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APPLICATION OF COMPUTER ALGEBRA FOR GLUCOSE-INSULIN CONTROL IN H_2/H_{inf} SPACE USING *MATHEMATICA*

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Abstract

In this case study, an optimal control in H_2/H_{inf} space is presented for glucose– insulin system of diabetic patients under intensive care. The analysis is based on a modified two-compartment Bergman model. To design the optimal controller, the disturbance rejection LQ method based on the minimax differential game is applied. The critical, minimax value of the scaling parameter γ_{crit} is determined by symbolic solution of the modified Riccati equation. The numeric evaluation of the symbolic computation for $\gamma > \gamma_{crit}$ leads to two different solutions, but the norms of the vectors $\{\lambda_1, \lambda_2\}$ formed by the eigenvalues of the pair of the gain matrices are the same. The numerical results are in good agreement with that of the μ-Toolbox of MATLAB. One of the gain matrices with increasing γ, approaches the gain matrix computed with the traditional LQ optimal control design. The symbolic and numerical computations were carried out with *Mathematica* 5, and with the CSPS Application 2 as well as with MATLAB 6.5.

Keywords: Glucose–insulin control, LQ control, disturbance rejection LQ method, symbolic computation, *Mathematica*

1. Introduction

From engineering point of view, treatment of diabetes mellitus can be represented by outer control loop to replace the partially or totally failing blood-glucose control system of the human body. To maintain the glucose level in a diabetic patient under intensive care is currently an actively researched topic in the field of Biomedical Engineering. To design an appropriate control, an adequate model is necessary. During the last 50 years, a variety of models for the interaction between glucose and insulin have been suggested in the literature [2, 8, 14, 18, 19] as well as control strategies have been designed and applied to the problem [3, 4, 6, 7, 12, 17]. Most of the models were realized for "artificial pancreas" function, in such conditions, where the patient's blood glucose level being monitored and insulin injection are performed continuously during surgery.

For this study the Bergman model was selected, which is not complicated, however it is able to properly describe the performance of the physiological system to be controlled [8]. Therefore, comparing the mentioned models, the authors choose a modified two-compartment model [5], considering it as the best appropriate model.

Improving the control strategy an optimal glucose-insulin control in H_2 /H_{inf} space (disturbance rejection LQ method) has been designed and simulation for food (sugar) intake was carried out. The symbolic and numerical computations were carried out with *Mathematica* 5, with the CSPS Application 2 as well as with MATLAB 6.5.

2. Materials and Methods

2.1. Model Equations

To simulate the insulin-glucose interactions in human body the following two-compartment Berman-model was employed [8]:

```
deq1==X′1[t]= p1X1[t]+p2h[t];
deq2==X′2'[t]=(p3-X1[t])X2[t]+i[t]+p4;
```
(1)

The terms $h(t)$ and $i(t)$ stand for exogenous insulin and glucose as inputs of the system. $X_1(t)$ and $X_2(t)$ are the concentration of glucose in the plasma and that of the insulin remote from plasma, respectively. In our case $X_1(t)$ and $X_2(t)$ represent both the states and the output of the system, because the dynamic of the measurement and actuator devices are considerably faster than that of the system itself. The constants $p_i(i = 1, 2, \ldots, 4)$ are the model parameters.

To design optimal control, the first step is the linearization of the nonlinear model in the vicinity of steady state [11, 12], namely at ($X_1 0$, $X_2 0$, $h0$, $i0$), where $x(t)$ is the state variable, $u(t)$ and $y(t)$ are the input and output variables:

$$\begin{aligned} \dot{x} &= \begin{pmatrix} p_1 & 0 \\ \frac{p_4}{p_3} & p_3 \end{pmatrix} x + \begin{pmatrix} p_2 & 0 \\ 0 & 1 \end{pmatrix} u \\ y &= \begin{pmatrix} 1 & 0 \\ 0 & 1 \end{pmatrix} x + \begin{pmatrix} 0 & 0 \\ 0 & 0 \end{pmatrix} u \end{aligned} , \qquad (2)$$

x, y and u are relative variables, deviations from the steady state.

To check the necessary conditions of the LQ problem (whether the system can be stabilized at all); first we should test the controllability of the linearized system. While the rank of the controllability matrix is equal with the rank of the system [11], [12], the system can be stabilized. Now, the LQ control can be realized based on *Eq.* (2).

2.2. LQ control

It is well known [20], that the dynamic of an LTI (linear time invariant) system can be described in the following way:

$$\begin{array}{l}\dot{x}(t) = Ax(t) + Bu(t) \\ y(t) = Cx(t)\end{array}, \tag{3}$$

where A, B, C are constant matrices. Using a classical LQ control, the requirement on designing is to minimize the following quadratic cost functional:

$$J(u, d) = \frac{1}{2}\int_0^\infty y^T(t)Qy(t) + u^T(t)Ru(t)\ dt\ . \tag{4}$$

The classical LQ attempts to find an optimal control $u^*(t)$, $t \in\ 0, \infty$, based on the CARE (Control Algebraic Riccati Equation) such that:

$$J(u^*(t)) \leq J(u(t)), \tag{5}$$

for all $u(t)$ on $t \in\ 0, \infty$, under properly chosen R and Q matrices. Hereafter, the system considered is characterized by the following parameter values, [9]:

```
numericalValues = {p₁ → -0.021151, p₂ → 0.092551,
p₃ → -0.014188, p₄ → 0.077947};
```
(6)

The first component of $u(t)$, the exogenous glucose, $h(t)$ stands for disturbance. Therefore, it should be eliminated from the LQ control. Consequently, R_{11} should be considerably greater than R_{22}. We choose the following matrices for R and Q:

$$R = \begin{pmatrix} 1000 & 0 \\ 0 & 0.001 \end{pmatrix}, \qquad Q = \begin{pmatrix} 0.001 & 0 \\ 0 & 0.001 \end{pmatrix}. \tag{7}$$

Then the optimal gain matrix and the eigenvalues can be easily computed by:

```
KLQ = LQRegulatorGains[ControlObjectSS
/.numericalValues, Q, R]; MatrixForm[KLQ]
```

$$\begin{pmatrix} 0.000068134 & -4.90865x\ 10^{-7} \\ -5.30373 & 0.985913 \end{pmatrix} \tag{8}$$

where `ControlObjectSS` represents the linearized Bergman model as control object in CSPS Application of *Mathematica*, [11, 16].

It can be seen that the first row in KLQ is negligible. The eigenvalues of the closed loop also can be computed:

```
Eigenvalues[(A-B.KLQ)/.numericalValues]
```

$$(-1.0001 \qquad\qquad - 0.021151) \tag{9}$$

2.3. Disturbance Rejection LQ Method

The disturbance rejection LQ method represents a generalization of the classical LQ method and is based on the minimax criteria. The system dynamics are generally described as before. However, now the input variable $u(t)$ is separated in control input $\bar{u}(t)$ and disturbance $d(t)$, which can be considered unmeasured, namely:

$$\begin{aligned} \dot{x}(t) &= Ax(t) + B\bar{u}(t) + Ld(t) \\ y(t) &= Cx(t) \end{aligned} \quad . \tag{10}$$

Therefore, in this situation the quadratic cost functional will be modified with the disturbance explicitly:

$$J(\bar{u}, d) = \frac{1}{2}\int_0^\infty y^T(t)y(t) + \bar{u}^T(t)\bar{u}(t) - \gamma^2 d^T(t)d(t)\ dt. \tag{11}$$

Now, the disturbance – while it appears with negative sign - attempts to maximize the cost, while we want to find a control $\bar{u}(t)$ that minimizes the maximum cost achievable by the disturbance (by the worst case disturbance). This is a case of so-called *"worst-case" design* and leads to the formulation of a differential-game, [20]:

$$\max_{d(t)} J(\bar{u}, d) \to \min_{\bar{u}(t)} J(\bar{u}, d) \quad , \tag{12}$$

$\bar{u}(t), \quad d(t)$ satisfying the state equation. It can be demonstrated that the unique solution of the differential-game $\{\bar{u}^*(t), d^*(t)\}$ exists and satisfies the saddle point condition:

$$J(\bar{u}^*, d) \le J(\bar{u}, d) \le J(\bar{u}, d^*), \tag{13}$$

where $\bar{u}^*$ is the optimal control and d^* is the worst-case disturbance. According to [20], the optimal control and the worst-case disturbance are given by:

$$\bar{u}^*(t) = -B^T P x^*(t) \tag{14}$$

$$d^*(t) = \frac{1}{\gamma^2} L^T P x^*(t) \tag{15}$$

where P is the positive definite symmetric solution of the modified control algebraic Riccati equation (MCARE), [20]:

$$PA + A^T P + C^T C - P(BB^T - \frac{1}{\gamma^2} LL^T)P = 0. \tag{16}$$

2.4. Symbolic Solution of MCARE with Mathematica

In case of glucose-insulin control, one of the system matrices, B should be modified and a new one, L will be introduced:

$$B = \begin{pmatrix} 0 & 0 \\ 0 & 1 \end{pmatrix}, \qquad L = \begin{pmatrix} p_2 & 0 \\ 0 & 0 \end{pmatrix}. \tag{17}$$

We are looking for the symmetric solution matrix of the modified Riccati equations in the following form:

$$P = \begin{pmatrix} p_{11} & p_{12} \\ p_{21} & p_{22} \end{pmatrix} \quad . \tag{18}$$

Keeping in mind, that in our case C is identity matrix, the left hand side of the Riccati equation becomes:

```
RI = P.A + Transpose[A].P + IdentityMatrix[2] -
- P.(B.Transpose[B] - 1/γ^2 L.Transpose[L]).P                    (19)
```

It is easy to see, ([16] that *RI* is a symmetric matrix, and therefore, to solve the modified Riccati equation, only three equations have to be solved, namely:

```
eq1 = RI[[1, 1]] == 0
```

$$1 - P_{12}^2 + 2P_{11}p_1 + \frac{P_{11}^2 p_2^2}{\gamma^2} + \frac{2P_{12}p_4}{p_3} == 0,$$

```
eq2 = RI[[1, 2]] == 0
```

(20)

$$-P_{12}P_{22} + P_{12}p_1 + \frac{P_{11}P_{12}p_2^2}{\gamma^2} + P_{12}p_3 + \frac{P_{22}p_4}{p_3} == 0,$$

```
eq3 = RI[[2, 2]] == 0
```

$$1 - P_{22}^2 + \frac{P_{12}^2 p_2^2}{\gamma^2} + 2P_{22}p_3 == 0 \quad .$$

However, to solve these three nonlinear equations in symbolic form is not an easy task. As a result we resort to a trick by solving only two equations for unknowns P_{11} and P_{22}, and with the third one P_{12} as parameter, [16]:

```
solR = Solve[{eq1, eq2},{P11, P22}];                             (21)
```

Because the elements of matrix P should be real numbers, the discriminator (it is the same in every solution):

$$\texttt{dRI}=4\gamma^4 p_1^2 p_3^2 - 4p_2^2 p_3\ (\gamma^2 p_3 - P_{12}^2\ \gamma^2 p_3 + 2P_{12}\ \gamma^2 p_4);$$

should be positive, $dRI \geq 0$. Now, we consider the worst case, namely $dRI = 0$:

```
solP12 = Solve[dRI == 0, P12]
```
(23)

$$\{\{P_{12} \to \frac{p_2^2 p_4 - \sqrt{-\gamma^2 p_1^2 p_2^2 p_3^2 + p_2^4 p_3^2 + p_2^4 p_4^2}}{p_2^2 p_3}\}\},$$

$$\{P_{12} \to \frac{p_2^2 p_4 - \sqrt{-\gamma^2 p_1^2 p_2^2 p_3^2 + p_2^4 p_3^2 + p_2^4 p_4^2}}{p_2^2 p_3}\}$$

Using the same technique, the critical value of γ can be computed from $dP12 = 0$, where:

```
dP12 = -γ²p₁²p₂²p₃²+p₂⁴p₃²+p₂⁴p₄²;
```
(24)

Solving this equation for γ:

```
solγcrt = Solve[dP12 == 0, γ]
```
(25)

$$\{\{\gamma \to -\frac{i\sqrt{-p_2^2 p_3^2 + p_2^2 p_4^2}}{p_1 p_3}\}, \quad \{\gamma \to \frac{i\sqrt{-p_2^2 p_3^2 + p_2^2 p_4^2}}{p_1 p_3}\}\}$$

The value of γ should be positive, therefore only the first solution, the positive one could be considered (model parameter p_2 is positive):

```
γcrit=Simplify[√(p₂²p₃²+p₂²p₄²)/(p₁p₃), Assumptions → p₂ >0]
```
(26)

$$\frac{p_2\sqrt{p_3^2 + p_4^2}}{p_1 p_3}$$

In case of $\gamma = \gamma_{crit}$, $P = P_{crit}$, the elements of the critical solution matrix are:

```
P12crit = ((P12/.solP12[[1]])/.  γ→γcrit)//Simplify
```
(27)

$$\frac{p_4}{p_3}$$

and then the critical solution for P_{11} will be:

```
P11crit = (P11/.solR[[1]])/.{γ→γcrit, P12 → P12crit})//Simplify
```
(28)

$$-\frac{p_3^2 + p_4^2}{p_1 p_3^2}$$

but for P_{22}, the critical solution is blowing up:

```
P22crit = (P22/.solR[[1]])/.{γ→γcrit, P12→ P12crit})//Simplify
```
(29)

```
ComplexInfinity
```

which means that the solution of the modified Riccati equation at $\gamma = \gamma_{crit}$ is a singular solution.

The optimal value of γ is just greater than γ_{crit} because the smallest admissible γ should be chosen. The modified Riccati equation for matrix P with numerical values of the model parameters is:

```
eqs[γ_] = Map[(#/.numericalValues)&,{eq1,eq2,eq3}];
```
(30)

Employing the numerical values of the model parameter, the critical value of γ is:

```
Nγcrit = SetPrecision[γcrit/.numericalValues, 20]
    24.434658651258303053
```
(31)

Let us consider $\gamma = (1 + \varepsilon)\gamma_{crit}$, where ε is a small number, for example, $\varepsilon = 10^{-10}$, than the corresponding admissible γ value is:

```
Nγ = SetPrecision[(1+ε)Nγcrit, 20]
    24.434658653701768918
```
(32)

Now the modified Riccati equation can be solved numerically:

```
NsolR = Solve[eqs[Nγ],{P11, P12, P22}];
```
(33)

The solutions providing positive definite P matrix should be selected:

```
solPD = Select[{{P11, P12}, {P12, P22}} /.NsolR,

(Eigenvalues[#][[1]] > 0∧ Eigenvalues[#][[2]] > 0) &]
    {{{1453.28, −5.41431}, { − 5.41431, 0.986123}},
    {{1494.44, −5.41751}, { − 5.41751, 0.986123}}}
```
(34)

Indeed, these solutions are positive definite:

```
Map[Eigenvalues[#] &, solPD]
    {{1453.3, 0.965938}, {1494.46, 0.966471}}
```
(35)

In order to use matrix norm, the following standard package should be loaded:

```
<< LinearAlgebra‘MatrixManipulation‘
```
(36)

These solutions satisfy the modified Riccati equation:

```
Map[MatrixNorm[RI/.Join[numericalValues, {P11→#[[1, 1]],

P12→#[[1, 2]], P22→#[[2, 2]],
γ → Nγ}]] /MatricesNorm[#] &, solPD]
    { 2.49617 x 10^-12, 2.42568 x 10^-12}
```
(37)

The L matrix is:

```
NL = L /.numericalValues                                        (38)
    {{0.092551, 0}, {0, 0}}
```

Having the solutions of the Riccati equation, the corresponding gain matrices can be computed as follows:

$$\texttt{K = Map[(Transpose[B].\# + } \frac{1}{N\gamma^2} \texttt{ Transpose[NL].\#) \&, solPD];} \quad (39)$$

```
Map[MatrixForm[#] &, K];
```

$$\left\{ \begin{pmatrix} 0.22578 & -0.000839538 \\ -5.41341 & 0.986123 \end{pmatrix}, \begin{pmatrix} 0.231658 & -0.000839786 \\ -5.41751 & 0.986123 \end{pmatrix} \right\}$$

These two solutions are fairly close to each other, so we consider the average value of them:

```
KLQR = (K[[1]] + K[[2]]) /2; MatrixForm[KLQR]                   (40)
```

$$\begin{pmatrix} 0.228533 & -8.39916\ x\ 10^{-8} \\ -5.41835 & 0.985913 \end{pmatrix}$$

The eigenvalues of the closed loop are:

```
Eigenvalues[(A/.numericalValues) - B.KLQR]
    { – 1.00031, –0.021151}                                     (41)
```

We should mention that MATLAB provides only numerical value for γ_{crit}, and only one solution for the gain matrix, which is very close to the average gain *KLQR*, namely the MATLAB solution for the gain matrix and eigenvalues are, [13]:

$$KLQR = \begin{pmatrix} 0.2284 & -0.00083 \\ -5.4159 & 0.9861 \end{pmatrix} \quad (42)$$

$$Eig = \begin{pmatrix} -1.00031 & -0.02115 \end{pmatrix}$$

These values show that the average of symbolic solutions of MCARE and the numeric solution of MATLAB are in very good agreement.

2.5. *Comparing LQ and Disturbance Rejection LQ Control Methods*

The gain matrix *KLQR*, provided by the disturbance rejection LQ method depends on the actual value of the scaling parameter γ. In case $\gamma \to \infty$, we get the gain matrix designed by the classical LQ method, namely: $\lim_{\gamma\to\infty} KLQR = KLQ$.

Considering γ = *100* γ_{crit}, we repeat the computations for solving Riccati equation. The obtained results are as follows [13]:

$$KLQR_\infty = \begin{pmatrix} 0.0000114139 & -8.22153 \text{ x } 10^{-8} \\ -5.30377 & 0.985913 \end{pmatrix} \quad (43)$$

$$EigLQ_\infty = \begin{pmatrix} -1.0001 & -0.02115 & 1 \end{pmatrix}$$

3. Results

First, the dynamical performance of the nonlinear system is simulated in case of food intake. We considered that the sugar absorption in the body has the following exponential form [10] (see *Fig. 1):*

```
δ[t_]:=0.034 Exp[-0.0323 t]/; t > 0

δ[t_]:=0/; t == 0                                    (44)
```

To illustrate the control action, first the simulation was carried out without control (see *Fig. 1, Fig 2*). A considerable drop in the insulin remote from the plasma can be seen, what indicates the necessity of control (see *Fig. 2*).

Using the classical LQ (with the given R and Q matrices), the decrease of the insulin concentration is now very small (see *Fig. 3*), demonstrating LQ's superiority over the other applied control strategies. However, the glucose concentration is not affected.

Moreover, *Fig. 3* and *Fig. 4* show that the LQR controller design provides a better control performance than the LQ controller design.

Employing symbolic computation, it was possible to determine the critical value of the scaling parameter γ as function of the model parameter:

$$\gamma_{crit} = \frac{p_2\sqrt{p_3^2 + p_4^2}}{p_1 p_3} \quad (45)$$

It turned out that for $\gamma > \gamma_{crit}$ there are more than one positive definite solutions of the modified Riccati equation (see *Table 1*), and they are in good agreement with the result of MATLAB. However, MATLAB gives only one of solutions, K^a. As an illustration, the K_{11} (γ) is computed for different γ (see *Fig. 6*).

4. Conclusion

The main advantage of the selected model, in comparison with the other mentioned models is, that it is on-line adaptive, based on strong theoretical foundations as

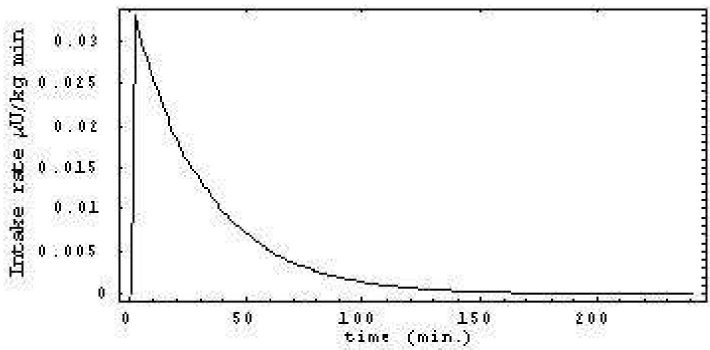

Fig. 1. Glucose concentration in the inlet stream, $h(t)$ as disturbance.

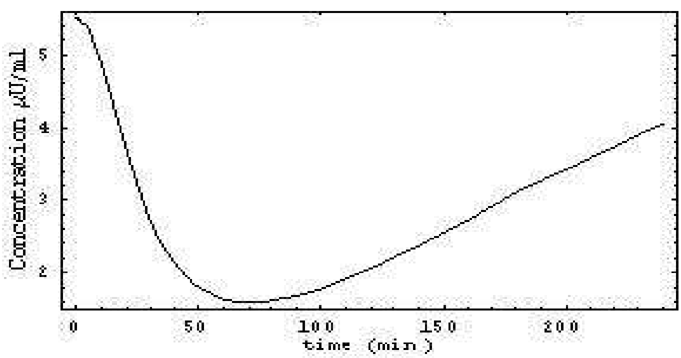

Fig. 2. The solution for the insulin concentration without control.

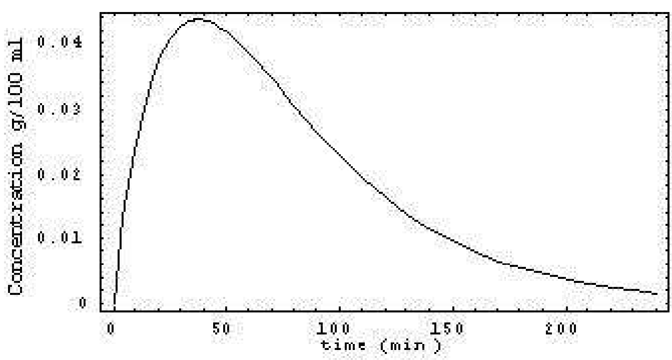

Fig. 3. The solution for the glucose concentration without control.

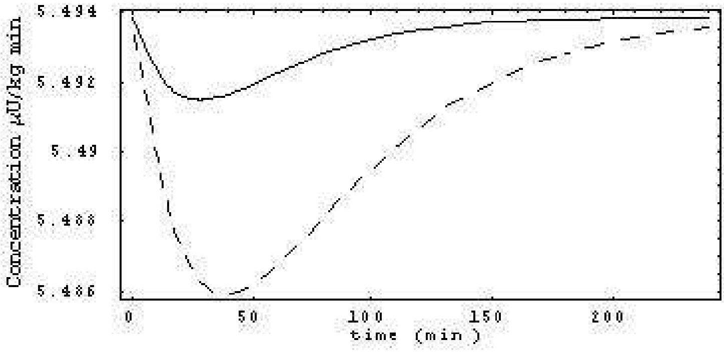

Fig. 4. The performances of LQ (dashed line) and disturbance rejection LQ control considering insulin concentrations.

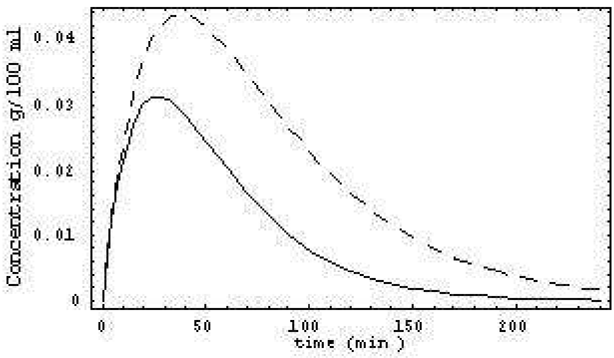

Fig. 5. The performances of LQ (dashed line) and disturbance rejection LQ control considering glucose concentrations.

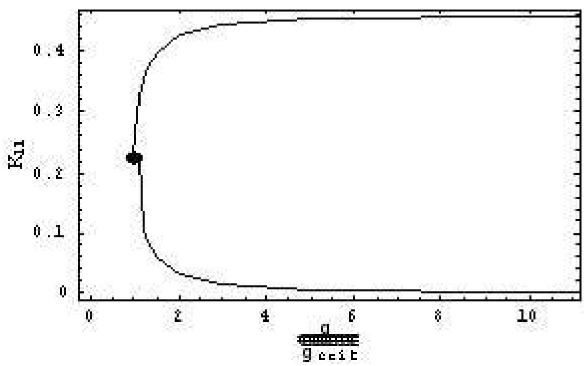

Fig. 6. Bifurcation of the gain matrix element K_{11} (γ) from the singular point, $\gamma = \gamma_{crit}$.

Table 1. Bifurcation of the gain matrix element K_{11} (γ)

$\frac{\gamma}{\gamma_{crit}}$	1.1	1.3	1.5	2	3	5
K_{11}^a	0.2284	0.0824	0.0580	0.0305	0.0130	0.0046
K_{11}^b	0.3237	0.3745	0.3988	0.4264	0.4439	0.4524

well as describes the physiological system appropriately. However, in the literature there are some articles dealing with more sophisticated models of glucose-insulin interaction, but they have not been applied to control problems, [2, 15]. Nowadays scientists are trying to obtain on-line adaptive control laws using compartment theory, but results are still in an initial phase [1]. As we illustrated in this study, the application of the computer algebra provides a considerable contribution to following this trend.

Using the presented control model, a continuous control input can be achieved. Moreover, the model is not complicated (it uses only two differential equations), so it could give a great advantage in case of practical implementation. According to this case-study, the disturbance rejection LQ control proved to be superior to the classical LQ.

However, the model is not implemented yet in a real (practical) application, but after the necessary further verifications it could provide a useful help to control the blood glucose level, and in the optimization process of diabetic administration.

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