\right) \tag{35}$$

is the emptying rate (min^{-1}) which depends on the total amount of glucose in the stomach Q_{sto} (mg), which has a solid (Q_{sto1}), and a liquid (Q_{sto2}) phase; Q_{gut} (mg) is the glucose mass in the intestine; k_{gri} (min^{-1}) is the rate of grinding; and k_{abs} (min^{-1}) is the rate constant of intestinal absorption; f is the fraction of intestinal absorption which actually appears in plasma; D (mg) is the amount of ingested glucose; δ is the impulse function; BW (kg) is the body weight. Parameter values, including a, b, c, d, k_{max} and k_{min} are reported in the Table II.

4 GRAPHICAL COMPARISON WITH ORIGINAL RESULTS – NORMAL SUBJECT

In this section the results obtained using our implementation of the model are graphically compared with the results reported in original article [12] and with the results reported in article [11], which presents the interactive simulation software GIM (glucose insulin model).

We briefly describe some important facts on our implementation of the model. In the zero step the computation of basal values is performed using equations (23) – (29), which define initial values of all signals. The sampling period T_{vz} is one minute. In one period the equations of each subsystem are sequentially solved. Firstly, the "*Ra* subsystem"(section 3), followed by subsystems in order as presented in the section 2. Also, the equations are solved in order they are presented in this article. The differential equation are solved using ODE solver. Initial conditions are the corresponding signal values at the beginning of period. Results are the corresponding



(a) Plasma Glucose G (b) Plasma Insulin I

(c) Endogenous Glucose Production EGP (d) Glucose Utilization U

(e) Glucose Rate of Appearance Ra (f) Insulin Secretion S

Fig. 2. Results obtained for normal subject using our implementation of the model

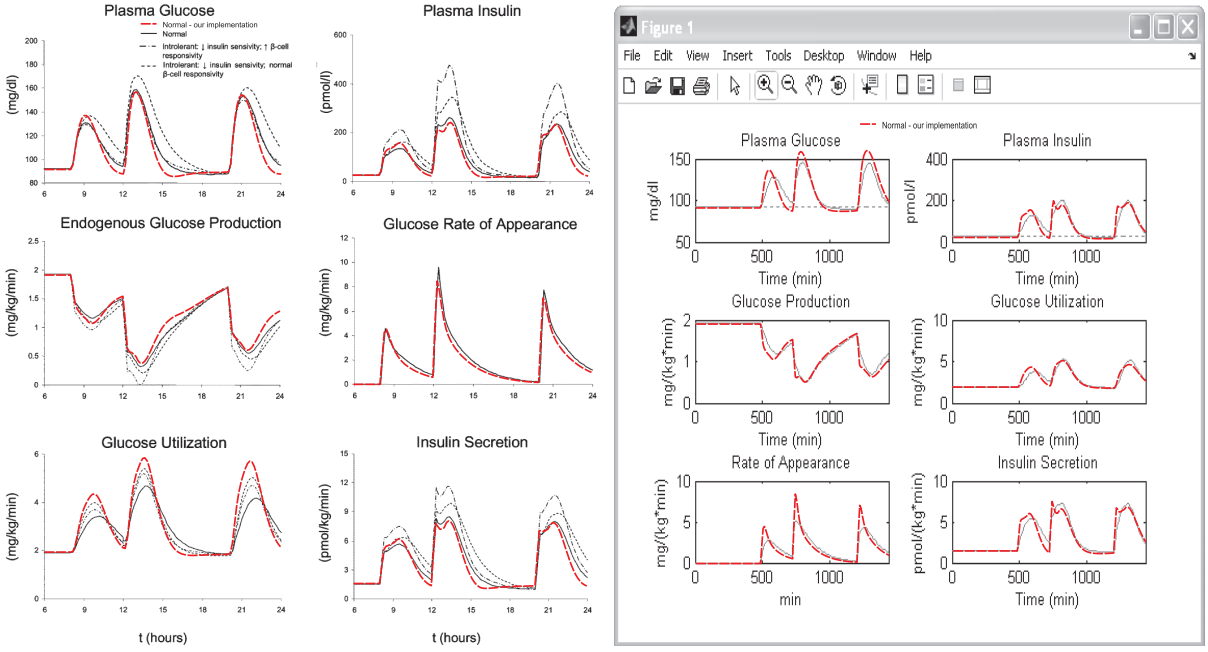
signal values at the end of period and the rest of signals of given subsystem are then updated using algebraic equations.

The results of the following scenario are presented in the original article [12] and the same scenario is simulated in article [11]. A typical day life of a normal subject receiving a mixed meal is simulated, with $D = 45000$ mg of glucose ingested at 8 a.m. (breakfast), $D = 70000$ mg at noon (lunch), and $D = 70000$ mg at 8 p.m (dinner). The signal δ is the impulse signal with the amplitude $1/T_{vz}$ and width T_{vz} (Dirac impulse approximation) at the meal time, otherwise the amplitude is zero. The model parameter values for the normal subject are reported in Table I and in Table II. Since insulin sensitivity and beta cell responsivity to glucose are not constant during the day [12], we assumed V_{mx} 25% lower in the evening meal as compared with breakfast and lunch, and β 25% lower both at lunch and evening meal as compared with breakfast. No external insulin is used, therefore $u(t) = 0$.

The results obtained using our implementation of the normal subject model are in the Fig. 2. The graphical comparison of the data from Fig. 2 and the original figures is in the Fig. 3a and Fig. 3b. The our model's fit is good. It may be reasonable to assume that the deviation is caused by a different way of implementation and numerical computations.

5 GRAPHICAL COMPARISON WITH ORIGINAL RESULTS – PID CONTROL

In order to simulate a type 1 diabetic subject, some modifications of the normal subject model are needed [11, 9, 6]. The insulin secretion is zero in the type 1 diabetic subject, and the endogenous glucose production is higher which results to higher basal glucose. With this in mind, we set $S_b = 0$ instead of equation (23) and $S_{po}(t) = 0$ (eq. (13) and $f(G)$ in Fig. 1). Further we set the gain $\eta = 1.185$ to get $G_b = 181.7$ mg/dl and $EGP_b \approx 2.4$ mg/kg/min. All the



(a) Original figure from [12], Fig.7. (b) Original figure from [11], Figure 4.

Fig. 3. Graphical comparison of the results obtained using our implementation of the model (Fig. 2) with the results reported in original articles [11, 12]

Table III. Parameter values of the PID controller

Parameter		Value	Unit
Proportional Gain	K_P	0.032	pmol/kg/min per mg/dl
Integral Time Constant	T_I	450	min^{-1}
Derivative Time Constant	T_D	66	min^{-1}

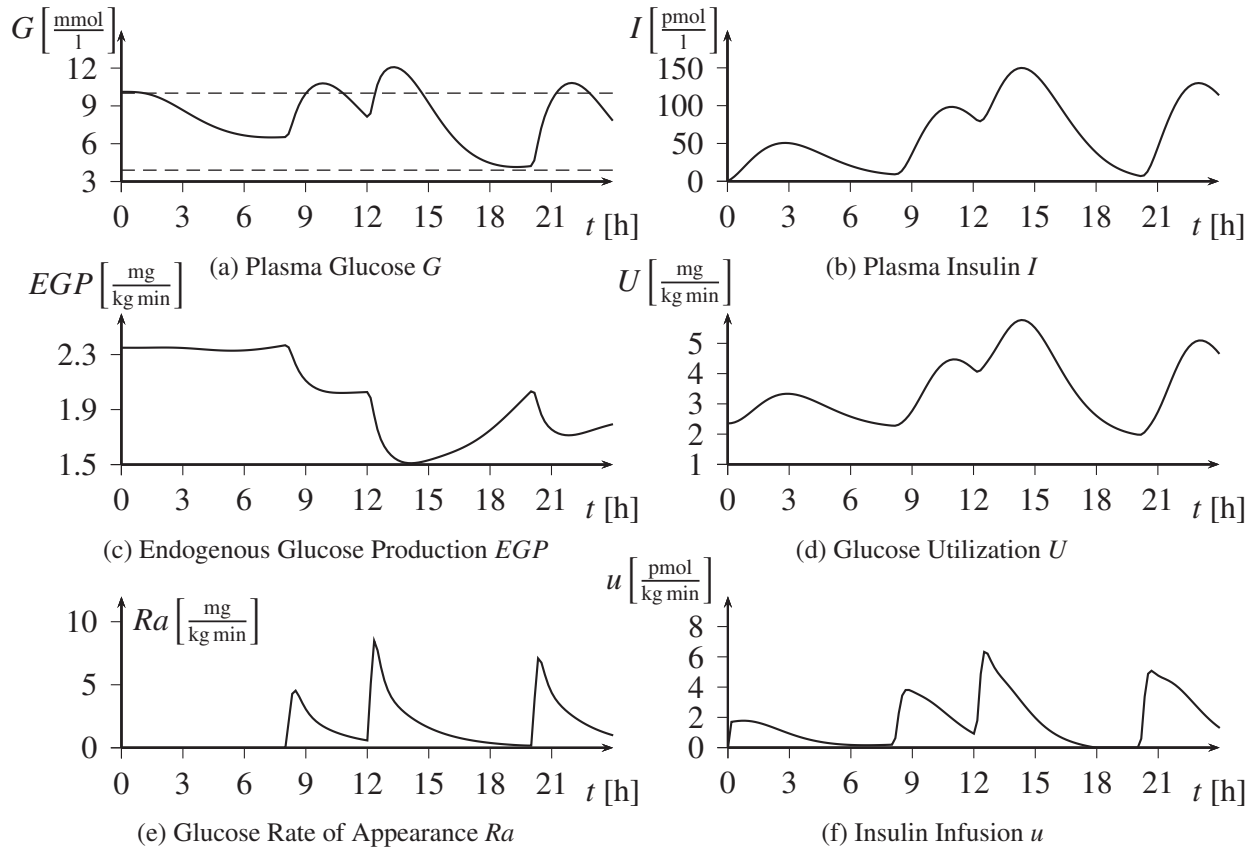
other parameters are kept at values of the normal subject (assumption that the subject is under good control).

In this section the external insulin delivery (u) is no longer zero and it is governed by PID controller as simulated in [11]. Same scenario as in section 4 is used. Based on the PID controller description in [11], we have used PID controller in the simplest discrete time form, with the controller output u constrained in interval $0 \leq u(t) \leq 10 \frac{\text{pmol}}{\text{kg min}}$. The parameters of the PID controller are reported in Table III ([11]—Table 1.). The setpoint for the subcutaneous glucose concentration glucose G_m equals to 130 mg/dl.

The blood glucose level is usually measured in either mg/dl or mmol/l. The following ratio is used for conversion [7]:

$$1 \left[\frac{\text{mmol}}{\text{l}}\right] \approx 18 \left[\frac{\text{mg}}{\text{dl}}\right]$$

The results of our implementation of PID control of blood glucose level are shown in the Fig. 4. For displaying the results we use mmol/l units, which is more convenient in our region. The results are graphically compared in the Fig. 5 with the original figure in the article [11]. We would like to emphasize that the aim of this comparison is verification of the our implementation of the glucose-insulin model, not the performance of PID control. Also this simulation experiment shows that the obtained results corresponds to the original results.



(a) Plasma Glucose G (b) Plasma Insulin I

(c) Endogenous Glucose Production EGP (d) Glucose Utilization U

(e) Glucose Rate of Appearance Ra (f) Insulin Infusion u

Fig. 4. Simulation results of a type 1 diabetic subject controlled in a closed loop with a PID controller. Dashed lines indicates the blood glucose target range

6 CONCLUSION AND FUTURE WORK

In this article, the complex model of glucose-insulin system is studied. The model is presented in convenient form for the engineers without bioengineering background. For this purpose some minor formal modifications in equations are introduced and the whole model is schematically represented by the diagram. The graphical comparison with original results is performed to verify the accuracy of the our implementation.

Having the model verified, it can be used in the future research of control algorithms of blood glucose levels. Simultaneously, the knowledge on modeling methods used in type 1 diabetes mellitus models is an advantage for the control engineer and for the development of the systems for management of type 1 diabetes mellitus.

7 ACKNOWLEDGEMENT

This work has been supported by Competence Center of intelligent technology for computerization of systems and services — Kompetenčné centrum inteligentných technológií pre elektronizáciu a informatizáciu systémov a služieb", ITMS kód projektu: 26240220072).

REFERENCES

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

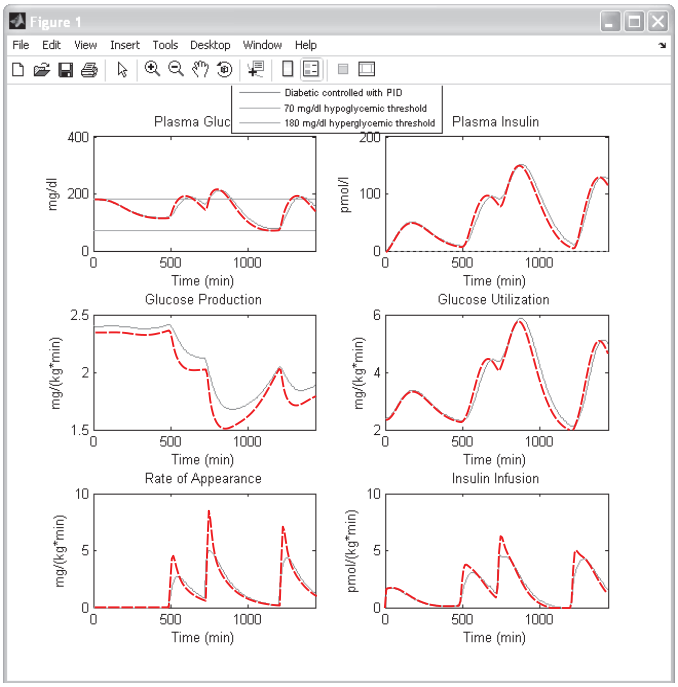


Fig. 5. Graphical comparison of the results obtained using our implementation of PID control of blood glucose level with the results reported in original article [11]

[2] C. Cobelli, C. Dalla Man, G. Sparacino, L. Magni, G. De Nicolao, and B.P. Kovatchev. Diabetes: Models, signals, and control. *IEEE Reviews in, Biomedical Engineering*, 2:54 –96, 2009.

[3] G. De Nicolao, L. Magni, C. Dalla Man, and C. Cobelli. Modeling and control of diabetes: Towards the artificial pancreas. In *Proceedings of the 18th IFAC World Congress*, 2011.

[4] Meriyan Eren-Oruklu, Ali Cinar, Lauretta Quinn, and Donald Smith. Adaptive control strategy for regulation of blood glucose levels in patients with type 1 diabetes. *Journal of Process Control*, 19(8):1333 – 1346, 2009. Special Section on Hybrid Systems: Modeling, Simulation and Optimization.

[5] Roman Hovorka. Management of diabetes using adaptive control. *International Journal of Adaptive Control and Signal Processing*, 19(5):309–325, 2005.

[6] B.P. Kovatchev, M. Breton, C.D. Man, and C. Cobelli. In silico preclinical trials: A proof of concept in closed-loop control of type 1 diabetes. *Journal of Diabetes Science and Technology*, 3(1):44–55, january 2009.

[7] A.L. Lassen and T.S.S. Nielsen. Modeling and simulation of glucose-insulin dynamics. Master's thesis, Technical University of Denmark, 2008.

[8] E. D. Lehmann, C. Tarín, J. Bondia, E. Teufel, and T. Deutsch. 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*, 2011.

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

[10] C.D. Man, M. Camilleri, and C. Cobelli. A system model of oral glucose absorption: Validation on gold standard data. *Biomedical Engineering, IEEE Transactions on*, 53(12):2472 –2478, dec. 2006.

[11] C.D. Man, D.M. Raimondo, R.A. Rizza, and C. Cobelli. Gim, simulation software of meal glucose–insulin model. *Journal of Diabetes Science and Technology*, 1(3), may 2007.

[12] C.D. Man, R.A. Rizza, and C. Cobelli. 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*, pages 307 –310, 30 2006-sept. 3 2006.