CLASSICAL AND MODERN CONTROL STRATEGIES IN GLUCOSE-INSULIN STABILIZATION

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Abstract: This paper presents an analysis of classical and modern control methods for blood glucose control of diabetic patients under intensive care. Employing a modified two- compartment model proposed by Bergman, *et al.* (1979), linear feedback control law leads to a fully symbolic solution. In case of nonlinear approach, considering glucose injection as the only control variable and using Pontryagin's maximum principle, a symbolic-numeric solution has been achieved. As modern control strategy, optimal glucose-insulin control in the H_2/H_∞-space is presented using LQ and disturbance rejection LQ methods, which result in a numerical solution to the control problem. *Copyright © 2005 IFAC.*

Keywords: diabetes mellitus, disturbance rejection method, glucose-insulin control, H_2/H_∞ control, minimax control, nonlinear control, Pontryagin's maximum principle, symbolic computation.

1. INTRODUCTION

From an engineering point of view, the treatment of diabetes mellitus can be represented by an outer control loop, to replace the partially or totally deficient blood-glucose-control system of the human body. The maintenance of 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. In the last 50 years, a variety of models for the interaction between glucose and insulin have been suggested in the literature such as Tolic, *et al.* (2000), Benett and Gourley (2003) and strategies have been designed and applied to the problem (Fischer and Teo, 1989; Juhász and Asztalos, 1996; Sano, 1986; Benyó *et al.*, 1998). Most of the models were realized for an "artificial pancreas" function, in conditions, where the patient blood glucose level monitoring and insulin injection were performed continuously (i.e. surgery) (Fischer and Teo, 1989; Sano, 1986).

The model selected for the control design should not be too complicated, however it should still describe properly the characteristics of the physiological system to be controlled. Therefore, comparing the models mentioned above (Juhász, 1993), the authors orientated on Benyó, *et al.* (2003) and considered a modified two compartment model (Bergman *et al.*, 1979), the so called minimal model, as the most appropriate model.

Symbolic computation was used to design a linear and nonlinear multivariable control, based on the state-space representation of this selected model. In this way the designed control strategy can be evaluated rapidly, and can be applied in on-line (real time) applications.

Furthermore, optimal glucose-insulin control strategies in H_2/H_∞-space - LQ, minimax (disturbance rejection LQ) control - have been designed for diabetic patients. Using these control strategies the simulations of the dynamical performance of the non-linear closed loop system in case of food (sugar) intake has been carried out. For computations Mathematica v.5.1 with its Control System Professional Suite 2 (CSPS2) Application, and Matlab v.6.5 have been used.

2. MODEL EQUATIONS

To simulate the insulin-glucose interaction in human body the following two-compartment model was employed (Benyó *et al.*, 1998; Benyó *et al.*, 2003):

$$\begin{aligned} \dot{X}_1(t) &= p_1 X_1(t) + p_2 h(t) \\ \dot{X}_2(t) &= (p_3 - X_1(t)) X_2(t) + i(t) + p_4 \end{aligned} \qquad (1)$$

The terms h(t) and i(t) are the exogenous insulin and glucose inlets, $X_1(t)$ and $X_2(t)$ stand for the concentration of glucose in the plasma and for the concentration of the insulin remote from plasma. In our case $X_1(t)$ and $X_2(t)$ represent both the states and the output of the system, as the dynamical performances of the measurement and actuator devices are considerably faster than that of the system itself.

The nonlinear system was linearized in the vicinity of steady state (Kovács and Paláncz, 2004), namely at (X_{1st}, X_{2st}, h_{st}, i_{st}). The obtained linear model is:

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

where x(t) represents the state, u(t) and y(t) are the input and output relative variables. While the rank of the controllability matrix is equal with the rank of the system, the system can be stabilized (Kovács et al, 2004).

3. LINEAR APPROACH OF THE GLUCOSE-INSULIN CONTROL

Firstly, the control can be solved by the classical state feedback method. Considering λ_1, λ_2 the eigenvalues of the matrix A-KB, the gain matrix, K can be computed in symbolic form, (Kovács and Paláncz, 2004):

$$K = \begin{pmatrix} \frac{-\lambda 1 + p_1}{p_2} & 0 \\ \frac{p_4}{p_3} & -\lambda 2 + p_3 \end{pmatrix} \qquad (3)$$

Consequently, for model (1) the designed control can be implemented, resulting the closed loop:

$$\begin{aligned} \dot{x} &= \begin{pmatrix} \lambda_1 & 0 \\ 0 & \lambda_2 \end{pmatrix} x + \begin{pmatrix} p_2 & 0 \\ 0 & 1 \end{pmatrix} u \\ y &= \begin{pmatrix} 1 & 0 \\ 0 & 1 \end{pmatrix} x + \begin{pmatrix} 0 & 0 \\ 0 & 0 \end{pmatrix} u \end{aligned} \qquad (4)$$

It can be seen, that the closed loop system is decoupled, while each output is dependant only on the corresponding input.

3.1 Simulation of the Linearized Closed Loop Model

As disturbance, let us perturbate the initial conditions $x_1 = \Delta X_1 = X_1(0) - X_{1st} > 0$ and $x_2 = \Delta X_2 = X_{2st} - X_2(0) > 0$. The system response can be given in symbolic form, i.e. choosing $\lambda_1 = p_1$ and $\lambda_2 = p_3$:

$$\begin{aligned} X_1(t) &= e^{p_1 t} \Delta X_1 \\ X_2(t) &= e^{0.5 \cdot p_3 t} \Delta X_2 \end{aligned} \qquad (5)$$

This is a feasible control, because both of the model parameters p_1 and p_3 are negative, (Juhász, 1993).

3.2 Nonlinear Closed Loop Model

In order to simulate the dynamical behavior of the nonlinear model, the control law, (3) based on the linearized system is substituted in equation (1). While the first equation is independent from the second one, it can be solved as a single equation. Substituting the obtained result into the second equation, the solution can be also achieved in symbolic form:

$$X_1(t) = e^{\lambda_1 t} X_1(0) \qquad (6)$$

$$X_2(t) = \frac{-p_4 + e^{\frac{X_1(0) - e^{\lambda_1 t} X_1(0) + \lambda_1 \lambda_2 t}{\lambda_1}} (X_2(0) p_3 + p_4)}{p_3} .$$

To finish the analysis, a hypoglykaemic episode was taken into consideration with the following numerical values:

$$\begin{aligned} p1 &= -0.021151 \\ p2 &= 0.092551 \\ p3 &= -0.014188 \\ p4 &= 0.077947 \end{aligned} \qquad (7)$$

Consider as initial values $X_1(0) = 0.1$ and $X_2(0) = 2$, now the eigenvalues are selected as: $\lambda_1 = 0.7p_1$; $\lambda_2 = 1.05p_3$.

4. NON-LINEAR APPROACH OF THE GLUCOSE-INSULIN CONTROL

4.1 Model Reduction and Objective Function

Assuming that we do not use glucose injection, namely $h(t) \equiv 0$ - which is a very reasonable assumption, because the reference value of the glucose concentration is zero - and the only control variable is the insulin inlet, the first equation of model (1) can be reduced as:

$$\dot{X}_1(t) = p_1 X_1(t) \qquad (8)$$

This state variable $X_1(t)$ is exponentially decreasing towards the steady state, because in our model the parameter $p_1 < 0$. Substituting this result into the second equation we get a single linear, but nonautonom equation as system equation:

$$\dot{X}_2(t) = i(t) + p4 + (-e^{p_1 t} X_1(0) + p3)\, X_2(t) \qquad (9)$$

The kernel of our objective function represents the deviation of the actual state from the steady state and the consumed insulin of the process during the return from the steady-state point:

$$\Omega = \alpha_1 (X_2(t) - X_{2st})^2 + \beta_1 i[t]^2 \qquad (10)$$

where α_1 and β_1 are weighting parameters. Therefore, the objective function to be minimized is:

$$y = \int_0^{\theta} \Omega dt \qquad (11)$$

where θ is the termination time of the control.

Using Pontryagin's Maximum Principle (PMP), the Hamiltonian of the problem involving the system equation (9) as a constraint, in form of Lagrangian multiplier is:

$$H = i(t)^2 \beta_1 + \alpha_1 (-X_{1st} + X_2(t))^2 + (i(t) + p_4 + \\ +(-e^{p_1 t} X_1(0)) + p_3) X_2(t))\lambda_1(t) . \qquad (12)$$

Pontryagin's maximum principle states that we should select an i(t) control function, which will in our case minimize the Hamiltonian:

$$2\, i(t)\beta_1 + \lambda_1(t) = 0 . \qquad (13)$$

This equation ensures that the stationary point is minimum, if $\beta_1 > 0$.

4.2 Solution of the split boundary problem

The steady state of the system can be easily computed, (Kovács and Paláncz, 2004), obtaining $X_{1st} = 0$, $X_{2st} = -\frac{p_4}{p_3} = 5.49387$. The adjoint function can be than also easily written using $\lambda_1(\theta) = 0$, $X_1(0) = 0.1$, $X_2(0) = 2$ as a split boundary condition problem.

This is a nonautonom, but linear system, with split boundary values, because of the substitution of i(t) in (9). We get:

$$\dot{X}_2(t) = p_4 + (-e^{p_1 t} X_1(0) + p_3) X_2(t) - \frac{\lambda_1(t)}{2\beta_1} \qquad (14)$$

Considering $\Theta = 300$ min. and the same numerical values as in (7), the system can be solved once again numerically using the CSPS of Mathematica. The boundary conditions are satisfied fairly well ($X_2(0) = 2.01953$, $\lambda_1(300) = 0$) and the steady state is also nearly reached:

$$\begin{aligned} X_1(300) &= 0.0001754 \\ X_2(300) &= 5.48098 \end{aligned} \qquad (15)$$

4.3 Simulation results

For the numerical values considered in both control cases, the simulations point out the differences between the two control strategies: linear and nonlinear approach of the glucose-insulin control. The presented situation belongs to the case of starting from a non-equilibrium point.

In case of the nonlinear approach using Pontryagin's maximum principle, the glucose concentration is stabilized faster (Fig.1), while the insulin concentration reaches the steady state value slower (Fig.2). Due to the fact, that the priority of the control is the stabilization of the glucose concentration, one can tell that the nonlinear approach using Pontryagin's maximum principle gives a better result. However, it must be mentioned that only one trajectory of the linear and nonlinear control has been compared here.

This conclusion is also demonstrated by Kovács and Paláncz (2004), by the evolution of the input signals. In case of a nonlinear approach, the variation of the exogenous insulin input is smoother than in case of linear approach. However, it must be taken into consideration that the glucose injection was considered zero using Pontryagin's maximum principle, but this is not a big constraint, while physiologically speaking we inject only insulin.

5. DESIGN OF OPTIMAL GLUCOSE-INSULIN CONTROL

5.1 LQ and Disturbance Rejection LQ (Minimax) Control

Using the general form of a dynamic LTI (linear time invariant) system, (Zhou, 1996), in case of a classical LQ control (Bokor, 2003), the requirement is to minimize the following quadratic cost functional:

$$J(u,d) = \frac{1}{2}\int_0^\infty [y^T(t)\,Q\,y(t) + u^T(t)\,R\,u(t)]dt \quad (16)$$

The classical LQ attempts to find an optimal control u*(t), $t \in [0,\infty]$, based on the CARE (Control Algebraic Ricatti Equation) for all u(t) on $t \in [0,\infty]$. The task is to choose adequate Q and R matrices.

The disturbance rejection LQ method represents a generalization of the classical LQ problem (Zhou, 1996; Bokor, 2003) and is based on the minimax criteria. The system dynamics is generally described as before, but now the input variable u(t) is separated in control input $\bar{u}(t)$ and disturbance d(t), which can be considered as unmeasurable:

$$\begin{aligned} \dot{x}(t) &= Ax(t) + B\bar{u}(t) + Ld(t) \\ y(t) &= Cx(t) \end{aligned} \quad . \qquad (17)$$

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

$$J(\bar{u},d) = \frac{1}{2}\int_0^\infty [y^T(t)y(t) + \bar{u}^T(t)\bar{u}(t) - \gamma^2 d^T(t)d(t)]dt \quad (18)$$

Now, the disturbance - while it appears with a 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 (Bokor, 2003):

$$\max_{d(t)} J(\bar{u},d) \rightarrow \min_{\bar{u}(t)} J(\bar{u},d) \quad , \qquad (19)$$

$\bar{u}(t)$, d(t) satisfying the state equation. It was demonstrated (Zhou, 1996; Bokor, 2003) that the solution of the differential-game (19) exists, it is unique and satisfies the saddle point condition.

According to Bokor (2003), the optimal control and the worst-case disturbance are given by:

$$\begin{aligned} \bar{u}^*(t) &= -B^T P x^*(t) \\ d^*(t) &= \frac{1}{\gamma^2} L^T P x^*(t) \end{aligned} \quad , \qquad (20)$$

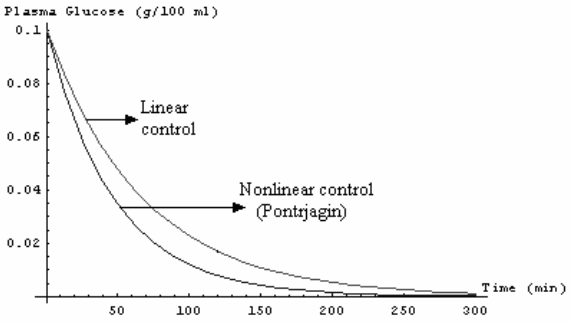

Fig. 1. Variation of the glucose concentration (output $X_1(t)$) in case of linear and nonlinear approach of glucose-insulin control.

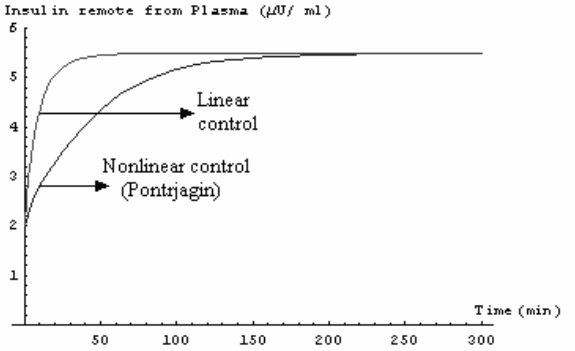

Fig. 2. Variation of the insulin concentration (output $X_2(t)$) in case of linear and nonlinear approach of glucose-insulin control.

where P is the positive definite symmetric solution of the modified control algebraic Ricatti equation (MCARE):

$$PA + A^T P + C^T C - P(BB^T - \frac{1}{\gamma^2} LL^T)P = 0 \quad (21)$$

5.2 LQ and Minimax Control Design

The LQ design is applied to the same model (2) and numerical values (7). The physiological interpretation of (16) is to optimize the output of the system, by minimizing the control input (energy / insulin). The first component of u(t) states for disturbance, consequently, R_{11} should be considerably greater than R_{22}:

$$R = \begin{pmatrix} 1000 & 0 \\ 0 & 0.001 \end{pmatrix},\ Q = \begin{pmatrix} 0.001 & 0 \\ 0 & 0.001 \end{pmatrix} \quad (22)$$

As a result, the eigenvalues of the closed loop system (EigLQ) and the LQ gain (KLQ) can be determined by solving the normal control algebraic Ricatti equation (CARE):

$$\begin{aligned} EigLQ &= \begin{pmatrix} -1.0001 & -0.0211 \end{pmatrix} \\ KLQ &= \begin{pmatrix} 0 & 0 \\ -5.3037 & 0.9859 \end{pmatrix} \end{aligned} \qquad (23)$$

One can see that the first row of KLQ is zero meaning that the first component is eliminated from control. In case of minimax control, first the optimal γ (γ_{min}) has been calculated by iteration, using the Control- and μ-Toolbox of MATLAB. To prove that the best disturbance rejection is reached for γ_{min}, the minimax control problem of the glucose-insulin control was tested for three different situations, namely: $\gamma = \{\gamma min, 2\ \gamma min, 100\ \gamma min\}$. The resulted solutions of the obtained eigenvalues and minimax control gains are given in Table 1. The same results were achieved by solving the MCARE equation in symbolic way via Mathematica (Paláncz and Kovács, 2004).

One can see that the LQ gain is very similar to the case of the minimax control for $\gamma = 100\ \gamma_{min}$. The obtained result demonstrates the theory, that for great values of γ, the minimax control solution becomes a classical LQ control.

5.3 Simulation results

To test our controllers via simulation, we considered the situation of food intake (disturbance), simulating the sugar absorption in the body. According to our clinical experiments we used the following function for input (for a duration of 20 minutes):

$$h(t) = 0.05 \cdot e^{-\frac{(t-10)^2}{45}} . \qquad (24)$$

To illustrate the control action, first the simulation was carried out without control (Fig.3, Fig.4). A considerable drop in the insulin remote from the plasma can be seen, which indicates the necessity of control (Fig.3). Using the classical LQ (with the given R and Q matrices), the decrease of the insulin concentration is now very small (Fig.5).

In case of minimax control, results are presented in Fig.5, Fig.6, demonstrating the numerical results obtained for different γ's in Table 1.

It can be seen from the history of the insulin concentration, the insulin input control signal and the glucose concentration that the minimax control gives the best result for γ_{min}. In addition, increasing values of γ approaches the performance of the classical LQ.

Table 1. The minimax control gains and the eigenvalues of the closed loop system for different γ.

γ	KLQmm		Eig LQmm
γ_{min}	0.2284	-0.00083	-1.00031
	-5.4159	0.9861	-0.02115
$2\ \gamma_{min}$	0.03059	-0.000206	-1.00015
	-5.3185	0.9859	-0.02115
$100\ \gamma_{min}$	1.0×10e-5	-8.2×10e-8	-1.0001
	-5.3037	0.98591	-0.02115

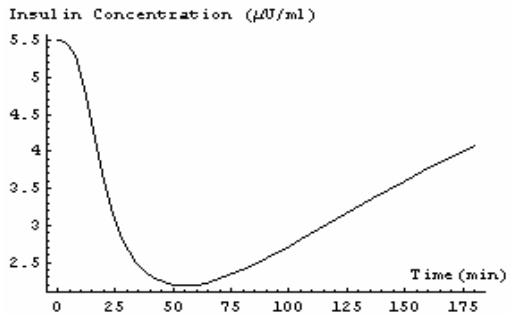

Fig. 3. Variation of insulin remote from plasma without control.

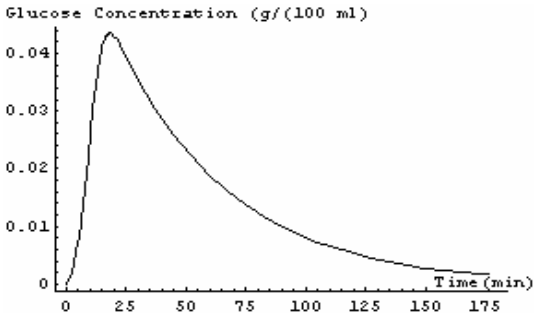

Fig. 4. Variation of glucose in plasma without control.

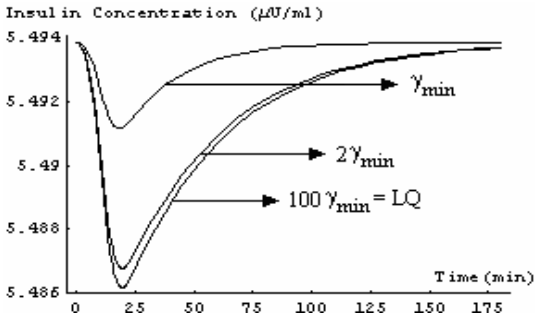

Fig. 5. Variation of insulin concentration in case of LQ and minimax control.

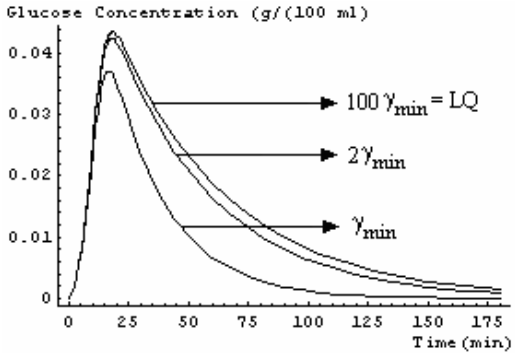

Fig. 6. Variation of glucose in plasma with LQ and minimax control.

Using these LQ and minimax control strategies, the dynamical performance of the non-linear closed loop system has been carried out for a food (sugar) intake.

6. CONCLUSIONS

The main advantage of the selected model from the control point of view, in comparison with the other mentioned models is, that it is on-line adaptive, based on strong theoretical foundations as well as describing 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 (Benett and Gourley, 2003; Mukhopadhyay *et al.*, 2004). Until now, the existing adaptive control models worked in a flip-flop manner, selecting the control command between two values, but they have neither physiological nor control theoretical background. Nowadays scientists are trying to obtain on-line adaptive control laws using compartment analysis, but results are still in an initial phase (Baura, 2002).

Although, in case of linear approach the control design was based on the linearized model, the control also improves the system response. The nonlinear optimal control employing only one control variable proved to be more effective than the traditional pole-placement control based on the linearized model (Benyo *et al.*, 1998; Benyo *et al.*, 2003). However, the existence of multiple solutions may jeopardize practical application. According to this case-study, the minimax control proved to be superior to the classical LQ. We plan to investigate other robust control strategies of this process employing models in the future.

However, until now these control strategies have not been implemented yet in a real (practical) application, after the necessary further verifications they could provide a useful help to control of blood glucose level, and in the optimization process of diabetic administration.

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