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Research Article

Quasi-Model-Based Control of Type 1 Diabetes Mellitus

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Glucose-insulin models appeared in the literature are varying in complexity. Hence, their use in control theory is not trivial. The paper presents an optimal controller design framework to investigate the type 1 diabetes from control theory point of view. Starting from a recently published glucose-insulin model a Quasi Model with favorable control properties is developed minimizing the physiological states to be taken into account. The purpose of the Quasi Model is not to model the glucose-glucagon-insulin interaction precisely, but only to grasp the characteristic behavior such that the designed controller can successfully regulate the unbalanced system. Different optimal control strategies (pole-placement, LQ, Minimax control) are designed on the Quasi Model, and the obtained controllers' applicability is investigated on two more sophisticated type 1 diabetic models using two absorption scenarios. The developed framework could help researchers engaging the control problem of diabetes.

1. Introduction

According to the data provided by the World Health Organization (WHO), diabetes mellitus is predicted to be the "disease of the future" especially in the developing countries (due to the stress and the unhealthy lifestyle). The diabetic population (in 2000, being estimated 171 million people) is predicted to be doubled by 2030 (366 million worldwide) [1].

The normal blood glucose concentration level in the human body varies in a narrow range (70–120 mL/dL). If for some reasons the human body is unable to control the normal glucose-insulin interaction (e.g., the glucose concentration level is constantly out of the above-mentioned range), diabetes is diagnosed. Type 1 (also known as insulin-dependent diabetes mellitus) is one of the four classified types of this disease (type 2, gestational-diabetes, and other types, like genetic deflections, are the other three categories of diabetes) and is characterized by complete pancreatic β-cell insufficiency [2]. As a result, the only treatment of patients is insulin injection (subcutaneous or intravenous, the latter only in case of patients in the Intensive Care Unit), usually administered in an open-loop manner.

From an engineering point of view, the treatment of diabetes mellitus can be represented by an outer control loop, to replace or artificially regulate the partially or totally deficient blood-glucose-control system of the human body. The quest for artificial pancreas can be structured in three different tasks: glucose sensor, insulin pump, and control algorithm problem [3, 4]. Current approaches to the artificial pancreas can be external (with subcutaneous insulin infusion and subcutaneous glucose sensing), internal (with intraperitoneal insulin infusion and intravenous glucose sensing), or hybrid (intraperitoneal insulin infusion and subcutaneous glucose sensing). Currently, the most affordable technology is the subcutaneous—subcutaneous route. This work investigates the case of internal artificial pancreas, therefore neglecting the sensor dynamics.

To design an appropriate control, an adequate model is necessary. In the last few decades many scientists have tried to create mathematical models describing the human blood glucose system. A brief overview can be found here [3, 5, 6]. The minimal model [7] proved to be the simplest one, but its simplicity proved to be its disadvantage, while in its formulation a lot of components of the glucose-insulin interactions were neglected. Therefore, more general models appeared [8–10]. These models focused on the physiology of glucose regulation. However, the regulation of glucose level by insulin involves multiple feedback controls at the

molecular and/or biochemical level. Although simplifications have been done, Liu and Tang [11] developed a new control model taking into account multiple signaling and metabolic pathways like insulin signaling pathway, the glucagon signaling pathway, and glycogen synthesis and degradation pathway.

Due to the fact that models of diabetic systems are imprecise by nature, the modeling of the glucose-insulin system and controlling its behavior are two tightly connected questions; hence the problems could not be discussed separately. Regarding the applied control strategies the palette is very wide [3, 5, 12].

In case of type 1 diabetes mellitus, the insulin secreted by the pancreas is insufficient, therefore, external insulin needs to be injected, whereas glucose intake can be regarded as disturbance to the system. Therefore, external automatic regulator needs to be applied in order to restore balance (Figure 1). In order to describe the problem formally, nomenclature of Control Theory should be applied. The patient that needs to be controlled has two inputs (intravenous insulin as control input (u), meal intake as disturbance (d)), and one output (blood glucose concentration (y)). The controller that must regulate the pathologic glucose household has one input (blood glucose concentration (y)) and one output (intravenous insulin—control input (u)). Several other conditions (stress, physical activity, illnesses) could effect glucose household of the patient, but their effect are not examined in this paper.

The aim of this paper is to present a controller design framework to investigate the type 1 diabetes from control theory point of view. A Quasi Model (a type 1 diabetes mellitus (T1DM) linear model) with favorable control properties is developed starting from the Liu-Tang model [11] minimizing the physiological states to be taken into account. Hence, different optimal control strategies can be designed for the simplified Quasi Model, and the obtained controllers can be tested on other more sophisticated glucose-insulin models. As a result, the developed framework could help researchers engaging in the control problem of diabetes.

The paper is organized as follows: in Section 2 the methodology is presented, including the brief description of the Liu-Tang model, the development of the Quasi Model, and the optimal control strategies to be used (pole-placement method, observer development, LQ, and Minimax control). Section 3 presents the results obtained on two sophisticated glucose-insulin models using two different absorption scenarios. This is followed by discussion part (Section 4) and ended with conclusions (Section 5).

2. Methods

The kernel of the controller design framework is represented by the created Quasi Model, which is summarized below. In order to develop this simple, but useful model, physiological and mathematical considerations are taken into account. The chapter also briefly summarizes the optimal control methods which are used to demonstrate the utility of the developed framework.

2.1. The Liu-Tang Model. In contrast with the previous models, like Bergman et al. [7] and Sorensen [8], the recently published model of Liu and Tang [11] applies a more straightforward approach: it describes some of the aspects of the human blood glucose system at molecular levels (more exactly takes some biochemical considerations into account). Consequently, the cause-effect relations are more plausible, and different functions and processes can be separated. Its complexity is somewhere halfway between the minimal model of Bergman et al. [7] and the most complex Sorensen model [8].

The model can be naturally divided into three subsystems: the transition subsystem of glucagon and insulin, the receptor binding subsystem, and the glucose subsystem. Here, only main parameters and variables are explained, and detailed description and parameters can be found in [11] or [13].

The first two equations denote concentrations of glucagon (s_1^p) and insulin in plasma (s_2^p):

$$\begin{aligned}\frac{ds_1^p}{dt} &= -k_{1,1}^p s_1^p - k_{1,2}^p s_1^p + w_1,\\ \frac{ds_2^p}{dt} &= -k_{2,1}^p s_2^p - k_{2,2}^p s_2^p + w_2,\end{aligned} \tag{1}$$

where w_1 and w_2 stand for glucagon and insulin produced by the pancreas (w_2 being zero in case of T1DM [13]). The positive constants $k_{j,1}^p$ denote transition rates and $k_{j,2}^p$ the degradation rates ($j = 1, 2$).

The receptor binding system is captured by four equations:

$$\begin{aligned}\frac{ds_1}{dt} &= -k_{1,1}^s s_1 (R_1^0 - r_1) - k_{1,2}^s s_1 + \frac{k_{1,1}^p s_1^p V_p}{V},\\ \frac{ds_2}{dt} &= -k_{2,1}^s s_2 (R_2^0 - r_2) - k_{2,2}^s s_2 + \frac{k_{2,1}^p s_2^p V_p}{V},\\ \frac{dr_1}{dt} &= k_{1,1}^s s_1 (R_1^0 - r_1) - k_1^r r_1,\\ \frac{dr_2}{dt} &= k_{2,1}^s s_2 (R_2^0 - r_2) - k_2^r r_2,\end{aligned} \tag{2}$$

where s_1 and s_2 stand for intracellular concentrations of glucagon and insulin, while r_1 and r_2 denote concentrations of glucagon- and insulin-bound receptors. As constants, R_1^0 and R_2^0 denote total concentrations of receptors, $k_{j,1}^s$ stand for the hormone-receptor association rates, $k_{j,2}^s$ for the degradation rates, and k_j^r for the inactivation rates ($j = 1, 2$). Plasma volume is denoted by V_p, whereas V is intracellular volume.

Finally, the glucose system is represented by two equations:

$$\begin{aligned}\frac{dg_1}{dt} &= \frac{k_1 r_2}{1 + k_2 r_1} \frac{V_{\max}^{gs} g_2}{K_m^{gs} + g_2} - k_3 r_1 \frac{V_{\max}^{gp} g_1}{K_m^{gp} + g_1},\\ \frac{dg_2}{dt} &= -\frac{k_1 r_2}{1 + k_2 r_1} \frac{V_{\max}^{gs} g_2}{K_m^{gs} + g_2} + k_3 r_1 \frac{V_{\max}^{gp} g_1}{K_m^{gp} + g_1} - F + G_{\text{in}},\end{aligned} \tag{3}$$

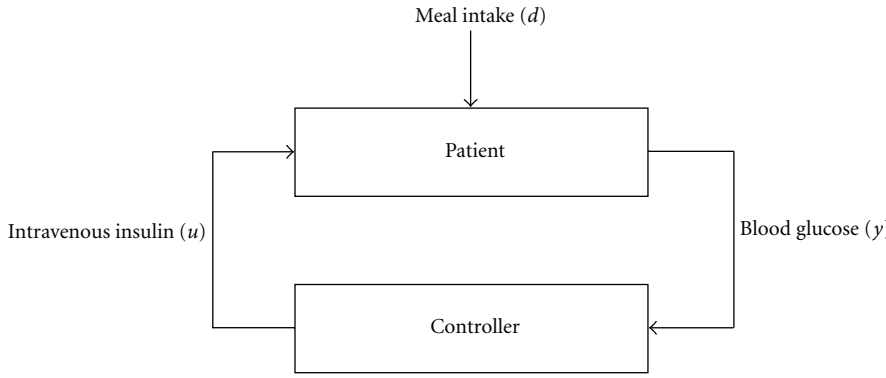


Figure 1: Diagram of the closed-loop system.

where g_1 represents the glycogen and g_2 the glucose concentration and

$$F = f_1(g_2) + f_2(g_2) f_3(s_2), \tag{4}$$

with

$$\begin{aligned} f_1(g_2) &= U_b\left(1 - e^{-g_2/C_2}\right), \\ f_2(g_2) &= \frac{g_2}{C_2}, \\ f_3(s_2) &= U_0 + \frac{(U_m - U_0)(s_2/C_4)^\beta}{1 + (s_2/C_4)^\beta}. \end{aligned} \tag{5}$$

$f_1(g_2)$ represents the insulin-independent part, while $f_2(g_2)$ and $f_3(s_2)$ the insulin-dependent part. U_b, C_2, U_0, U_m, C_4, and β are constants [11].

Hormones of the pancreas have a cardinal role in blood glucose regulation and homeostatic stability, since negative feedback of glucagon and insulin through blood glucose level assures controllability (in medical sense):

$$w_1(g_2) = \frac{G_m}{1 + b_1 e^{a_1(g_2 - C_5)}}, \tag{6}$$

$$w_2(g_2) = \frac{R_m}{1 + b_2 e^{a_2(C_1 - g_2)}}, \tag{7}$$

where $w_1(g_2)$ and $w_2(g_2)$ denote glucagon and insulin secretion of the pancreas.

2.2. Physiologic Evaluation and Model Reparametrization. In order to analyze the model in a quantitative manner, a physiologically correct input has to be defined for G_{in}. Using the absorption curve presented in [14] (the same used in [11] for model validation) gut-blood circulation transfer function can be neglected, since it has already been taken into account.

Observing Figure 2 (reproducing results of Liu and Tang [11]) it can be seen that the behavior of the system is in accordance with physiologic expectations: the absorption of exogenous glucose is followed by the activation of the insulin pole. The "two-hump" behavior of the system is widely known in medical practice: the first intense and short phase of hormone secretion is followed by a long and moderate

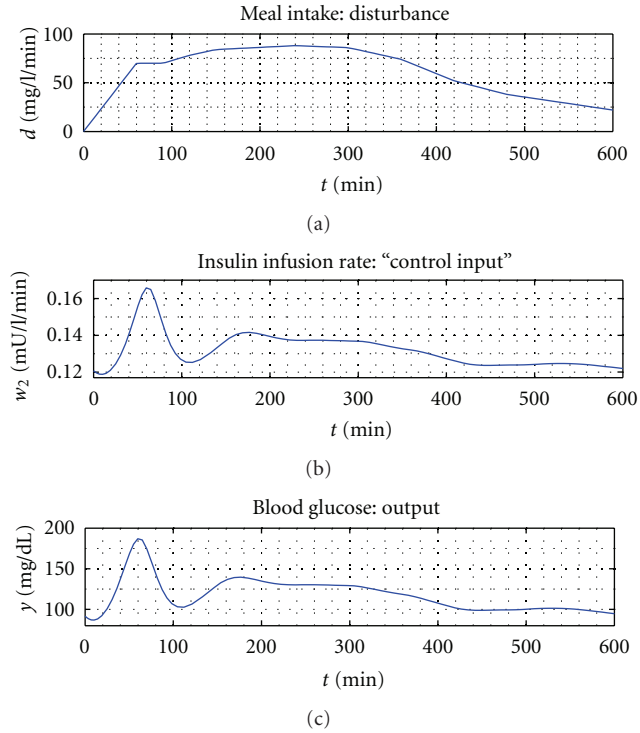


Figure 2: Open-loop simulation results of the original Liu-Tang model.

period assuring rapid reaction and precise correction as well [2].

The original Liu-Tang model is only capable of describing the healthy human blood glucose system, although a type 1 diabetic model is required for controller design. Therefore, the model is reparameterized in order to describe type 1 diabetes mellitus [13].

In case of type 1 diabetes mellitus, insulin secretion of the pancreas becomes insufficient to regulate blood glucose. Equation (7) describes the insulin infusion rate of the pancreas, where R_m denotes the saturation value of pancreatic insulin secretion. In order to model type 1 diabetes mellitus, R_m has to be decreased resulting in unsatisfactory pancreatic insulin secretion. By setting the

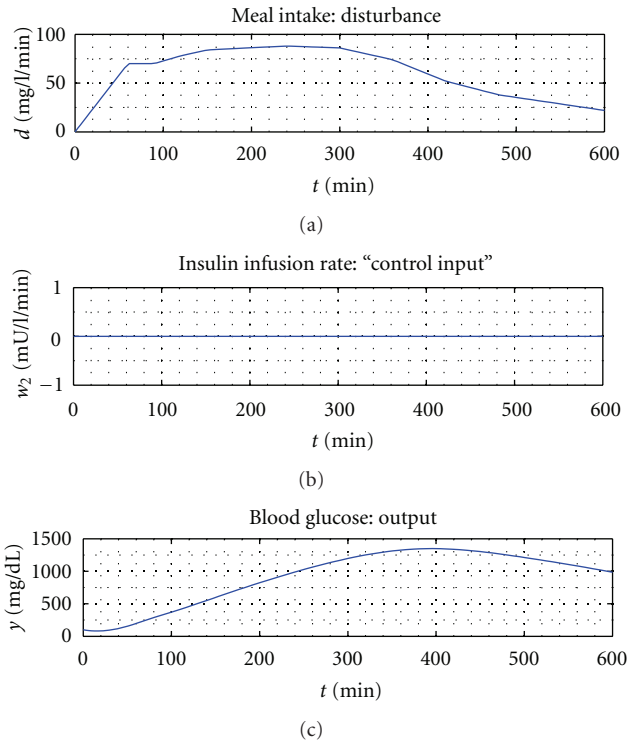


Figure 3: Open-loop simulation results of the modified Liu-Tang model (type 1 diabetic).

value of R_m to zero, simulation results can be seen in Figure 3. As it is expected, blood glucose level is far out of healthy region, and only decreasing due to glucose utilization, not because of insulin's control effect [2].

2.3. Quasi Model. The Liu-Tang model is a nonlinear system, and controlling a nonlinear system is not a trivial task. Controlling linear systems however has a vast theoretical background, and there is a wide range of tools available to implement a proper controller. Therefore, especially in our current case when the system is needed to be maintained in a certain steady state, linearization and creating controller for this linearized system are good approach. Linearizing the Liu-Tang model, one may face some serious problems.

(1) Elements of the system matrix vary in a wide range, since it spans to 10^{16}. Therefore, the full rank system is extremely sensitive to numerical imprecisions, and further usage is problematic given the fact that it is ill conditioned.

(2) Control properties of the full rank system are not perfect, since the rank of the controllability matrix is 6, whereas the rank of the observability matrix is 5. Therefore, the system is neither controllable, nor observable.

(3) Model reduction results in a transformed system where state variables do not have any physiological meaning. Therefore, their application cannot be carried out since measurements will not have any connection to actual state variables.

(4) Simply selecting state variables from the full-rank system do not take interconnections into account. For instance, selecting plasma insulin, glucagon, and glucose the system matrix is

$$A_3 = \begin{bmatrix} -0.44 & 0 & -9.21 \times 10^{-14} \\ 0 & -0.31 & 0 \\ 0 & 0 & -0.02 \end{bmatrix}, \tag{8}$$

and it can be seen that neither of the control hormones has any effect on glucose, therefore the model is completely useless.

Therefore, another solution has to be found.

2.3.1. Creating the Quasi Model. In order to avoid the above-mentioned problems, a simple, but useful linear model can be created. The goals are as follows:

(1) elements of the system matrix should be from a narrow range,

(2) controllability and observability,

(3) state variables should have physiological meaning,

(4) interconnections should be taken into account.

In order to create a physiologically plausible and useful model, three state variables should be considered: the two control hormones, insulin (x_1) and glucagon (x_2), and the regulated variable, plasma glucose (x_3 and y). Control input of the model is intravenous insulin (u), whereas glucose intake should be considered disturbance (d).

The developed Quasi Model is a simple linear system with one control input (intravenous insulin), one output (plasma glucose), and one disturbance (glucose intake):

$$\dot{x} = Ax + Bu + Ld, \tag{9}$$

$$y = Cx, \tag{10}$$

where $B = [1\ 0\ 0]^T$, $L = [0\ 0\ 1]^T$, and $C = [0\ 0\ 1]$. It has to be remarked that the Quasi Model has only one output: plasma glucose concentration.

The main contribution of this modeling technique which helps us overcome the above-mentioned problems is that we do not derive the simplified model directly from a complex nonlinear model, but we define the structure of the model based on theoretical and control theoretic aspects, and we use the behavioral simulation of the more complex Liu-Tang model for parameter tuning of the system matrix A in (9) of the Quasi Model.

In order to check the physiologically correct behavior of the model, glucose absorption input based on experiments presented in [14] and reproduced by Liu and Tang [11] is applied. In normal individuals the plasma glucose is restored to premeal basal levels in approximately 120 min for a normal meal (≈1 g glucose/kg body weight), but for a very large meal (≈4.5 g glucose/kg body weight) this period is up to 360 min [14]. Korach-André et al. [14] experimented 8

healthy active male subjects (age 22.4 ± 0.6; weight 68.0 ± 0.9 kg; height 175.7 ± 1.5 cm; BMI (kg/m^2) = 22.1 ± 0.6) after a starch meal in form of polished and parboiled rice (5 g dry mass/kg body mass). Absorption profile of the experiment (see Figure 4 of [14]) was reproduced by Liu and Tang [11] (see Figure 6 of their paper) presenting a 120 g CHO absorption scenario.

For our case this situation can be regarded as a worst-case disturbance (= large meal intake) as meal intake is not directly incorporated in the model, but treated as a disturbance, which makes the control task harder. This method is used for long time in control theory, and the bigger the meal intake (disturbance) is, the harder the control task becomes.

It has to be remarked that the system is linearized in steady state [10 10 100] [11], which should be handled as the equilibrium of the Quasi Model. In the following subsection we show the numerical values for the system matrix A of the Quasi Model (9) in case of a healthy patient.

2.3.2. Healthy System. In case of the healthy system, regulation mechanism is intact and it functions properly: there is enough insulin to decrease the elevated glucose level and insulin receptors are not insensitive to insulin.

The system matrix is

$$A = \begin{bmatrix} -1 & -0.05 & 0.5 \\ -0.05 & -2 & -0.05 \\ -1.2 & 0.01 & -0.05 \end{bmatrix}, \tag{11}$$

as a result of iterative parameter tuning. The initial values of the entries are chosen such that they are in accordance with theoretical expectations [2], and they are tuned by Monte Carlo algorithm until they are in accordance with simulation results made on the original Liu-Tang model. For an example of Monte Carlo methods regarding glucose-insulin modeling the reader should check [16].

It should be emphasized here that the aim of this linear model is not to describe the accurate operation of the human blood glucose regulation system. The main contribution of the Quasi Model is to get a simple model which holds the characteristics of the original system, which yields only qualitative, but not quantitative description. This model can be used for controller designs, which can be tested on the clinically more reliable models. Hence, the Quasi Model is only a tool for control engineers, and it cannot be directly used in clinical aspects.

One good property of the system matrix (11) of the Quasi Model is that the entries of the matrix have physiological meaning. In particular, the entry $a_{1,2}$ means that the glucagon concentration decreases insulin secretion, while $a_{1,3}$ means that the plasma glucose concentration increases insulin secretion. The meaning of the other entries is straightforward.

2.3.3. Type 1 Diabetes Mellitus. In case of type 1 diabetes mellitus, regulation mechanism does not function properly: there is no insulin to decrease the elevated glucose level; however, insulin receptors are not insensitive to insulin. We can get a system matrix for the type 1 diabetes mellitus by canceling the terms $a_{1,2}$ and $a_{1,3}$ from (11) that describe the sensitivity of the insulin secretion on plasma glucose and glucagon, thus turning the pancreas off.

Therefore, the system matrix is

$$A = \begin{bmatrix} -1 & 0 & 0 \\ -0.05 & -2 & -0.05 \\ -1.2 & 0.01 & -0.05 \end{bmatrix}. \tag{12}$$

In control theoretic point of view, the resulting system matrix gives a stable system, since the eigenvalues of the system matrix (12) have negative real part:

$$\begin{aligned} \lambda_1 &= -0.0503, \\ \lambda_2 &= -1.9997, \\ \lambda_3 &= -1.0000. \end{aligned} \tag{13}$$

Despite that the subsystem of the insulin x_1 is not affected by the other two state variables, it still has effect on the blood glucose concentration and the glucagon concentration, so the output in question is still controllable. One can easily check this by calculating the controllability matrix of the system, which is full rank.

2.4. Controller Design. This section presents optimal control methods used to test the utility of the Quasi Model defined in the previous section. The purpose of the developed framework is to help control engineers create and test control laws for blood glucose regulation system. In this section, several examples are elaborated.

In order to check the applicability of the Quasi Model, different feedback controllers are designed and checked later on clinically more comprehensive models. First we design a feedback control with pole-placement, which is one of the simplest feedback design techniques. Then we design an observer, since in practice only the blood glucose concentration can be measured, and we need all the state variables available for feedback. Next, LQ control and H_2/H_∞ (also known as Minimax) control [17] are considered.

2.4.1. Pole-Placement. General feedback scenarios mean that the input signal is calculated from the state variables as

$$u = -Kx, \tag{14}$$

where K is the feedback matrix. This yields a closed-loop system:

$$\dot{x} = (A - BK)x, \tag{15}$$

where the new system matrix is $A - BK$ which can be influenced by the K feedback. The closed-loop system matrix can be defined by its eigenvalues in case of pole-placement design technique, so the engineer has to specify the new poles of the controller system, thus specifying the speed of the regulation.

The feedback matrix (K) can be calculated by the well-known Ackermann formula [18], namely,

$$K = e_n^T M_c^{-1} \varphi_c(A), \tag{16}$$

where e_n is the nth unity vector, M_c is the controllability matrix of the system and $\varphi_c(\cdot)$ is the characteristic polynomial of the (desired) closed-loop system.

By setting the desired poles bigger than the original ones, four scenarios are observed and the feedback matrices are

$$\begin{aligned} K_{2\lambda} &= \begin{bmatrix} 3.0500 & -0.0070 & -0.1655 \end{bmatrix}, \\ K_{5\lambda} &= \begin{bmatrix} 12.2000 & -266.4993 & -11.0642 \end{bmatrix}, \\ K_{10\lambda} &= \begin{bmatrix} 27.4500 & -1369.2061 & -73.4722 \end{bmatrix}, \\ K_{20\lambda} &= \begin{bmatrix} 57.9500 & -4321.5648 & -435.9781 \end{bmatrix}. \end{aligned} \tag{17}$$

Simulating closed-loop responses on the Quasi Model, it can be seen in Figure 4 that control properties get better by increasing the value of closed-loop poles; however, control input gets bigger too (for glucose absorption scenario we have used the same curve that was used in [11], e.g., large meal intake of Korach-André et al. [14]). This is completely in accordance with theoretical expectations, since the bigger the λ (bigger eigenvalues), the faster the system [18]. In the following we will take into account only the case of 2λ as this case is physiologically plausible.

This technique is not as explicit as the upcoming LQ and Minimax design techniques in the means of the resulting signals; however it is not negligible since the engineer can freely define the closed-loop model.

2.4.2. Observer Design. In the general feedback scenario we need the values of the state variables, however in practice only the blood glucose concentration can be measured. To overcome this problem we design an observer that estimates the state variables from the measured blood glucose concentration and the insulin input defined by the controller.

Let us consider the observer in the form

$$\frac{d\hat{x}}{dt} = F\hat{x} + Gy + Hu, \tag{18}$$

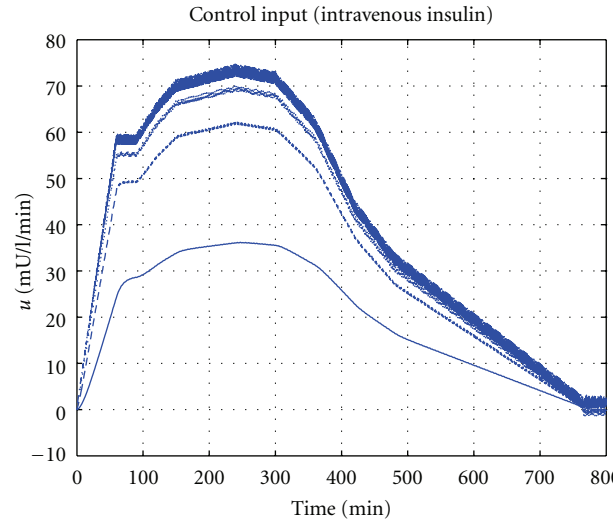
where $\hat{x}$ is the approximated state vector, and let $\tilde{x}$ denote estimation error. Hence

$$\tilde{x}(t) = x(t) - \hat{x}(t). \tag{19}$$

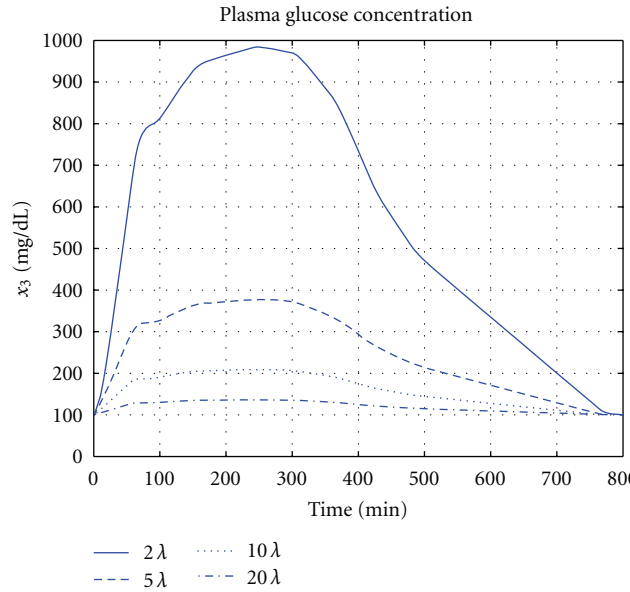
Therefore, design requirement is [18]

$$\lim_{t \to \infty} \tilde{x}(t) = 0. \tag{20}$$

According to Ackermann's formula [18], the $K_{\text{virtual}} = G^T$ controller can be calculated as the virtual feedback for a virtual system represented by $A_{\text{virtual}} = A^T$ and $B_{\text{virtual}} = C^T$. Desired poles of the observer should be fast, at least faster than the poles of the closed-loop system, therefore, a possible choice can be ten times faster [18].



(a) Control Input (Intravenous Insulin)



(b) Output (Plasma Glucose)

Figure 4: Closed-loop simulation results in case of Pole-Placement Control.

Consequently, the observer can be designed in three steps:

(i) $G = K_{\text{virtual}}^T$,

(ii) $F = A - GC$,

(iii) $H = B$.

2.4.3. LQ and Minimax Control. Using the general form of a dynamic LTI (linear time invariant) system

$$\begin{aligned} \dot{x} &= Ax + Bu, \\ y &= Cx, \end{aligned} \tag{21}$$

in case of a classical linear quadratic (LQ) control [17, 18] the requirement is to minimize the following quadratic cost functional:

$$J(x,u,d) = \frac{1}{2}\int_0^\infty \left[x^T(t)Qx(t) + u^T(t)Ru(t)\right]dt. \quad (22)$$

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 $t \in [0,\infty]$ such that $J(u^*(t)) \leq J(u(t))$. However, the optimal solution is satisfied only under the chosen Q and R matrices. Hence, adequate matrices are key issues of the LQ method.

Considering the Quasi Model the disturbance (glucose) should be overweighted in the discussion of Q and R matrix, as it is much "cheaper" than insulin [19]. Hence, the obtained LQ controller for the $u^x = -Kx$ control law is [20]

$$K = \begin{bmatrix} 0.1942 & -0.0009 & -0.1775 \end{bmatrix}. \quad (23)$$

Minimax control is greatly similar to classical LQ method, however, it takes disturbance into account [17]. Let us consider the LTI system

$$\begin{aligned} \dot{x} &= Ax + Bu + Ld, \\ y &= Cx \end{aligned} \quad (24)$$

with initial condition $x(0) = x_0$ and disturbance $d(t)$.

Now, the problem is to find a control $u(t)$ that minimizes the quadratic functional:

$$J(x,\overline{u},d) = \frac{1}{2}\int_0^\infty \left[x^T(t)x(t) + \overline{u}^T(t)\overline{u}(t) - \gamma^2 d^T(t)d(t)\right]dt. \quad (25)$$

Now, the disturbance $d(t)$—as it appears with a negative sign—attempts to maximize the cost, while we want to find a control $\overline{u}(t)$ that minimizes the maximum cost achievable by the disturbance (by the worst case disturbance). This is a case of the so-called "worst-case" design and leads to the formulation of a differential-game [17]:

$$\max_{d(t)} J(\overline{u}(t), d(t)) \longrightarrow \min_{\overline{u}(t)} J(u(t), d(t)). \quad (26)$$

According to Zhou [17], the solution of the $\overline{u} = -Kx$ optimal control problem in case of the considered Quasi Model is in the form of [20]

$$K = \begin{bmatrix} 0.3582 & -0.0016 & -0.3154 \end{bmatrix}. \quad (27)$$

2.4.4. Closed-Loop System. Consequently, the general closed-loop system consists of four blocks (Figure 5)

(1) Type 1 Diabetic Model: $(u,d) \rightarrow y$.

(2) Absorption Model: $m \rightarrow d$.

(3) Observer: $(u,y) \rightarrow \hat{x}$.

(4) Feedback Gain: $\hat{x} \rightarrow u$.

The Controller consists of two subsystems: the observer and the feedback gain, which can be either the pole-placement, LQ Control or the minimax control feedback matrix.

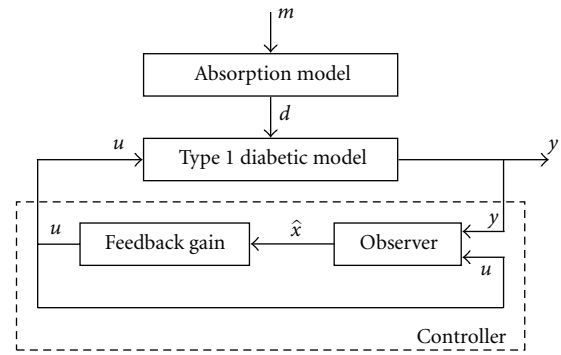


Figure 5: Structure of the closed-loop system.

3. Results

In order to observe the performance and robustness of the designed controller, several different input data should be used on the reparameterized Liu-Tang model and modified Sorensen model [21].

The required input of the model is glucose absorbed from the gut, so providing plausible data is not a trivial task. One possibility is to use a static absorption profile like the one presented in [14]. Through this virtual, but realistic, absorption data can be generated. A more convenient approach would be the use of validated dynamic system for approximating oral glucose absorption, such as the one presented by Dalla Man et al. [15]. In this chapter, both methods will be examined and used.

3.1. Virtual Absorption Scenarios Based on Large Meal Intake Absorption. Based on theoretical models of absorption [23], the glucose absorption rate can be considered to follow a Weibull curve:

$$g = p_3\left(\frac{t}{p_1}\right)^{p_2} e^{-(t/p_1)^{p_2}}, \quad (28)$$

where g stands for glucose absorption rate. Observing the role of parameters p_1, p_2, and p_3, it can be seen that

(i) p_1 corresponds to the input scaling; in other words, it scales the curve along the horizontal axis,

(ii) p_2 determines the shape of the curve, since it can be interpreted as a time constant of the system,

(iii) p_3 scales the curve along the vertical axis.

3.2. Absorption Scenarios Based on Dalla Man et al. [15]. The meal simulation model of Dalla Man et al. [15] describes the glucose transit through the stomach and intestine to the plasma in case of enteral feeding. Glucose intestinal absorption is modeled by a three-compartment model: the stomach being described by two compartments and the gut by a single compartment.

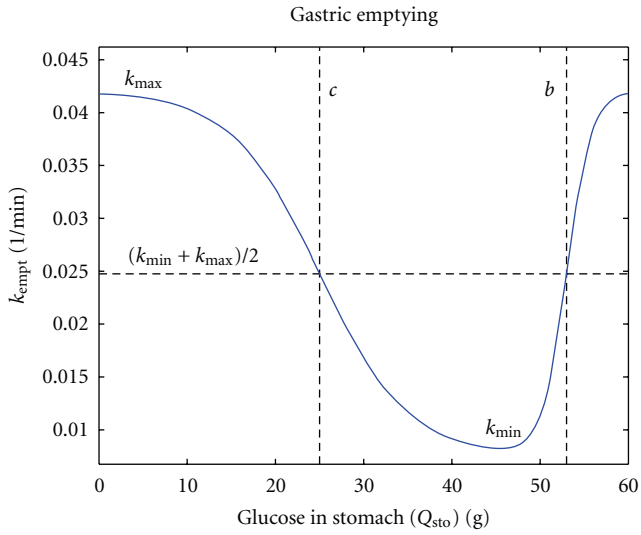


FIGURE 6: Change of gastric emptying rate (k_{empt}) using the meal model of Dalla Man et al. [15] for 60 g CHO.

The key issue of the model is the rate of gastric emptying (k_{empt}), a nonlinear function of the glucose amount in the stomach (Q_{sto}):

$$k_{empt} = k_{min} + \frac{k_{max} + k_{min}}{2} \times \left[\tanh(\alpha(Q_{sto} - bD)) - \tanh(\beta(Q_{sto} - cD)) + 2\right],$$
$$\alpha = \frac{5}{2D(1-b)},$$
$$\beta = \frac{5}{2Dc}. \tag{29}$$

It can be seen that k_{empt} is on its maximum value (k_{max}) when the stomach contains D amount of ingested glucose. Then k_{empt} decrease with the rate of α to a minimal value (k_{min}), but shortly after it rises back to the maximum with the rate of β.

c is the percentage of the dose for which k_{empt} decreases at the value $(k_{max} + k_{min})/2$, and similarly b represents the percentage of the dose for which k_{empt} rises back from its minimal value to $(k_{max} + k_{min})/2$ [15]. The change of k_{empt} is shown on Figure 6, where the usual amount of 60 g carbohydrate (CHO) intake used in the literature was considered.

3.3. Considered Absorption Scenarios. In our case three carbohydrate intake absorption scenarios are considered (Figure 7): small meal intake (30 g CHO), normal meal intake (60 g CHO), and large meal intake (100 g CHO). When using the Weibull-curve, the same meal scenarios were used, where the parameters of the Weibull-curve were set to approximate the output of the model of Dalla Man et al. [15] during small meal intake, while when using a large meal intake the curve was fitted to the absorption profile of

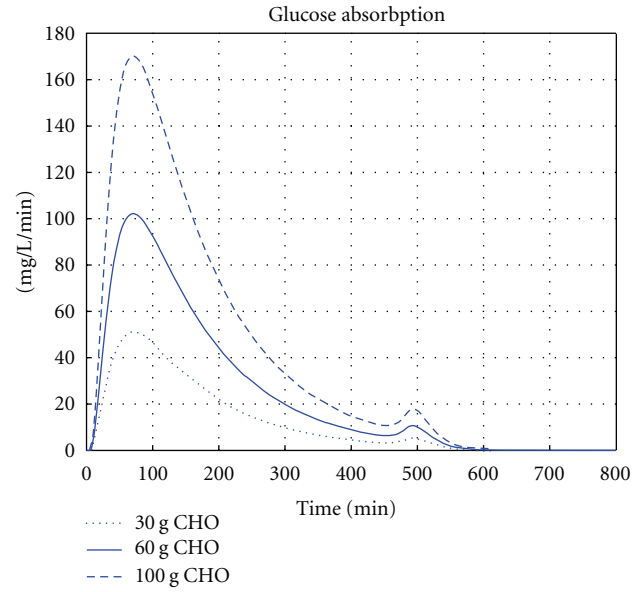


FIGURE 7: Absorption scenarios taken into account based on the meal model of Dalla Man et al. [15].

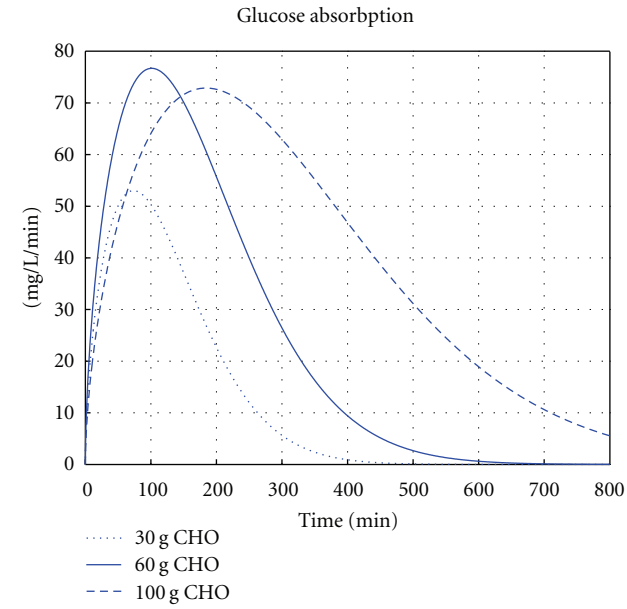
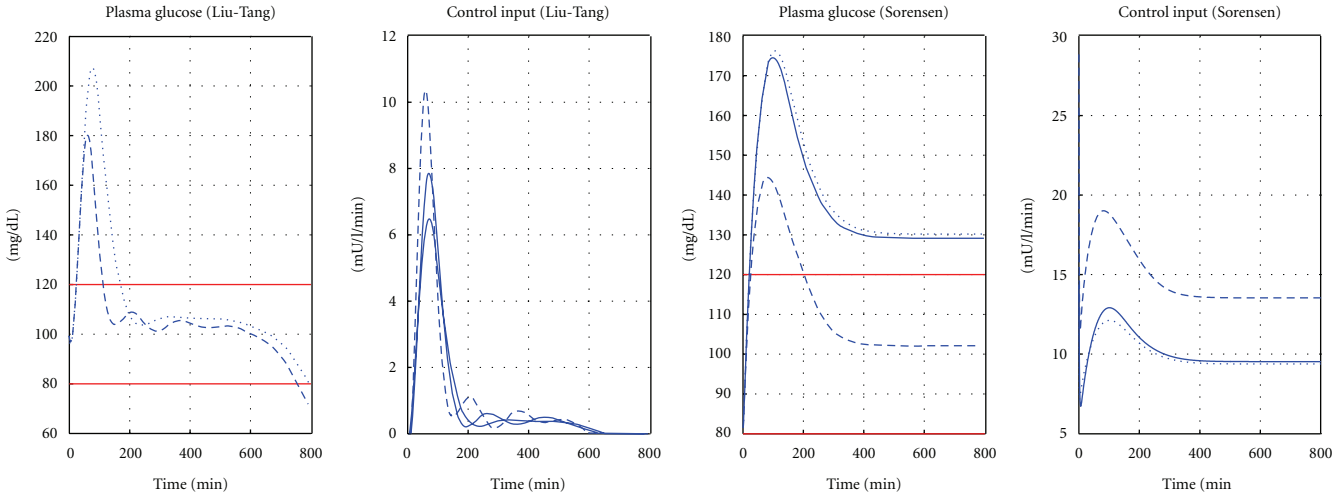


FIGURE 8: Absorption scenarios taken into account based on the use of the Weibull-curve.

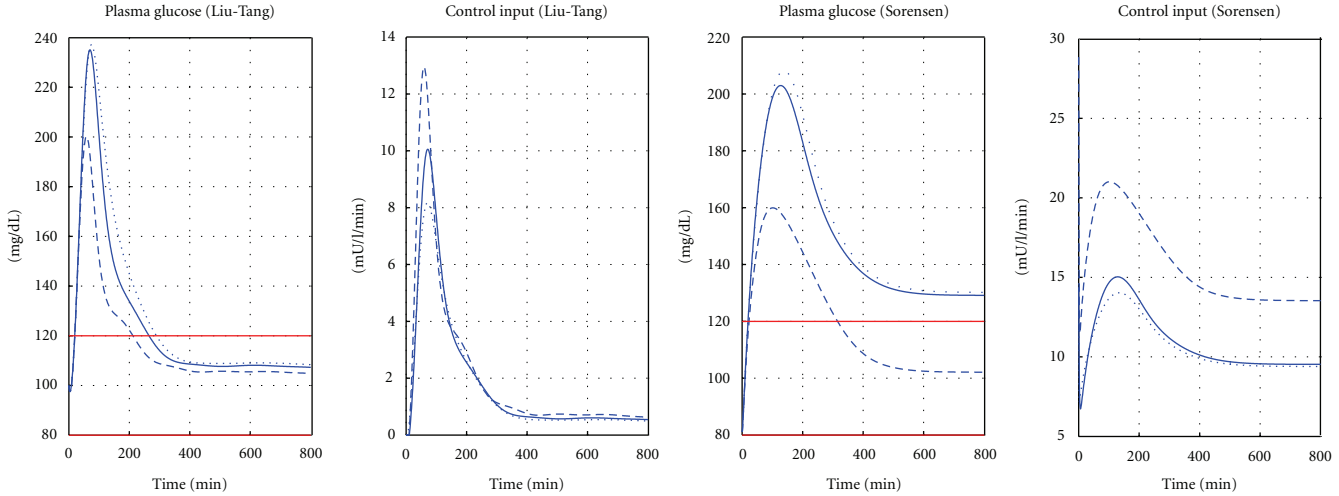
Korach-André et al. [14]. Finally, normal meal intake was using both characteristics (Figure 8).

All three meal scenarios through static and dynamic meal absorption were tested on both the reparameterized Liu-Tang model and the modified version of the Sorensen-model [21] using pole-placement (for the case of 2λ), LQ, and Minimax control methods.

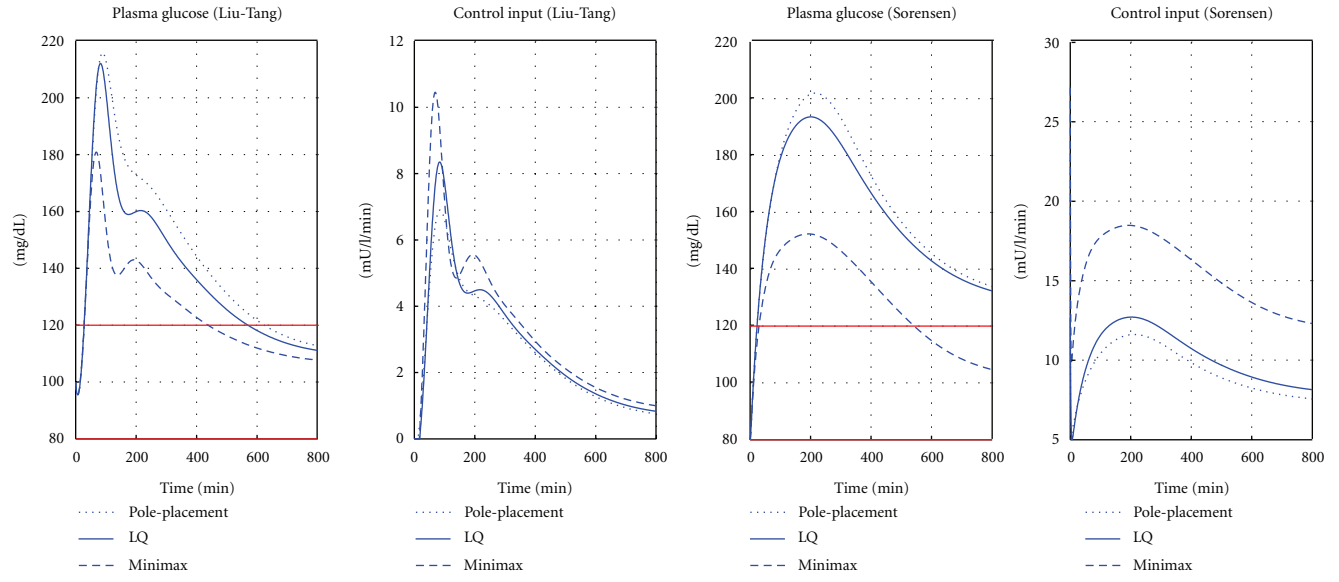
Figures 9(a)–9(c) represent the static absorption profiles, while Figures 10(a)–10(c) represent the dynamic system of Dalla Man et al. [15] with the carbohydrate intake in ascending order. in all figures the plasma glucose concentration and



(a) Glucose and control input variation for 30 g CHO absorption scenario

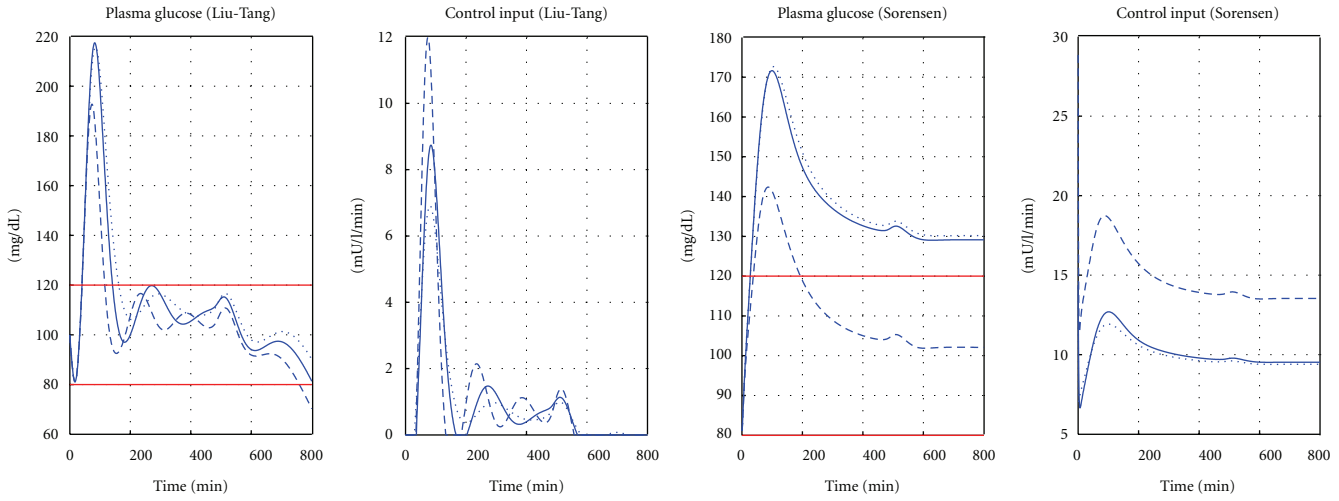


(b) Glucose and control input variation for 60 g CHO absorption scenario

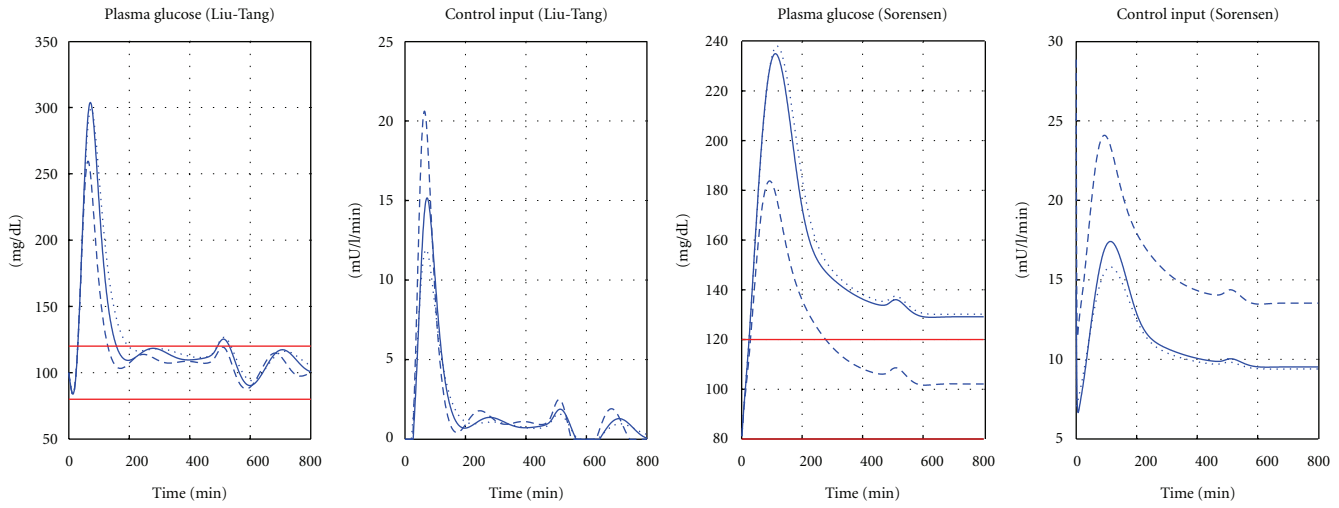


(c) Glucose and control input variation for 100 g CHO absorption scenario

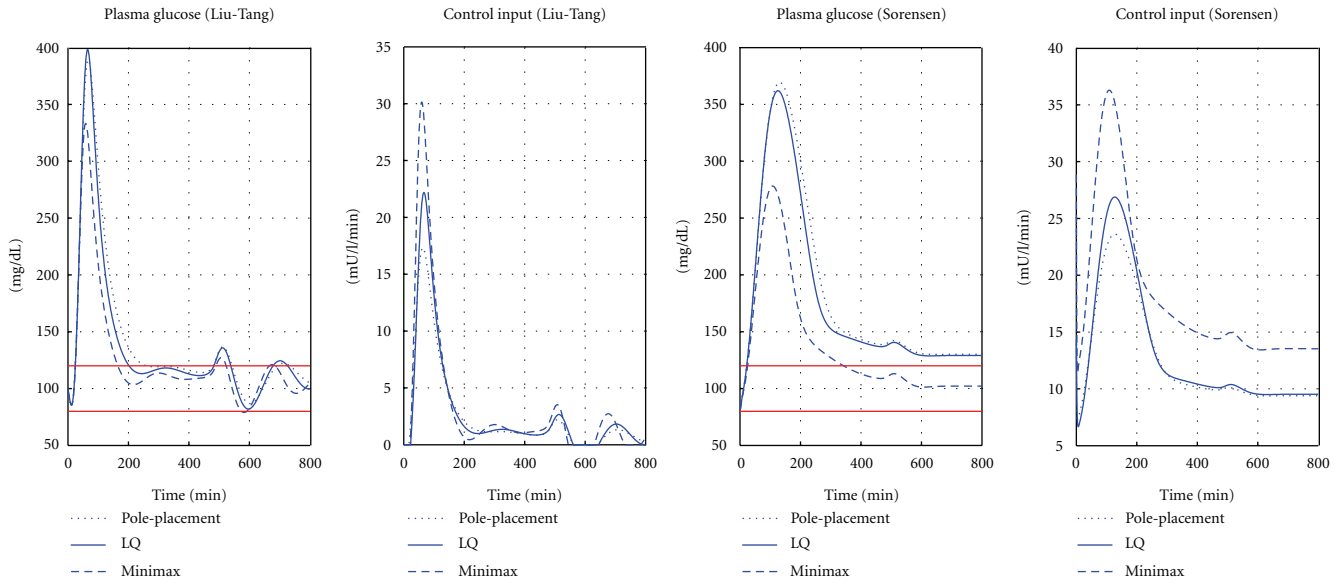
Figure 9: Comparison of pole-placement, LQ, and minimax control methods on the modified Liu-Tang model and modified Sorensen-model for the three dynamic absorption scenarios taken into account.



(a) Glucose and control input variation for 30 g CHO dynamic absorption scenario



(b) Glucose and control input variation for 60 g CHO dynamic absorption scenario



(c) Glucose and control input variation for 100 g CHO dynamic absorption scenario

Figure 10: Comparison of pole-placement, LQ, and minimax control methods on the modified Liu-Tang model and modified Sorensen model for the three static absorption scenarios taken into account.

the controller output are displayed for both physiological models (reparameterized Liu-Tang and modified Sorensen) with the three control methods compared.

4. Discussion

For the considered absorption scenarios results can be seen in Figures 9 and 10 for both modified Liu-Tang model and Sorensen model. All controllers manage to bring the output of the reparameterized Liu-Tang model within the desired range, but only Minimax control can acceptably regulate the Sorensen-model. This is in accordance with theoretical acceptation as the Minimax control is connected to modern robust control methodology based on hard constraints [17].

The widely known "two-hump behavior" can be observed only on the Liu-Tang model. Due to the differences in the considered models, the glucose peaks also differ. This can be explained with the fact that the Liu-Tang model was created on the Korach-André et al. [14] large meal (e.g., 120 g CHO) absorption scenario and also on the fact that the created framework started from the Lui-Tang model.

We should emphasize again that our goal was not to create the precise model of glucose absorption with the Weibull-curve, but to generate plausible absorption curves based on Korach-André et al. [14]. The Weibull-curve originally meant to describe drug absorption, which is usually not as complex as oral glucose absorption after mixed meal.

Regarding the applied control methods, it can be seen that the Minimax control gives better results, especially by means of maximal plasma glucose concentration, proving control theory results [17]: Minimax control is an extension of the classical LQ method.

The hypoglycemia trend observed in Figures 9(a) and 10(a) can be explained as the dual effect of small CHO intake and sufficiently long time to absorb the meal intake. Consequently, in case of these scenarios the next CHO intake should take place sooner.

It has to be remarked that the controller is developed for the Quasi Model, which is only a rough approximation of the type 1 diabetic system; however, when the controller is applied to the modified Liu-Tang model and the modified version of the Sorensen-model the closed-loop system produces the desired behavior.

5. Conclusion

An optimal controller design framework to investigate T1DM from control theory point of view was developed. First we created the structure of a linear Quasi Model (both healthy and type 1 diabetic versions) based on theoretical and control aspects, and then the parameters were tuned using Monte Carlo algorithm. The Liu-Tang model was used for validation in parameter tuning. Next, optimal control techniques (pole-placement, LQ, and Minimax methods) were applied to the type 1 diabetic version of the Quasi Model, proving that it can be successfully and easily used for controller design. Validation of the developed controllers, as well as demonstration of the performance and robustness of the developed framework was emphasized on different absorption scenarios and use of two more sophisticated glucose-insulin models: the reparameterized Liu-Tang model and the modified Sorensen-model. Consequently, the developed framework could help researchers engaging the control problem of diabetes as well as in physiological control education.

Further research directions could focus on applying modern control methods to the Quasi Model (e.g., modern robust control) or testing the developed framework on other well-known and sophisticated type 1 diabetic models (e.g., [9, 10]). Moreover, the additional dynamics resulting from subcutaneous insulin infusion and subcutaneous glucose sensing should be added and handled by the controller. In [22] suitable models are presented.

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