**Proceedings of the 18th World Congress**
**The International Federation of Automatic Control**
**Milano (Italy) August 28 - September 2, 2011**

# Quasi Model Based Optimal Control of Type 1 Diabetes Mellitus ⋆

**Levente Kovács, * András György, Péter Szalay, Dániel A. Drexler, Balázs Benyó, Zoltán Benyó**

* *Dept. of Control Engineering and Information Technology, Budapest University of Technology and Economics (BME IIT), Hungary e-mail: {lkovacs, gyorgya, szalaip, drexler, bbenyo, benyo}@iit.bme.hu).*

**Abstract:** The paper presents an optimal controller design framework to investigate the type 1 diabetes from control theory point of view. The starting point of the problem is based on a recently published glucose-insulin model (Liu and Tang [2008]). Based on this a Quasi Model (a type 1 diabetes linear model) with favorable control properties is developed minimizing the physiological states to be taken into account. Consequently, different optimal control strategies (LQ, minimax control) can be designed on the Quasi Model, and the obtained controller applicability is investigated on more sophisticated type 1 diabetic models. It has to be remarked that it is not the purpose of the Quasi Model to model precisely the glucose-glucagon-insulin interaction, only to grasp the characteristic behavior such that the designed controller can successfully regulate the unbalanced system. In order to validate the applicability of this method, absorption scenarios taken from the model of Dalla Man et al. [2007] are generated and the controller is tested on the modified Liu-Tang model (Liu and Tang [2008]) as well as on the modified Sorensen model (Parker et al. [2000]).

Keywords: Type 1 diabetes mellitus, Quasi Model, Liu-Tang model, Sorensen model, Minimax Control

## 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. The diabetic population (in 2000, being estimated 171 million people) is estimated to be doubled by 2030 (Wild et al. [2004]).

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 quest for artificial pancreas can be structured in three different tasks: glucose sensor, insulin pump, and control algorithm problem (Cobelli et al. [2009], Harvey et al. [2010]).

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 minimizing the physiological states to be taken into account. Different optimal control strategies are developed for the Quasi Model and tested in case of the transformed Liu-Tang model (Liu and Tang [2008]).

⋆ The research was supported in part by the National Office for Research and Technology (NKTH), Hungarian National Scientific Research Foundation grant OTKA CK80316, K82066. It is connected to the scientific program of the "Development of quality-oriented and harmonized R+D+I strategy and functional model at BME" project, supported by the New Hungary Development Plan (Project ID: TÁMOP-4.2.1/B-09/1/KMR-2010-0002).

### *1.1 Earlier Results*

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 (Chee and Fernando [2007]). The minimal model (Bergman et al. [1981]) 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 interaction were neglected. Therefore, more general models appeared (Sorensen [1985], Hovorka et al. [2004], Dalla Man et al. [2007], Liu and Tang [2008]).

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 (Parker et al. [2001], Makroglou et al. [2006], Cobelli et al. [2009]).

### *1.2 Problem Formulation*

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. 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 consitions (stress, physical activity, illnesses) could effect glucose household of the patient, but their effect are not examined in this paper.

The article is organized as follows: in Section 2, the novel Quasi Model is presented, which is followed by observer development and the presentation of LQ and Minimax (extended LQ or $H_2/H_\infty$ control in Section 3. Absorption scenarios and simulation results can be found in Section 4, which is followed by the conclusions in Section 5.

## 2. QUASI MODEL

The kernel of the controller design framework is represented by the created Quasi Model summarized below. In order to develop this simple but greatly useful model, physiological and mathematical considerations are taken into account.

### *2.1 The Liu-Tang Model*

A recently appeared model of the human blood glucose system capable of describing some aspects at molecular level too, is the Liu-Tang model Liu and Tang [2008] with its eight state variables. Since the original model only describes the healthy system, type 1 diabetic version can be found in Kovács et al. [2009].

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, detailed description and parameters can be found in Liu and Tang [2008] or Kovács et al. [2009].

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

$$\frac{\mathrm{d}s_1^p}{\mathrm{d}t} = -k_{1,1}^p s_1^p - k_{1,2}^p s_1^p + w_1, \tag{1}$$

$$\frac{\mathrm{d}s_2^p}{\mathrm{d}t} = -k_{2,1}^p s_2^p - k_{2,2}^p s_2^p + w_2, \tag{2}$$

where $w_1$ and $w_2$ stand for glucagon and insulin produced by the pancreas ($w_2$ being zero in case of T1DM (Kovács et al. [2009])). 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:

$$\frac{\mathrm{d}s_1}{\mathrm{d}t} = -k_{1,1}^s s_1 \left(R_1^0 - r_1\right) - k_{1,2}^s s_1 + \frac{k_{1,1}^p s_1^p V_p}{V}, \tag{3}$$

$$\frac{\mathrm{d}s_2}{\mathrm{d}t} = -k_{2,1}^s s_2 \left(R_2^0 - r_2\right) - k_{2,2}^s s_2 + \frac{k_{2,1}^p s_2^p V_p}{V}, \tag{4}$$

$$\frac{\mathrm{d}r_1}{\mathrm{d}t} = k_{1,1}^s s_1 \left(R_1^0 - r_1\right) - k_1^r r_1, \tag{5}$$

$$\frac{\mathrm{d}r_2}{\mathrm{d}t} = k_{2,1}^s s_2 \left(R_2^0 - r_2\right) - k_2^r r_2, \tag{6}$$

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:

$$\frac{\mathrm{d}g_1}{\mathrm{d}t} = \frac{k_1 r_2}{1 + k_2 r_1} \frac{V_{max}^{gs} g_2}{K_m^{gs} + g_2} - k_3 r_1 \frac{V_{max}^{gp} g_1}{K_m^{gp} + g_1}, \tag{7}$$

$$\frac{\mathrm{d}g_2}{\mathrm{d}t} = -\frac{k_1 r_2}{1 + k_2 r_1} \frac{V_{max}^{gs} g_2}{K_m^{gs} + g_2} + k_3 r_1 \frac{V_{max}^{gp} g_1}{K_m^{gp} + g_1} - F + G_{in}, \tag{8}$$

where $g_1$ represents the glycogen and $g_2$ the glucose concentration.

$$F = f_1(g_2) - f_2(g_2) f_3(s_2), \tag{9}$$

with

$$f_1\left(g_2\right) = U_b \left(1 - e^{-\frac{g_2}{C_2}}\right), \tag{10}$$

$$f_2\left(g_2\right) = \frac{g_2}{C_2}, \tag{11}$$

$$f_3\left(s_2\right) = U_0 + \frac{\left(U_m - U_0\right) \left(\frac{s_2}{C_4}\right)^\beta}{1 + \left(\frac{s_2}{C_4}\right)^\beta}. \tag{12}$$

$f_1(g_2)$ 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 $\beta$ are constants (Liu and Tang [2008]).

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 need to be maintained in a certain steady state, linearization and creating controller for this linearized system is a good approach.

### *2.2 Problems of Linearization and Model Reduction*

Linearizing the original Liu-Tang model Liu and Tang [2008], 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 partially controllable and observable.
(3) Model reduction results in a transformed systems where state variables do not have any physiological meaning (Kovács et al. [2009]). Therefore, their application can not 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

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

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

### *2.3 Creating the Quasi Model*

In order to avoid the above mentioned problems, a simple but greatly useful linear model can be created. The goals are:

(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):

$$\begin{aligned} \dot{x} &= Ax + Bu + Ld \\ y &= Cx \end{aligned}, \tag{13}$$

where $B = [\,1\ 0\ 0\,]^T$, $L = [\,0\ 0\ 1\,]^T$ and $C = [\,0\ 0\ 1\,]$ (system matrix $A$ is presented later on). It has to be remarked, that the Quasi Model has only one output: plasma glucose concentration.

In order to check the physiologically correct behavior of the model, the same glucose absorption input (Korach-Andre et al. [2004]) was applied, which was used in the simulation process of the Liu-Tang model (Liu and Tang [2008]). This can be as a worst-case disturbance, since it is recorded in case of large meal intake. It has to be remarked that the system is linearized in the steady state $[\,10\ 10\ 100\,]$ taken from Liu and Tang [2008].

In case of T1DM, regulation mechanism does not function properly: there is no insulin to decrease the elevated glucose level, however, insulin receptors are not insensitive to insulin.

Therefore, the system matrix is György [2010]

$$A = \begin{bmatrix} -1 & 0 & 0 \\ -0.05 & -2 & -0.05 \\ -1.2 & 0.01 & -0.05 \end{bmatrix}, \tag{14}$$

and simulation results can be seen in Fig. 1.

It can be seen in Fig. 1 that glucagon and glucose concentration do not have any effect on insulin, and plasma glucose concentration increases without any regulation. It has to be noted that blood glucose level reaches lethal region and only decreases because of decreasing meal intake.

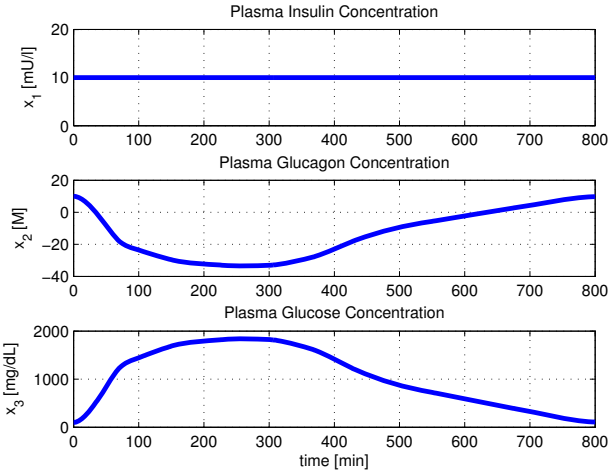



Fig. 1. Open-loop simulation results for the Quasi Model in case of type 1 diabetes mellitus

During the simulations, state variables are sometimes negative in case of T1DM, which is senseless in a physiological context (see variation of glucagon in Fig. 1). However, the Quasi Model is only a rough estimation and its purpose is to be used only together with the designed controller. Hence, in realistic situations it will not cause a problem at all (as it will be demonstrated later in the paper).

## 3. CONTROLLER DESIGN

This section is dedicated to the real purpose of the created framework, controller design. First, observer design is presented, since only plasma glucose is measurable under clinical conditions. Next, in order to check the applicability of the Quasi Model, LQ control and $H_2/H_\infty$ (also known as Minimax) control is considered Zhou [1996].

### *3.1 Observer Design*

Let us consider the observer in the form

$$\frac{d\hat{x}}{dt} = F\hat{x} + Gy + Hu, \tag{15}$$

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

$$\tilde{x}(t) = x(t) - \hat{x}(t). \tag{16}$$

Therefore, design requirement is (Lantos [2005])

$$\lim_{t\to\infty} \tilde{x}(t) = 0. \tag{17}$$

According to Ackermann's formula Lantos [2005], the $K_{virtual} = G^T$ controller can be calculated as the virtual feedback for a virtual system represented by $A_{virtual} = A^T$ and $B_{virtual} = C^T$. 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 Lantos [2005].

Consequently, the observer can be designed in three steps:

- $G = K_{virtual}^T$,
- $F = A - GC$,
- $H = B$.

### *3.2 LQ and Minimax Control*

Using the general form of a dynamic LTI (linear time invariant) system

$$\begin{array}{l} \dot{x} = Ax + Bu \\ y = Cx \end{array}, \tag{18}$$

in case of a classical linear quadratic (LQ) control (Zhou [1996], Lantos [2005]) the requirement is to minimize the following quadratic cost functional:

$$J(x,u,d) = \frac{1}{2}\int_0^\infty \left[x^T(t)Qx(t) + u^T(t)Ru(t)\right] dt, \tag{19}$$

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 (Kovács and Paláncz [2007]). Hence, the obtained LQ controller for the $u^x = -Kx$ control law is (György [2010]):

$$K = [\,0.1942\ \ -0.0009\ \ -0.1775\,]\,. \tag{20}$$

Minimax Control is greatly similar to classical LQ method, however, it takes disturbance into account Zhou [1996]. Let us consider the LTI system

$$\begin{array}{l} \dot{x} = Ax + Bu + Ld \\ y = Cx \end{array}, \tag{21}$$

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

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

Now, the disturbance $d(t)$ - as 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 Zhou [1996]:

$$\max_{d(t)} J\left(\overline{u}(t), d(t)\right) \rightarrow \min_{\overline{u}(t)} J(u(t), d(t)). \tag{23}$$

According to Zhou [1996], the solution of the $\bar{u} = -Kx$ optimal control problem in case of the considered Quasi Model is in the form of (György [2010])

$$K = [\,0.3582\ \ -0.0016\ \ -0.3154\,]\,. \tag{24}$$

### *3.3 Closed-Loop System*

The general closed-loop system consists of four blocks (see Fig. 2):

(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: $\hat{x} \rightarrow u$.

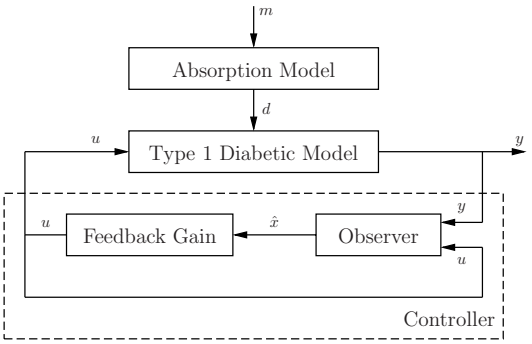



Fig. 2. Structure of the closed-loop system

The Controller consists of two subsystems: the Observer and the Feedback Gain, which can be either the LQ Control or the Minimax Control feedback matrix.

## 4. RESULTS

In order to observe the real performance and robustness of the designed controller, several different input data should be used in case of the transformed Liu-Tang model (Kovács et al. [2009]) and the modified Sorensen model (Parker et al. [2000]).

### *4.1 Absorption Scenarios*

In order to validate the applicability of this method, absorption scenarios taken from the model of Dalla Man et al. [2007] are generated.

The meal simulation model of Dalla Man et al. [2007] 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, the gut by a single compartment. The key issue of the model is the rate of gastric emptying ($k_{empt}$), a nonlinear function of the glucose amount in the stomach ($Q_{sto}$):

$$\begin{aligned} k_{empt} = k_{min} + \frac{k_{max} + k_{min}}{2}[\tanh\left(\alpha\left(Q_{sto} - bD\right)\right) - \\ - \tanh\left(\beta\left(Q_{sto} - cD\right)\right) + 2] \end{aligned} \tag{25}$$

$$\alpha = \frac{5}{2D\left(1-b\right)} \tag{26}$$

$$\beta = \frac{5}{2Dc}. \tag{27}$$

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 $\alpha$ to a minimal value ($k_{min}$), but shortly after it rises back to the maximum with the rate of $\beta$. $c$ is the percentage of the dose for which $k_{empt}$ decreases at the value $\frac{k_{max} + k_{min}}{2}$, and similarly $b$ represents the percentage of the dose for which $k_{empt}$ rises back from its minimal value to $\frac{k_{max} + k_{min}}{2}$ (Dalla Man et al. [2007]). The change of $k_{empt}$ is shown on Fig. 3, where the usual amount of 60 g carbohydrate (CHO) intake used in the literature was considered.

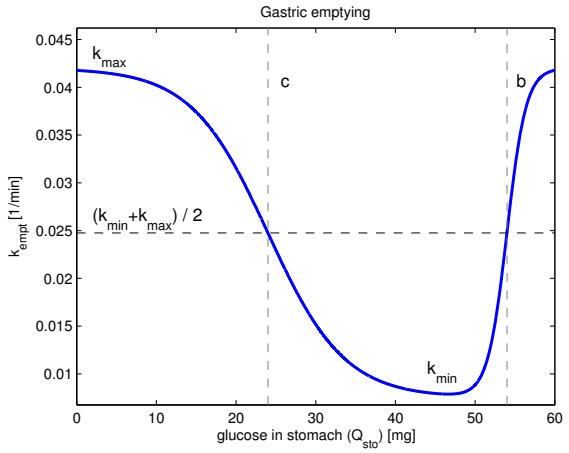



Fig. 3. Change of gastric emptying rate ($k_{empt}$) using the meal model of Dalla Man et al. [2007] for 60 g CHO

In our case three carbohydrate intake absorption scenarios are considered (Fig. 4): small meal intake (30g CHO), normal meal intake (60g CHO) and big meal intake: 100 g CHO. In all cases two consecutive meal intakes occurred with 8 hour interval between them.

### *4.2 Simulation Results*

For the considered absorption scenarios results can be seen in Fig. 5a–5c for both modified Liu-Tang model and Sorensen model. The controller performance is acceptable, since glucose level is kept in the desired range. The widely known "two-hump behavior" can be observed. Due to the differences in the considered models, the glucose peaks also differs. This can be explained with the fact that the Liu-Tang model was created on the Korach-Andre et al. [2004] big meal (e.g. 120g CHO) absorption scenario.

Regarding the applied control methods, it can be seen that the minimax control gives better results proving control theory results (Zhou [1996]) that it is an extension of the classical LQ method. Closed-loop stability has been confirmed in certain steady-state points for both models using the indirect method of Lyapunov (Lantos [2005]).

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 model of Sorensen, the closed-loop system produces the desired behavior. The parameters of the quasi model is identical in both simulations.

## 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. The Liu-Tang model was used for validation in parameter tuning. Next, optimal control techniques (LQ and Minimax methods) were applied to the type 1 diabetic version of the Quasi Model, proving that it can be successfully used for controller design. Validation of the developed controllers, as well as demonstration of

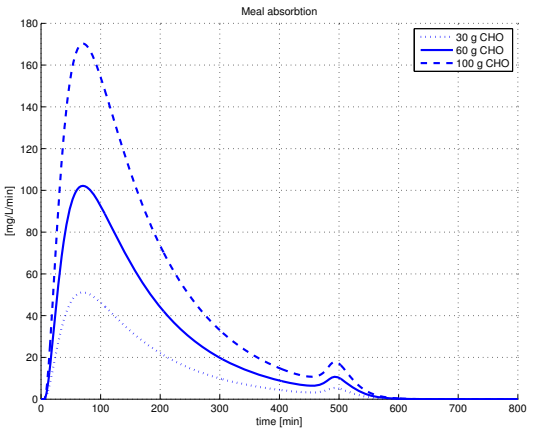



Fig. 4. Absorption scenarios taken into account based on the meal model of Dalla Man et al. [2007]

the performance of the developed framework were emphasized on different absorption scenarios and using of two 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.

## REFERENCES

R.N. Bergman, L.S. Phillips, and C. Cobelli. Physiological evaluation of factors controlling glucose tolerance in man. *Journal of Clinical Investigation*, 68:1456–1467, 1981.

F. Chee and T. Fernando. *Closed-Loop Control of Blood Glucose*. Springer, 2007.

C. Cobelli, C. Dalla Man, G. Sparacino, L. Magni, G. de Nicolao, and B. Kovatchev. Diabetes: Models, Signals, and Control (Methodological Review). *IEEE Reviews in Biomedical Engineering*, 2:54–96, 2009.

C. Dalla Man, R.A. Rizza, and C. Cobelli. Meal simulation model ofthe glucose-insulin system. *IEEE Transactions on Biomedical Engineering*, 54(10):1740–1749, 2007.

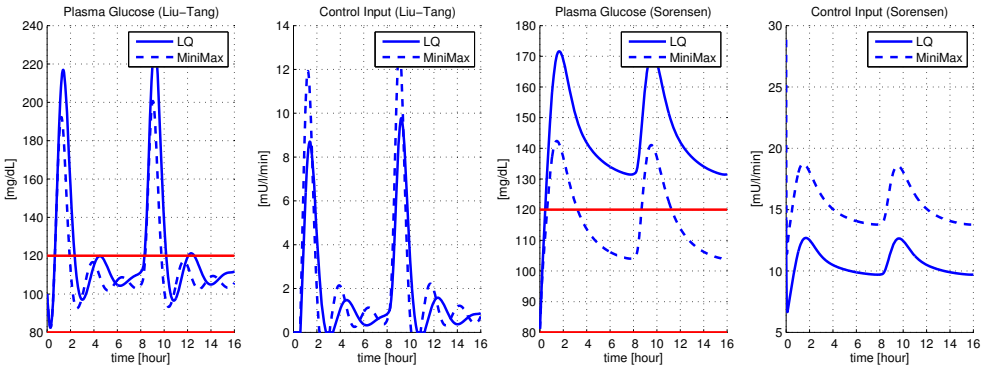
A. György. *Quasi Model Based Optimal Control of Type 1 Diabetes Mellitus*. MSc thesis, Budapest University of Technology and Economics, 2010.

R.A. Harvey, Y. Wang, B. Grossman, M.W. Percival, W. Bevier, D.A. Finan, H. Zisser, D.E. Seborg, L. Jovanovic, F.J.III. Doyle, and E. Dassau. Quest for the Artificial Pancreas. *IEEE Engineering in Medicine and Biology*, 29(2):53–62, 2010.

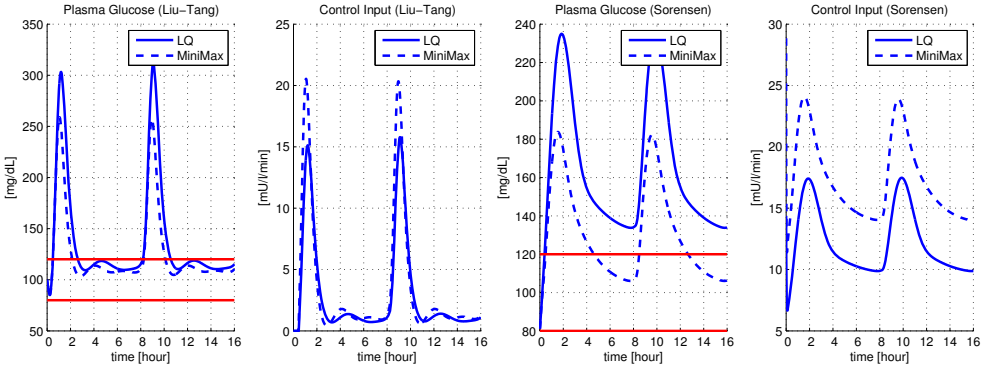
R. Hovorka, V. Canonico, L.J. Chassin, U. Haueter, M. Massi-Benedetti, M.O. Federici, T.R. Pieber, H.C. Schaller, L. Schaupp, T. Vering, and M.E. Wilinska. Nonlinear model predictive control of glucose concentration in subjects with type 1 diabetes. *Physiological Measurement*, 25:905–920, 2004.

M. Korach-Andre, H. Roth, D. Barnoud, M. Pan, F. Pronnet, and X. Leverve. Glucose appearance in the peripheral circulation and liver glucose output in men after a large 13c starch meal. *American Journal of Clinical Nutrition*, 80:881–886, 2004.

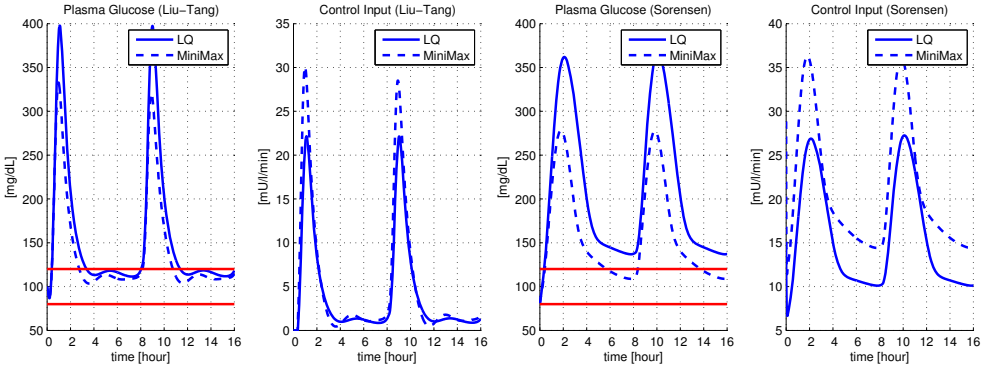
L. Kovács and B. Paláncz. Glucose-insulin control of type 1 diabetic patients in $H_2/H_\infty$ space via computer algebra. *Lecture Notes in Computer Science*, (4545):95–109, 2007.




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




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




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

Fig. 5. Comparison of classical LQ and Minimax control methods on the transformed Liu-Tang model and modified Sorensen model for the three absorption scenarios taken into account.

L. Kovács, A. György, Zs. Almássy, and Z. Benyó. Analyzing a novel model of human blood glucose system at molecular levels. *In Proceedings of the 10th European Control Conference*, pages 2494–2499, 2009.

B. Lantos. *Theory and Design of Control Systems I-II (in Hungarian)*. Akadémia, Budapest, 2005.

W. Liu and F. Tang. Modeling a simplified regulatory system of blood glucose at molecular levels. *Journal of Theoretical Biology*, 252:608–620, 2008.

A. Makroglou, J. Li, and Y. Kuang. Mathematical models and software tools for the glucose - insulin regulatory system and diabetes: an overview. *Applied Numerical Mathematics*, 56(3-4):559–573, 2006.

R.S. Parker, F.J.III. Doyle, J.H. Ward, and N.A. Peppas. Robust $H_\infty$ glucose control in diabetes using a physiological model. *AIChE Journal*, 46(12):2537–2549, 2000.

R.S. Parker, F.J.III. Doyle, and N.A. Peppas. The intravenous route to blood glucose control. *IEEE Engineering in Medicine and Biology*, 20(1):65–73, 2001.

J.T. Sorensen. *A Physiologic Model of Glucose Metabolism in Man and its Use to Design and Assess Improved Insulin Therapies for Diabetes*. PhD thesis, Massachusetts Institute of Technology, 1985.

S. Wild, G. Roglic, A. Green, R. Sicree, and H. King. Global prevalence of diabetes – estimates for the year 2000 and projections for 2030. *Diabetes Care*, 27(5): 1047–1053, 2004.

K. Zhou. *Robust and Optimal Control*. Prentice Hall, New Jersey, 1996.