Design of the $H_\infty$ regulator for the control of glucose concentration in patients with first type diabetes

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Abstract. Glucose is a basic source of energy for the living organism and is assimilated by tissues with the help of insulin receptors attached to the cell membrane. A lot of research has focused on improvement the quality of regulation of glucose concentration by applying modern methods of control theory. Mathematical descriptions of glucose and insulin metabolism are nonlinear processes with uncertainty in parameters. Therefore article is purposed at creating a corresponding simulation model, which would allow the research different approaches to controlling blood glucose levels in the presence of disturbances due from the acceptance of nutrients, physical activity and parametric uncertainty.

1. Introduction
Type 1 diabetes is an autoimmune disease in which the immune system attacks and kills beta cells responsible for secreting the hormone insulin, which has an essential role in regulating blood and tissue glucose concentrations. Beta cells are located in an area of the pancreas called Islets of Langerhans. In global, the number of people which are suffering from type 1 diabetes is about 300 million, and in Bulgaria they are about 100 000, however there is also a hidden morbidity and many from cases of diabetes remain undiagnosed.

Until the first administration of insulin treatment in 1922, type 1 diabetes runs as a disease incompatible with life, resulting in a fatal end within a few months. Modern insulin treatment is realized by periodically injecting insulin substitutes several times a day. Patients should also carefully monitor their glucose concentration in blood to prevent other diseases (cardiovascular, blindness, diseases of the nervous system) related to increased concentration (hyperglycemia). It is technically possible to continuously feed insulin through a specialized pump that injects the substance into the organism through a small subcutaneously mounted tubule. Excessively low glucose concentration (hypoglycemia) should not be allowed, in which also develop not so long-lasting, but requiring emergency intervention states (loss of consciousness, speech difficulties, anxiety).

2. Model of Glucose and Insulin metabolism
The processes of regulation of glucose concentration in blood are usually described by pharmacokinetic models for insulin dosage purposes [1-4]. Pharmacokinetic models refer to the rate
and extent of distribution of a given the dosage form to different tissues as well as to the rate of elimination (metabolism) of the medicament. Most frequently applies a two-component pharmacokinetic model according to which the body is divided of central and peripheral compartment [4]. The central compartment consists of blood plasma and tissues, in which the distribution of substances is practically instantaneous. The peripheral compartment consists of tissues in which the diffusion of the medicament is slower. The metabolism of glucose and insulin can be decomposed into the following processes - assimilation of subcutaneously injected insulin, assimilation of carbohydrates from the digestive tract and interaction between insulin and glucose. These processes will be examined sequentially and will serve to form a nonlinear model in Simulink®.

a) Model for the absorption of subcutaneously injected insulin
A classic two-component pharmacokinetic model for the species was used:

\[ \dot{Q}_{i1}(t) = u(t) - \frac{Q_{i1}(t)}{T_i}, \]

\[ \dot{Q}_{i2}(t) = \frac{Q_{i1}(t)}{T_i} - \frac{Q_{i2}(t)}{T_i}, \]

where \( Q_{i1}(t) \) and \( Q_{i2}(t) \) are the amounts of insulin in the primary and secondary compartments, \( u(t) \) is the flow rate of the introduced insulin substitute from an external source, and \( T_i \) is the time constant of the process determined by the time to reach the maximum concentration of insulin in the blood plasma after injection of a single dose of medicine. The concentration of insulin in blood plasma is determined by the expression (2)

\[ I_P(t) = \frac{Q_{i2}(t)}{T_iwK_{MCR}} + I_b \]

\( K_{MCR} \) is the rate of elimination of the insulin substitute, \( I_b \) is the average background concentration of insulin, and \( w \) is the body weight of the investigated subject. The commented model was implemented in Simulink® as the diagram show in Figure 1.

![Figure 1. Simulink® model for the assimilation of subcutaneously injected insulin](image)

b) Model of absorption of carbohydrates from the digestive system
The main external disturbance factor on glucose concentration in the body appears the mode on eating, with the predominant influence falls on the consumption of carbohydrates presented in the model as a kinetic value \( d(t) \):

\[ \dot{Q}_{m1}(t) = K_D d(t) - \frac{Q_{m1}(t)}{T_m}, \]

\[ \dot{Q}_{m2}(t) = \frac{Q_{m1}(t)}{T_m} - \frac{Q_{m2}(t)}{T_m}. \]
Here, analogous to the previous case $Q_{m1}(t)$ and $Q_{m2}(t)$ are the amounts of carbohydrates in the primary and secondary compartments, and $T_m$ is the time constant of the diffusion between them. $K_D$ determines glucose units obtained from one gram of carbohydrates. Figure 2 contains model of Simulink® for assimilation on carbohydrate. Accordingly, glucose debit towards organism is described as:

$$U_m(t) = \frac{Q_{m2}(t)}{T_m}$$

\[ \text{(4)} \]

**Figure 2.** Simulink® model of assimilation of carbohydrates from digestive system

c) Model of the influence between glucose and insulin

The glucose concentration in the organism is again described by a two-component model with states $Q_1(t)$ and $Q_2(t)$, but also taking into account the importance of the following processes - glucose synthesis, assimilation of glucose in tissue and glucose transport. The rate of glucose synthesis $x_{EGP}(t)$ is given by the expression (5)

$$x_{EGP}(t) = \begin{cases} x_{EGP,0}(1 - x_3(t)) & , x_3(t) < 1 \\ 0 & , x_3(t) \geq 1 \end{cases}$$

\[ \text{(5)} \]

where $x_{EGP}(t)$ is the rate of glucose synthesis in the absence of insulin, $x_3(t)$ is a state variable that indicates how much insulin quantity received has affected glucose synthesis. Similarly, the impact of insulin on the processes of glucose transport and absorption are given by state variables $x_1$ and $x_2$, which will be explained below. The glucose concentration model is obtained as:

$$\dot{Q}_1(t) = -F_{01} \frac{Q_1(t)}{1 + Q_1(t)} - x_1(t)Q_1(t) + k_{12} Q_2(t) + x_{EGP}(t) + U_m(t)$$

$$\dot{Q}_2(t) = x_1(t)Q_1(t) - (k_{12} + x_2(t))Q_2(t)$$

\[ \text{(6)} \]

where $F_{01}$ determines the rate of glucose metabolism to adenosine triphosphate and pyruvate, and $k_{12}$ is the diffusion coefficient between the primary and secondary compartments in the pharmacokinetic model.

d) Activity model of the insulin preparation

The dynamics of the impact of insulin on glucose concentration can be considered in three components [2], which are characterized from specific for each person parameters (Figure 3). The impact of insulin on glucose transport is expressed by (7)

$$\dot{x}_1(t) = -k_{a1}x_1(t) + k_{a1}S_t l_p(t)$$

\[ \text{(7)} \]

and is characterized by time constant $1/k_{a1}$ and sensitivity $S_t$. The impact of insulin on glucose absorption is expressed by the expression (8)

$$\dot{x}_2(t) = -k_{a2}x_2(t) + k_{a2}S_d l_p(t)$$

\[ \text{(8)} \]
with time constant $1/k_{a2}$ and sensitivity $S_d$. Analogous, the impact of insulin on glucose synthesis is with parameters $k_{a3}$ and $S_e$.
\[
\dot{x}_3(t) = -k_{a3}x_3(t) + k_{a3}S_eI_p(t)
\]  
(9)

Figure 3. Simulink® model for activity of insulin preparation

Figure 4 shows the complete model of insulin and glucose metabolism, which is created based on the presented equations. For the practical determination of its parameters may be used experimental data obtained from organisms put on a controlled diet and with suppressed internal secretion of insulin. For the purposes of this research, exemplary values of the commented parameters have been selected, which are given in Table 1 together with their units of measurement. In the nonlinear model, it is also necessary to include some blocks for conversion between units of measure, as well as for introduction limit values for external signals.

Figure 4. A non-linear Simulink® model of insulin and glucose metabolism
Table 1. Parameters of nonlinear model

| Indication | Value | Unit | Indication | Value | Unit |
|------------|-------|------|------------|-------|------|
| $T_1$      | 60    | [min]| $k_{a2}$   | 1     | [min$^{-1}$]|
| $T_m$      | 30    | [min]| $k_{a3}$   | 1/40  | [min$^{-1}$]|
| $\omega_1$| 80    | [kg] | $S_t$      | 0.3   | [L/μIU/min] |
| $I_b$      | $20 \times 10^3$ | [μIU/L]| $S_d$      | 0.3$k_{a2}$ | [L/μIU/min] |
| $K_{MCR}$  | 0.024 | [L/kg/min]| $S_e$      | 0.3$k_{a3}$ | [L/μIU/min] |
| $F_{01}$   | 1.62/180 | [mmol/kg/min]| $k_{12}$   | 1/30  | [min$^{-1}$]|
| $x_{EGP,0}$| 10    | [mmol/L]| $V$        | 7     | [L] |
| $k_{a1}$   | 0.1   | [min$^{-1}$]|

3. Linearized model

The presented model of interaction between insulin and glucose has non-stationary parameters $x_1$, $x_2$, and $x_3$ representing insulin action upon glucose distribution, transportation and generation which multiply the first and second compartment glucose concentration [5]. However do to smooth variation of the insulin action states and considering that model operates around a fixed steady state complying with homeostasis conditions the model can be sufficiently well approximated with its linearization [6,7,8]. Of course the full model can also be employed for direct nonlinear controller design by sliding-mode or feedback linearization techniques. The advantage of using linearized model is that we can employ linear controller, however it has to be tested on the nonlinear model to prove it guarantees closed-loop stability and performance. Additionally the use of linearization is justified if we represent the nonlinear model as a corresponding set of linear models or equivalently as nominal model with uncertainty which describe all input-output behaviors. When the bound of uncertainty is not too large and if the controller is robust with respect to it then we may be sure that the linear controller will perform well in the nonlinear system under all conditions.

The purpose in controlling glucose concentration by injection an insulin substitute is to adjust the glucose level around the operating point of $x_{trim}$ within $\pm 1$ [mmol/L], so that negative effects of hyperglycemia or hypoglycemia do not occur. Linearization was performed around a selected equilibrium state with parameters given in Table 2. When determining the parameters of the equilibrium state, the values of $u_{trim}$ and $y_{trim}$ are fixed, and the remaining values are determined by an optimization procedure so that the derivatives by state are as close as possible to zero, i.e. $\dot{x}_{trim}(t) \approx 0$.

Table 2. Parameters of equilibrium state

| Variable | Value | Unit | Variable | Value | Unit |
|----------|-------|------|----------|-------|------|
| $Q_{1,trim} = x_{1,trim}$ | 42 | [mmol]| $x_{3,trim} = x_{7,trim}$ | 16.1 | [mmol/min] |
| $Q_{2,trim} = x_{2,trim}$ | 4.2 | [mmol]| $Q_{m1,trim} = x_{6,trim}$ | 10.2 | [μmol/kg] |
| $Q_{12,trim} = x_{3,trim}$ | 0.173 | [μIU]| $Q_{m2,trim} = x_{9,trim}$ | 10.2 | [μmol/kg] |
| $Q_{1,trim} = x_{4,trim}$ | 0.173 | [mmol]| $u_{trim}$ | 0.1 | [g/min] |
| $x_{1,trim} = x_{6,trim}$ | 645 | [min$^{-1}$]| $d_{trim}$ | 0.00488 | [g/min] |
| $x_{2,trim} = x_{6,trim}$ | 6450 | [min$^{-1}$]| $y_{trim}$ | 6 | [mmol/L] |

After linearization around the equilibrium state, a model in state-space (SS) from a ninth-order:

$$\dot{x} = A(x - x_{trim}) + B(u - u_{trim}) + G(d - d_{trim})$$

$$y - y_{trim} = C(x - x_{trim})$$ (10)
where the matrices in this description are:

\[
A = \begin{bmatrix}
-645 & 0 & 0 & -42 & 0 & -70 & 0 & 2667 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 26 & 0 & -0.1 & 0 & 0 & 0 & 0 & 0 \\
0 & 2604 & 0 & 0 & -0.1 & 0 & 0 & 0 & 0 \\
0 & 0.2 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
645 & 0 & 0 & 42 & -4.2 & 0 & 0 & 0 & -6450 \\
\end{bmatrix}
\]

\[
(B \ G)^T = \begin{bmatrix}
0 & 0.0288 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 69.3875 & 0 & 0 & 0 \\
0.1429 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
\end{bmatrix}
\]

\[
C = \begin{bmatrix}
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
\end{bmatrix}
\]

In Figure 5 and Figure 6 shows step responses of the linearized system respectively in the control signal and external disturbance. From these graphics show that the researched system has aperiodic character.

![Figure 5. Step response of control input (debit of insulin)](image)

![Figure 6. Step response of disturbance (intake of carbohydrates)](image)

4. Design of the H\(_\infty\) controller

The purpose of artificial pancreas control system is to guarantee that blood glucose is within healthy limits in presence of imprecisely measured disturbances like food ingestion, physical activity, metabolism variation, etc [9,10,11]. The idea behind H-infinity controller is to minimize the magnitude of H-infinity norm of the closed-loop system with respect to external disturbances and performance measures. Let first examine the extended linearized open-loop model on Figure 7.

The first input is food ingestion disturbance \(d\) with unit norm, which is scaled in frequency domain by the corresponding weighting filter:

\[
W_d(j\omega) = 0.001 \frac{1 + j\omega}{1 + 0.1j\omega}
\] (11)
Its gain and frequency band are selected with respect to the amplitude of the food intake rate in $g_{\text{min}}$. The food intake is the major driver of blood glucose in the organism, so it should be taken into account during the controller design. The second input is the reference glucose value $r$, which for first-type diabetes patients is typically around $6$ [mmol/L]. It is very important to regulate glucose to that reference in the whole frequency range as much as possible to limit its negative effects for the health. The manipulated variable is the insulin intake rate in $g_{\text{min}}$ represented by the third input signal $u$.

The first performance index of the system is the weighted error signal between reference and actual glucose levels. The weighting filter is given by the expression

$$W_e(j\omega) = 100 \frac{1 + j10\omega}{1 + j2000\omega}$$

(12)

is selected to guarantee 100 times attenuation of the external disturbances or $0.01$ [mmol/L] glucose error in the low frequency range. With this filter we also specify the desired bandwidth of the closed-loop system which is determinant of the settling time and oscillations around the reference value. The second performance index is the weighted control signal which is filtered.

$$W_u(j\omega) = 0.02 \frac{1 + j\omega}{1 + j0.1\omega}$$

(13)

This filter is selected to limit the amplitude and rate of the insulin flow rate to satisfy physical limitations of the insulin pump and to minimize local physiological stress in the tissue. The third output is the measured error signal which is used by the controller to calculate the control signal. The H-infinity design looks to find an optimal controller $K$ such that minimize the H-infinity norm of the closed-loop system with respect to uncontrolled disturbances and performance indices as

$$\min_K \| F_L(T_{zd}, K) \|_\infty = \min_K \max_\omega \bar{\sigma}(F_L(T_{zd}, K)) < \gamma$$

(14)

where $F_L$ is the lower fractional transform of the controller $K$ with the extended plant $T_{zd}$. $\bar{\sigma}$ is the upper bound of largest singular value of the closed-loop system. A summary of the iterative procedure for synthesis of the H-infinity controller is presented on Figure 8. As we can see the achieved value of gamma ($\gamma$) is smaller than unity which means that the closed-loop system satisfies the prescribed requirements.

Figure 9 shows the magnitude response of the controller $K$, where $u = K(r - y)$. The controller dynamics is located in low-frequency range and includes zeros to compensate some of the plant dynamics. Figure 10 shows the complementary sensitivity of the closed-loop system with the
controller. The achieved bandwidth is $0.118 \text{[rad/s]}$, which is enough for the glucose closed-loop control.

$$
gamma \quad \text{hmx} \_\text{eig} \quad \text{xinf} \_\text{eig} \quad \text{hamy} \_\text{eig} \quad \text{yinf} \_\text{eig} \quad \text{nrho} \_\text{w}y \quad \text{p} / \text{E}
gamma \quad 1.422 \quad 2.6e-02 \quad 3.5e-20 \quad 5.0e-04 \quad -1.5e-11 \quad 0.0906 \quad p
0.567 \quad 2.6e-02 \quad -9.5e-20 \quad 5.0e-04 \quad 0.0e+00 \quad 0.7887 \quad p
0.730 \quad 2.6e-02 \quad -7.7e+01\# \quad 5.0e-04 \quad 0.0e+00 \quad 0.4135 \quad f
0.546 \quad 2.6e-02 \quad -1.5e+02\# \quad 5.0e-04 \quad 0.0e+00 \quad 1.6013\# \quad f
0.503 \quad 2.6e-02 \quad -1.0e-14 \quad 5.0e-04 \quad -2.2e-11 \quad 3.1560\# \quad r
0.532 \quad 2.6e-02 \quad -3.6e-15 \quad 5.0e-04 \quad 0.0e+00 \quad 1.2450\# \quad r
0.947 \quad 2.6e-02 \quad -1.1e-14 \quad 5.0e-04 \quad 0.0e+00 \quad 0.9518 \quad p
0.939 \quad 2.6e-02 \quad -1.8e-15 \quad 5.0e-04 \quad -1.1e-11 \quad 1.0793\# \quad r
$$

Gamma value achieved: $0.9465$

**Figure 8.** Iterative procedure for synthesis of controller using bisection algorithm.

**Figure 9.** Singular values of H-infinity controller

**Figure 10.** Complementary sensitivity of the closed-loop system with H-infinity controller

**Figure 11.** Output sensitivity of the closed loop system compared with its inverted weighting filter

**Figure 12.** Sensitivity of control signal to output noises compared with its inverted weighting filter
On Figure 11 is presented the output sensitivity of the closed-loop where we can observe that the system attenuates the output disturbances 100 times. Also the closed-loop system satisfies the requirements specified by the filter $W_e$. Figure 12 presents the sensitivity of control action to output noise. The system satisfies the prescribed requirements and no amplification of high frequency noise is observed.

![Figure 13. Simulated step response of the closed-loop system with the linearized model](image.jpg)

![Figure 14. Simulated control signal of the closed-loop system with the linearized model](image.jpg)

![Figure 15. Glucose response of the nonlinear model with the H-infinity controller to periodic ingestion disturbance](image.jpg)

![Figure 16. Calculated insulin dosage by the H-infinity controller with the nonlinear model](image.jpg)

5. Conclusions

In this article has been reviewed one approach for design $H_\infty$ regulator to stabilization glucose concentration in patients diagnosed with their first type diabetes by subcutaneous injected of an insulin substitute. The main limiting factor for achieving quality control of closed-loop glucose concentration is the slow assimilation of the subcutaneously injected insulin substitute, which creates the risk of an excessive increase in insulin concentration in the tissues immediately after eating, as it is possible the regulator to deliver insulin doses in for 1-2 hours as a reaction to increased glucose concentration. This in turn would lead to an effect of hypoglycemia, which may be for a long period of time.

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References

[1] A. Haidar 2016 *The Artificial Pancreas* IEEE Control Systems Magazine doi: 10.1109/MCS.2016.2584318.

[2] E. Ferrannini, J.D. Smith, C. Cobelli et al. 1985 *Effect of Insulin on the Distribution and Disposition of Glucose in Men* Journal of Clinical Investigation vol. 76 pp. 37-364

[3] B. Kovatchev, W.V. Tamborlane, W.T. Cefalu, et al. 2016 *The artificial pancreas in 2016: A digital treatment ecosystem for diabetes* Diabetes Care vol. 39 pp. 1123-1126

[4] R. Hovorka 2006 *Continuous glucose monitoring and closed-loop systems* Diabetic Med. vol. 23(1) pp. 1-12

[5] P. Biswas, S. Bhaumik, I. Patiyat. 2016 *Estimation of glucose and insulin concentration using nonlinear Gaussian filters* Proc. IEEE 1st In. Conf. Control Measurement Instrumentation pp. 16-20

[6] L. M. Huyett, E. Dassau, H. C. Zisser, et al. 2015 *Design and evaluation of a robust PID controller for a fully implantable artificial pancreas* Ind. Eng. Chem. Res vol. 54(42) pp. 10311-10321

[7] G. M. Steil, K. Rebrin, C. Darwin, et al. 2006 *Feasibility of automating insulin delivery for the treatment of type 1 diabetes* Diabetes vol. 55(12) pp. 3344-3350

[8] C. C. Palerm 2011 *Physiologic insulin delivery with insulin feedback: A control system perspective* Comput. Methods Program Biomed vol. 102(2) pp. 130-137

[9] P. Dua, F. J. Doyle, III, E. N. Pistikopoulos 2006 *Model-based blood glucose control for type 1 diabetes via parametric programming* IEEE Trans. Biomed. Eng. vol. 53 pp. 1478-1491

[10] E. D. Lehmann and T. Deutsch 1992 *A physiological model of glucose-insulin interaction in type 1 diabetes mellitus* J. Biomed. Eng. vol. 14 pp. 235-242

[11] D. R. Worthington 1997 *Minimal model of food absorption in the gut* Med. Inform. (Lond.) vol. 22 pp. 35-45