SLOVAK UNIVERSITY OF TECHNOLOGY IN BRATISLAVA
FACULTY OF ELECTRICAL ENGINEERING
AND INFORMATION TECHNOLOGY

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DUAL-HORMONE CONTROL OF BLOOD GLUCOSE

Summary of dissertation thesis

Thesis submitted in fulfillment of the requirements
for the degree Doctor of Philosophy, PhD.
at the
Institute of Robotics and Cybernetics

Study Program:	Robotics and Cybernetics
Branch of Study:	9.2.7 Cybernetics

Bratislava 2016

Thesis was developed in a full-time doctoral study at Institute of Robotics and Cybernetics, Faculty of Electrical Engineering and Information Technology, Slovak University of Technology in Bratislava.

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Thesis summary was submitted on .....

Date and location of the dissertation thesis defense: .....
at Faculty of Electrical Engineering and Information Technology, Slovak University of Technology in Bratislava, Ilkovičova 3, 812 19 Bratislava.

Názov
Bihormonálne riadenie glukózy v krvi

Anotácia dizertačnej práce
Dizertačná práca sa zaoberá reguláciou hladiny glukózy v krvi u pacientov s diabetom typu 1. V práci sú popísané základné fyziologické znaky diabetu, liečebné postupy a dostupné technológie a je uskutočnená analýza súčasných riešení. Na základe analýzy je navrhnutý bihormonálny riadiaci algoritmus využívajúci inzulín a glukagón. Algoritmus využíva model s ARMAX štruktúrou na popis dynamiky glykémie. Model je možné identifikovať zo základných dát o pacientovi, prípadne jednoduchým experimentom, ak dáta nie sú známe. Štruktúra riadenia sa skladá z Kálmanovho filtra, prediktívneho regulátora (MPC) pre podávanie inzulínu, MPC alebo proporcionálno-derivačného regulátora pre podávanie glukagónu a z kalkulátora bolusového inzulínu. Glukagón predstavuje v uzavretej slučke iba bezpečnostný prvok. Inzulín je podávaný neagresívne, bez toho, aby regulátor dopredu uvažoval s možnosťou podania glukagónu. Inzulín a glukagón nikdy nie sú podávané súčasne. Prepínanie medzi regulátormi je riadené buď prekročením definovanej úrovne glykémie s hysteréziou alebo na základe predikcie hypoglykémie. Ďalej je predstavený adaptívny algoritmus s parametrami ARMAX modelu priebežne identifikovanými pomocou rekurzívnej metódy najmenších štvorcov. Výsledky dokazujú, že navrhnutý bihormonálny algoritmus riadenia poskytuje bezpečnú reguláciu glykémie a výrazne skracuje čas strávený v hypoglykémii. Algoritmus využíva glukagón efektívne a je schopný zabrániť vzniku ťažkej hypoglykémie aj pri neočakávanom zvýšení citlivosti na inzulín alebo po podaní nadmerného množstva bolusového inzulínu.

Title
Dual-hormone Control of Blood Glucose

Abstract
The thesis discusses blood glucose control algorithms, called an artificial pancreas (AP), for people with type 1 diabetes. The thesis provides an overview of the basic diabetes physiology, treatment and available technology and analyzes the current state-of-the-art solutions for the AP. Based on the analysis, we propose a control algorithm for a dual-hormone AP incorporating both insulin and glucagon. The algorithm utilizes an ARMAX model describing the glucose dynamics, which can be identified from the commonly known patient-specific data, or by conducting a simple experiment if the data is not available. The control structure includes a Kalman filter, a model predictive controller (MPC) for insulin infusion, an MPC or a proportional-derivative controller for glucagon infusion and

a bolus calculator. Glucagon is included as a safety feature in the closed-loop system, and the insulin dosing is performed non-aggressively without anticipating future glucagon administration. Insulin and glucagon are never administered simultaneously. The switch between insulin and glucagon is based either on a measured glucose level threshold with hysteresis or a prediction of upcoming hypoglycemia. In addition, an adaptive version of the algorithm is presented, where the ARMAX model is continuously identified using a recursive least squares method. The results indicate that the proposed dual-hormone control algorithm provides a safe glucose regulation and reduces the time spent in hypoglycemia significantly. The algorithm uses glucagon efficiently and prevents severe hypoglycemia even in the cases when the insulin sensitivity increases unexpectedly or the patient overestimates the mealtime insulin bolus sizes.

Introduction

The control theory offers numerous potential applications in biological systems and medical technology. The largest progress has been achieved in the field of cardiology and endocrinology [1]. One of the currently most interesting topics among the medical control applications is the blood glucose regulation in people with type 1 diabetes. International Diabetes Federation (IDF) already considers diabetes a worldwide epidemic and expects the number of diabetic patients to reach almost 600 million within a generation [2]. In several regions, the estimates show an alarming increase in type 2 diabetes among younger population as well as a rapid increase in newly onset type 1 diabetes [2]. According to Doyle et al. [1], development of a partial human pancreas replacement to improve glucose control remains the greatest challenge for control theory applications in biological systems.

Nowadays, patients with type 1 diabetes often still have to rely on a conventional insulin therapy, which requires their full attention to the glucose level monitoring, meal regimen and proper insulin dosing throughout the day and often also at night.

For decades, scientists have been in pursuit of an automated glucose control system called an artificial pancreas. The continuous insulin infusion systems together with recent development in the continuous glucose sensors and smart devices opened unprecedented possibilities for building a fully functional autonomous pancreas replacement. However, the glucose regulatory system in human body is incredibly complex. Despite a huge development in the glucose sensing, insulin pumps and control technology, safety of the artificial pancreas systems remains an issue that is still not fully resolved [3]. There is a variety of physiological limitations associated to the current way of insulin administration and glucose sensing. Together with the technical imperfections including sensor precision and reliability, these put large requirements on the control algorithm to ensure safe operation. A functional glucose control system would unburden the patients with type 1 diabetes from the demanding everyday routine of diabetes self-management and considerably increase the quality of their lives. Therefore, development of new control algorithms and their testing is still of extremely high importance.

The largest challenge in type 1 diabetes treatment is the compensation of the postprandial glucose peaks without inducing hypoglycemia later on, when the meal effects diminish and the insulin action prevails. Currently, even the fastest rapid acting insulin also offers the peak action too late and the action lasts too long. A possible solution to lower the risks arising from the mismatch between carbohydrate and insulin dynamics is to incorporate glucagon, a pancreatic hormone antagonistic to insulin, into

the control system. Glucagon action is opposite to insulin. It increases glucose concentration if it drops too low. Control system incorporating both insulin and glucagon is called a dual-hormone artificial pancreas. With glucagon available, the dual-hormone artificial pancreas has means to prevent hypoglycemia automatically, without the need for carbohydrate intervention by the patient. So far, the major problem associated with glucagon has been a lack of formulation stable in liquid form. Recently, several biotechnological companies have announced glucagon formulations with long-term stability in liquid form.

By combining the desired effects of insulin and glucagon, the dual-hormone control has a large potential to provide a better compensation of the blood glucose and improve the safety of artificial pancreas systems. This has been documented by several in- and out-patient trials [4–6].

The thesis provides an overview of the basic physiological principles related to type 1 diabetes and investigates the current solutions for the artificial pancreas including single- (insulin only) and dual-hormone control strategies. The second part of the thesis presents a dual-hormone control algorithm based on a linear model identifiable from basic patient-specific data. The algorithm consists of a Kalman filter, an insulin controller, a glucagon controller, a logic for controller switching and a bolus calculator. A continuous glucose monitor provides the glucose feedback to the control algorithm. In our solution, glucagon serves only as a safety feature. We focus on using glucagon efficiently, in a non-aggressive way. Therefore, safety of the insulin controller is the key aspect of the proposed control algorithm.

Thesis Goals

Safety remains the main concern of the AP systems. Most solutions focus solely on insulin to maintain euglycemia with no means available to counteract the effects of insulin on board in case of overdosing. Overdosing may result from an erroneous sensor reading, change in insulin sensitivity or other patient-specific parameters, intensive exercise or overestimation of a meal size. A number of clinical trials in [4–7], among others, provide strong evidence that a dual-hormone AP is able to reduce the risk and duration of hypoglycemic episodes and outperform the standard insulin therapy in terms of hyperglycemia compensation at the same time.

Nevertheless, performance of all the discussed current solutions is still incomparable with the quality of glucose regulation in a healthy individual. Therefore, further development of control algorithms for the artificial pancreas remains an important challenge for both medical and control engineering field. Hence, we summarize the thesis goals in the following

points.

- Develop patient-specific models of glucose-insulin and glucose-glucagon dynamics from available basic clinical data;
- Implement a Kalman filter as a state estimator and predictor;
- Design a dual-hormone control system for insulin and glucagon infusion based on the patient-specific models;
- Design a linear MPC for insulin infusion with input constraints and soft output constraints (asymmetric penalty function) and a time-varying reference trajectory to increase robustness;
- Investigatea different options for glucagon controller - a PD controller and an MPC (with asymmetric penalty function);
- Design a switching logic between insulin and glucagon controller;
- Investigate implementation of a single MIMO (in fact, MISO) MPC manipulating both insulin and glucagon infusion;
- Implement a method for continuous identification of the patient model used in the control system combining a priori known clinical data with CGM measurement to ensure meaningful physiological representation of the identified models;
- Design an adaptive control system for blood glucose control based on the continuous patient model identification;
- Test and validate the designed control systems using suitable simulation models.

1 Diabetes Mellitus

1.1 What Is Diabetes?

Diabetes is a chronic disease manifested by impaired control of blood glucose concentration. It occurs when pancreas is not able to produce enough insulin or when the body cannot use the insulin effectively. Insulin is needed for transportation of glucose into the cells where it is used as a source of energy. In people with diabetes the limited transportation causes hyperglycemia - increased glucose concentration in the blood and the interstitial tissue. Chronic hyperglycemia is associated to severe health complications [2, 8].

1.2 Type 1 Diabetes

Type 1 diabetes (T1D) results from a destruction of the β-cells of the islets of Langerhans in pancreas by own immune system. Hence, T1D belongs to autoimmune disorders. Development of the disease is related to genetic predispositions and other factors, such as illnesses, infections or diet in early years [8]. However, true causes of the autoimmune reaction are still not fully understood and the disease cannot be prevented. T1D can occur at any age, but mostly develops during childhood or young adulthood [2].

Even though the β-cells elimination occurs at various rates, most people with T1D will eventually end up with little or no insulin secretion. Without insulin, the glucose regulatory system of the body is critically impaired. Consequently, they need to administer exogenous insulin every day to keep their blood glucose under control and avoid serious complications or even death.

Acute Diabetes Complications

Diabetic ketoacidosis and severe hypoglycemia are the most common acute, life-threatening diabetic complications. These complications are mostly associated with T1D.

People with T1D have an impaired glucose counter-regulatory system, which is not able to react to decreasing glucose level. Overestimation of the insulin dose or change in insulin sensitivity over time may result in insulin-induced hypoglycemia. Mild hypoglycemia causes hunger, nervousness or changes in mood. Severe hypoglycemia (below ca. 2 mmol/L) may in extreme situations lead to a life-threatening diabetic coma [11].

1.3 Maintaining Euglycemia in T1D

Due to the lack of endogenous secretion of insulin, patients with T1D are required to administer exogenous insulin in order to maintain euglycemia. Nowadays, in addition to the conventional therapy, new technologies and progressive therapies are emerging.

1.3.1 Conventional Therapy

Usual insulin therapy is based either on multiple daily injections of insulin per day (MDI) with an insulin pen or on a continuous subcutaneous insulin infusion (CSII) using an insulin pump.

Drawbacks of the Conventional Therapy

MDI strategy is a very simple method of substituting the pancreatic insulin secretion in people with diabetes (T1D or T2D). Nevertheless, MDI with

carefully chosen insulin regimen is capable of providing a remarkable improvement in the diabetic control. Meta-studies indicate, that CSII with pre-meal insulin boluses gives good results for the patients who are not able to reach the glycemic control targets with MDI, but show little improvement for the patients with successful MDI strategy [19].

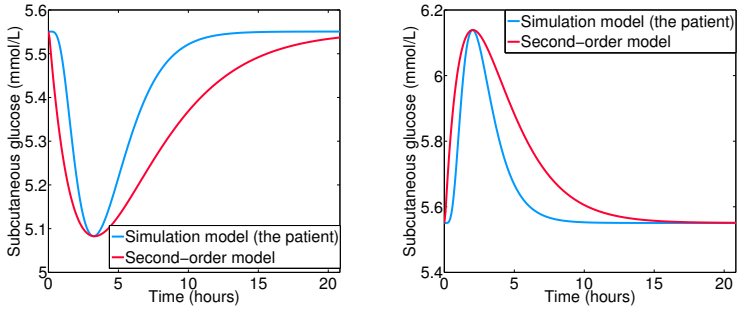
1.4 Technology & T1D Treatment

Since the discovery of insulin, it has been common for people with diabetes (either T1D or late stage of T2D) to inject themselves insulin several times a day to keep glycemia under control. Besides the conventional treatment drawbacks briefly discussed in 1.3.1, from the control point of view the usual therapy is far from perfect. For decades, missing measurement devices, which could be practically used and limited means of insulin administration represented fundamental problems in development of more advanced strategies of blood glucose control. Development of CGMs is an important step in both patient self-monitoring of blood glucose as well as in designing advanced algorithms for insulin administration. CGMs made the missing real-time glucose feedback practically available and therefore increase the potential of the intensive insulin therapy using CSII.

1.5 Artificial Pancreas

AP consists of a subcutaneous glucose sensor (a CGM), a subcutaneous insulin infusion system (insulin pump) and a control algorithm. This is often referred to as a sc-sc route [34]. Crucial part of the glucose control system is the control algorithm.

Research in the field of AP shows a remarkable progress. With both the CSII systems and CGMs available, various control strategies for glucose concentration control have been investigated. Among others, PID control [37–39], adaptive control [40–43], but also neural networks or fuzzy logic control [44, 45]. So far, the most successful control approach is the model predictive control (MPC), partly due to its ability to elegantly handle a broad range of system constraints [35,46,47]. Some groups have already included glucagon in their control systems [5, 6, 39, 54–57].



(a) Insulin pulse response

(b) Glucagon pulse response

Figure 1: Responses to insulin and glucagon boluses of the dual-hormone simulation model (the patient) and the second-order approximations. The sizes of the insulin and the glucagon boluses are 1U and 10μg, respectively.

2 Prediction Model and Filtering

2.1 Patient-specific Model for Glucose Prediction

2.1.1 The Deterministic Model

The deterministic part of the model takes form [69–72]

$$Y_D(s) = G_I(s)U_I(s) + G_G(s)U_G(s) \tag{1}$$

where $G_I(s)$, $G_G(s)$ are the glucose-insulin and glucose-glucagon transfer functions. $U_I(s)$, $U_G(s)$ denote the Laplace transforms of the subcutaneous insulin and glucagon infusion rates. Unlike the above mentioned studies on modeling the glucose dynamics, we use the following second order continuous-time transfer functions to describe the effects of subcutaneously administered insulin and glucagon [72]

$$G_I(s) = \frac{K_I}{(\tau_I s + 1)^2} \tag{2}$$

$$G_G(s) = \frac{K_G}{(\tau_G s + 1)^2} \tag{3}$$

Fig. 1 illustrates responses of the simulation model (a patient), and the corresponding linear models (2)-(3) identified as described above. The impulse-like responses correspond to 1 U insulin and 10 μg glucagon doses. The figure displays glucose concentrations in the subcutaneous tissue.

2.1.2 The Stochastic Model

By augmenting the noise term described in [42] to the discretized deterministic dual-hormone model we obtain a simple dual-hormone ARMAX model

$$y(t) = \frac{B_I(q^{-1})}{A_I(q^{-1})}u_I(t) + \frac{B_G(q^{-1})}{A_G(q^{-1})}u_G(t) + \frac{C(q^{-1})}{A_I(q^{-1})}\varepsilon(t), \tag{4}$$

After a rearrangement the model takes form

$$\bar{A}(q^{-1})y(t) = \bar{B}_I(q^{-1})u_I(t) + \bar{B}_G(q^{-1})u_G(t) + \bar{C}(q^{-1})\varepsilon(t) \tag{5}$$

2.1.3 Innovation Form State Space Model

The ARMAX model (5) can be expressed in an equivalent form as a linear time-invariant innovation form state space model [76] [77]

$$x_{k+1} = Ax_k + Bu_k + K\varepsilon_k \tag{6a}$$
$$y_k = Cx_k + \varepsilon_k \tag{6b}$$

where $\varepsilon_k \sim \mathcal{N}(0, R_\varepsilon)$ and $u_k = [u_{Ik} \;\; u_{Gk}]^T$ is a vector of the insulin and glucagon infusion rates computed at time instant k. We can realize the time-invariant matrices A, B, C, K in the canonical observer form as described in [76]. In reality, the white noise process, ε_k, is unknown. Therefore, we substitute the white noise, ε_k, with innovation, e_k, given by

$$e_k = y_k - C\hat{x}_{k|k-1} \tag{7}$$

where $\hat{x}_{k|k-1}$ is a one-step prediction of the state vector x_k computed at the previous sampling instant, $k-1$.

2.2 Kalman Filter - State Estimator and Predictor

Each time a new measurement is available, we update (estimate) the state vector using a stationary Kalman filter. As shown by Jørgensen et al. [77], due to the perfect correlation between the process and measurement noise in innovation form systems we can compute the filtered estimates as

$$e_k = y_k - \hat{x}_{k|k-1} \tag{8}$$
$$\hat{x}_{k|k} = \hat{x}_{k|k-1} + K_{fx,k}e_k = \hat{x}_{k|k-1} \tag{9}$$
$$\hat{w}_{k|k} = K_{fw,k}e_k = e_k \tag{10}$$

and the one-step prediction and the predictions further ahead (with $\hat{x}_{k|k} = \hat{x}_{k|k-1}$) are [77]

$$\hat{x}_{k+1|k} = A\hat{x}_{k|k-1} + Bu_{k|k} + Ke_k \tag{11a}$$

$$\hat{y}_{k+1|k} = C\hat{x}_{k+1|k} \tag{11b}$$

$$\hat{x}_{k+1+j|k} = A\hat{x}_{k+j|k} + Bu_{k+j|k} \qquad j = 1,2,...N-1 \tag{11c}$$

$$\hat{y}_{k+1+j|k} = C\hat{x}_{k+1+j|k} \qquad j = 1,2,...N-1 \tag{11d}$$

where N is the length of prediction horizon (number of samples).

The Kalman filter receives information about the current insulin and glucagon doses, and the computed future infusion profiles. The feedback from CGM enters the Kalman filter through the innovation (8). All the information is used for computation of the one-step prediction of the glucose concentration as well as the predictions further ahead.

It is important to note that by identifying the ARMAX model (5) with the innovation form state space representation (6), we directly obtain the Kalman filter one-step prediction gain, K.

3 Dual-hormone Control System

In this chapter we describe the design of a dual-hormone control system, which utilizes the patient-specific models introduced in Chapter 2. The CGM measurement provides feedback to the controller. The Kalman filter (Section 2.2) is used for state estimation and predictions.

The insulin and glucagon controllers are separated to easily avoid simultaneous infusion of insulin and glucagon. Insulin infusion is controlled by an MPC, while for glucagon we consider an MPC and a PD controller.

3.1 Insulin and Glucagon Controller Switching

The main reason for separating the insulin and glucagon controller, even under the MPC framework suiting MIMO systems well, is to avoid simultaneous infusion of insulin and glucagon in a straightforward way. We consider 2 different approaches to switching between the controllers.

Threshold Switching

The first strategy is based on the principle of a relay with additional hysteresis to prevent oscillations around the decision level. The insulin delivery is suspended and the glucagon controller is activated when the measured glycemia decreases below 4.5 (mmol/L). The insulin controller is activated again when the glycemia reaches 5 (mmol/L). At the same time we disable the glucagon controller.

Predictive Switching

The second strategy is based on the Kalman filter predictions. Whenever the Kalman filter predicts future hypoglycemia within a 2-hour horizon, we switch on the glucagon controller and switch off the insulin controller.

3.2 Insulin Controller

The insulin MPC uses prediction and control horizons of identical length, N. Due to the slow glucose-insulin dynamics discussed earlier, we use prediction (control) horizon of 10 hours, corresponding to $N = 120$. At each sampling instant, the optimal insulin dosing over the control horizon is obtained by solution of the constrained convex quadratic program (QP) in the form [70, 71]

$$\min_{\{u_{I;j},\eta_{j+1}\}_{j=0}^{N-1}} \phi \tag{12a}$$

$$s.t. \quad \hat{x}_{k+1|k} = A\hat{x}_{k|k-1} + B_I u_{I;\,k|k} + Ke_k \tag{12b}$$

$$\hat{y}_{k+1|k} = C\hat{x}_{k+1|k} \tag{12c}$$

$$\hat{x}_{k+1+j|k} = A\hat{x}_{k+j|k} + B_I u_{I;\,k+j|k} \quad j \in \mathcal{N}_1 \tag{12d}$$

$$\hat{y}_{k+1+j|k} = C\hat{x}_{k+1+j|k} \quad j \in \mathcal{N}_1 \tag{12e}$$

$$u_{I;\min} \leq u_{I;\,k+j-1|k} \leq u_{I;\max} \quad j \in \mathcal{N}_0 \tag{12f}$$

$$\hat{y}_{k+j|k} \geq y_{\min} - \hat{\eta}_{k+j|k} \quad j \in \mathcal{N}_0 \tag{12g}$$

$$\hat{y}_{k+j|k} \leq y_{\max} + \hat{\eta}_{k+j|k} \quad j \in \mathcal{N}_0 \tag{12h}$$

$$\hat{\eta}_{k+j|k} \geq 0 \quad j \in \mathcal{N}_0 \tag{12i}$$

with $\mathcal{N}_0$={1,...,N}, $\mathcal{N}_1$={1,...,N-1}. Apart from the system (model) dynamics, (12b) - (12e), we impose hard input constraints, (12f), and soft output constraints, (12g) - (12i). Using the soft constraints, the objective function, ϕ, takes the form [72]

$$\phi = \frac{1}{2}\sum_{j=0}^{N-1} \overbrace{\|\hat{y}_{k+1+j|k} - r_{k+1+j|k}\|^2 + \gamma\|\hat{\eta}_{k+1+j|k}\|^2}^{\text{glucose penalty function}} + \frac{1}{2}\sum_{j=0}^{N-1} \underbrace{\lambda_I \|\Delta u_{I;k+j|k}\|^2}_{\text{regularization term}} \tag{13}$$

In the glucose penalty function, the first term penalizes the error of tracking the reference trajectory, $r_{k+1+j|k}$, while the term,$\gamma\|\hat{\eta}_{k+1+j|k}\|^2$ penalizes violations of the soft output constraints (12g)-(12h), $\hat{\eta}_{k+j|k}$. The

lower and upper soft constraints, $y_{\min} = 4.5$ mmol/L and $y_{\max} = 10$ mmol/L, are asymmetrical with respect to the target (steady-state) glucose concentration of 5.5 mmol/L. The constraints setting corresponds to the limits of hypo- and hyperglycemia. By using a large weighting factor, $\gamma = 100$, we heavily penalize the glucose excursions into hypo- and hyperglycemic range [69–71].

By penalizing the changes in insulin delivery, the regularization term $\lambda_I \|\Delta u_{I;k+j|k}\|^2$ smoothens the control action, reduces the aggressiveness of insulin dosing and reduces the sensitivity to measurement noise. For each patient, the algorithm is individualized using the weighting coefficient λ. Based on simulation results, we empirically obtained the rule $\lambda_I = 600/u_{I;b}$ for the individualization using the basal insulin infusion rate, $u_{I;b}$, which maintains steady-state glucose level 5.5 mmol/L.

The computed insulin infusion rate is a deviation from the basal infusion rate, $u_{I;b}$.

3.2.1 Safety Modifications

Asymmetric Reference Trajectory

In order to avoid aggressive control actions due to the effects of sensor (estimation) error and increase robustness of the controller, we implement a time-varying reference trajectory. This approach has been applied previously [42, 80]. Computation of the desired trajectory is based on the current estimate of the glucose concentration, y_k, and depends on whether the estimate is above or below the target as follows [69–71]

$$r_{k+j|k}(t) = \begin{cases} y_k e^{-t/\tau_r} & \text{if } y_k \geq 0 \ \ (\sim BG \geq 5.5) \text{ mmol/L} \\ 0 & \text{if } y_k < 0 \ \ (\sim BG < 5.5) \text{ mmol/L} \end{cases} \tag{14}$$

Both r and y are deviations from the target concentration. If the glycemia is too high, we apply an asymptotic reference converging to the target, where the aggressiveness is limited by the time constant $\tau_r = 60$ min.

Limitation of the Maximal Insulin Dose

To further increase the safety of the algorithm, in each sampling instant we determine a maximal allowed insulin infusion rate from a set of simple rules as follows [42, 69–71]

$$u_{I;\max} = \begin{cases} 1.5u_{I;b} & \text{if } y_k \geq 4.5 \ \ (\sim BG \geq 10) \text{ mmol/L} \\ u_{I;b} & \text{if } 0 \leq y_k < 4.5 \ \ (\sim 5.5 \leq BG < 10) \text{ mmol/L} \\ 0 & \text{if } y_k < 0 \ \ (\sim BG < 5.5) \text{ mmol/L} \end{cases} \tag{15}$$

where $u_{I;max}$ and y are deviations from the basal insulin infusion rate and glucose target, respectively.

3.2.2 Mealtime Bolus Administration

We consider 2 different strategies of the bolus calculator implementation. Both strategies include bolus calculation based on the insulin-to-carbohydrate ratio, IC (U/g), and the meal size (g). The IC is easy to estimate from the ISF and the patient's glucose rise after meal of a known size. In principle, the value of IC itself describes the amount of bolus insulin units (U) needed to compensate the postprandial glucose peak following a meal of size 1g. Hence, the correct (full) bolus to compensate the peak following a meal containing CHO g of carbohydrates is given by

$$IB_{100} = IC \cdot CHO \quad (U) \tag{16}$$

Controller administers the bolus only if the meal and its size is announced by the patient at meal time. In addition, the control algorithm will not allow glucagon infusion in a 30 minute period following the announced meal ingestion.

Standard Bolus

To prevent an insulin overdose, we do not administer 100% of the bolus computed by (16). Instead, we adjust the dose according to the current glucose level estimate

$$IB = \begin{cases} 0.7\, IB_{100} & \text{if } y_k \geq -1 \;\; (BG \geq 4.5)\ \text{(mmol/L)} \\ 0.4\, IB_{100} & \text{if } -1.6 \leq y_k < -1 \;\; (3.9 \leq BG < 4.5)\ \text{(mmol/L)} \\ 0 & \text{if } y_k < -1.6 \;\; (BG < 3.9)\ \text{(mmol/L)} \end{cases} \tag{17}$$

Bolus with Insulin Suspension

In [72, 73] we consider a modified bolus administration strategy, where the bolus is also adjusted with a safety factor, $\kappa \in [0\,,\,1]$

$$IB = \kappa\, IB_{100} \tag{18}$$

In contrast to the first strategy, κ is not dependent on the current glucose level. We estimate its value for each virtual patient empirically with respect to the individual glucose-insulin dynamics. The slower the dynamics is, the lower κ is chosen to avoid late hypoglycemia.

Results of Walsh and Roberts [84], Bondia et al. [85] and Boronat et al. [86] provide evidence supporting this approach due to mismatch between the insulin and meal dynamics. The results indicate that the so-called "super bolus" [84] provides better compensation of the glucose peak following a meal. In addition, suspending the insulin infusion after the bolus lowers the risk of insulin-induced hypoglycemia in the late postprandial period [84, 86].

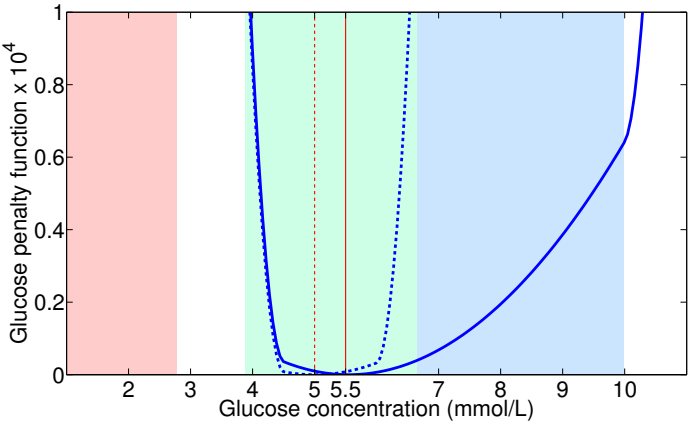


Figure 2: Penalization of the glucose concentration excursions in the insulin (full line) and glucagon (dashed line) MPC.

3.3 Glucagon Controller

3.3.1 Glucagon MPC

The glucagon MPC is based on the same structure as the insulin MPC (12b)-(12i). However, in the predictions we only use the glucagon control action, u_G, and the vector B_G corresponding to the glucagon input of the model.

Soft constraints (12g)-(12h) are used to prevent hypoglycemia and to avoid excessive glucagon dosing. The lower and upper bounds correspond to 4.5 mmol/L and 6 mmol/L. The soft constraint violation penalty remains the same as in the insulin MPC with $\gamma = 100$. To reduce sensitivity to measurement and process noises we penalize the changes in glucagon infusion using weighting coefficient $\lambda_G = 0.1$. The glucagon MPC uses a constant target set to 5 mmol/L ($\sim r_g = -0.5$ mmol/L expressed as a deviation from the target). Fig. 2 provides a comparison of the glucose penalty functions used in the insulin and the glucagon MPC.

3.3.2 Glucagon PD Controller

The second controller for glucagon infusion that we consider is a PD controller with the control law

$$u_{G;k} = K_{PD}(e_{g;k} + T_d/T_s \Delta e_{g;k}) \tag{19}$$

$$e_{g;k} = r_g - y_k \tag{20}$$

$$\Delta e_{g;k} = e_{g;k} - e_{g;k-1} \tag{21}$$

where the controller setpoint, r_g, corresponds to 5 mmol/L ($\sim r_g$=-0.5 mmol/L expressed as a deviation from the steady state glucose concentration of 5.5 mmol/L), T_s is the sampling time and K_{PD}, T_d are the controller parameters. Aggressiveness of the controller depends on the current glucose level estimate. Below 3.9 mmol/L ($y_k \leq -1.6$ mmol/L as a deviation variable) the controller is more aggressive ($K_{PD} = 2/K_G$, $T = 2\tau_G$) than above this threshold ($K_{PD} = 1/K_G$ $T_d = 0.33T$). For tuning of the controller parameters, K_{PD} and T_d, we employ the "t-sum rule" proposed by Kuhn [87].

To reduce sensitivity of the derivative part to the CGM noise (even after filtering), we evaluate the changes in the control error, e_g, between the current and previous sample (r_g is a constant, therefore, any change in y_k is directly reflected into the change in e_g). If necessary, we limit the changes in e_g according to the maximal values considered physiologic (+/- 0.22 mmol/L/min) [88].

3.4 Dual-hormone Adaptive Control

For the purpose of continuous identification we express the ARMAX model (5) in the form

$$y_{f;k} = \phi_{1;k}^T \theta_1 + \phi_{2;k}^T \theta_2 + \phi_k^T \hat{\theta}_k + e_k \tag{22}$$

where θ_1 and θ_2 are constant vectors, as we do not identify the parameters of insulin and glucagon action on glucose or glucose action per se. We only identify the vector $\hat{\theta}$, which represents coefficients of the polynomial $C(q^{-1})$ in the noise term of the ARMAX model. ϕ_1, ϕ_2 and ϕ are matrices containing the past input/output data. $y_{f;k-1} - y_{f;k-4}$ denote CGM measurements filtered using a low pass filter. The continuous identification of parameters c_1, c_2 is performed in each sampling instant by minimizing the one-step prediction error, e_k, using the recursive least squares algorithm (RELS) as follows

$$e_{a;k} = y_{f;k} - \phi_{1;k}^T \theta_1 - \phi_{2;k}^T \theta_2 - \phi_k^T \hat{\theta}_{k-1} \tag{23a}$$

$$K_{a;k} = \frac{P_{k-1}\phi_k}{\mu + \phi_k^T P_{k-1} \phi_k} \tag{23b}$$

$$\hat{\theta}_k = \hat{\theta}_{k-1} + K_{a;k} e_{a;k} \tag{23c}$$

$$P_k = \frac{1}{\mu}\left(P_{k-1} - \frac{P_{k-1}\phi_k \phi_k^T P_{k-1}}{\mu + \phi_k^T P_{k-1}\phi_k}\right) \tag{23d}$$

$K_{a;k}$ denotes the adaptation gain, P_k is the disperse matrix initialized with a diagonal matrix - $P_0 = diag(100, 100)$. The forgetting factor, μ, defines the algorithm memory. We use $\mu = 0.99$, which corresponds to memory length $n_m = 1/(1-\mu) \doteq 100$ samples, or 500 minutes.

We only accept the identified parameters if the roots of $C(q^{-1})$ lie within the unit circle of the complex plane. The accepted values are used to compute the polynomial $\bar{C}(q^{-1}) = A_G(q^{-1})C(q^{-1})$, which directly determines the Kalman filter gain in the innovation form state space model.

4 Simulation Results

4.1 Dual-hormone Simulation Model

A wide range of models of various complexity describe the glucose metabolism and the glucose-insulin dynamics [47]. a few dual-hormone models incorporate the effects of insulin as well as glucagon [39, 59, 60].

For simulation purposes we use a model proposed in [39], which extends the minimal model of plasma glucose and insulin kinetics with glucagon action on endogenous glucose production, a subcutaneous insulin absorption model and a gastrointestinal absorption model proposed by Hovorka [50]. A system of ordinary differential equations (ODEs) describes the dual-hormone model as follows [39].

In our simulations, feedback to the controller is provided by a CGM. The sensor does not measure blood glucose concentration directly. Instead, it measures glucose concentration in the interstitial tissue. In the following we consider CGM models proposed by Breton and Kovatchev [61], and Facchinetti et al. [62].

4.2 Verification of the Insulin Controller Using Hovorka Model

The control algorithm is equipped with the bolus calculator, which suspends the insulin delivery for 3 hours following the bolus administration. Due to the fact that the carbohydrate absorption in Hovorka model is relatively fast compared to the insulin absorption, the bolus calculator utilizes a fixed safety factor $\kappa = 0.65$.

The simulation scenario includes a meal regimen consisting of breakfast at 06:00, lunch at 12:00 and dinner at 18:00. We consider daily carbohydrate intake of $3g$ *per* kg of body weight with 33% contained in breakfast, 40% in lunch and 27% in dinner. We simulate the scenario for 100 randomly generated VPs and evaluate the controller closed-loop performance by means of a control variability grid analysis (CVGA) plot [90]. In addition, we provide the mean glucose and insulin traces together with corresponding standard deviations.

The results presented in Fig. 3 and Fig. 4 confirm that we managed to meet the MPC design goals. The major concern in T1D treatment is insulin-

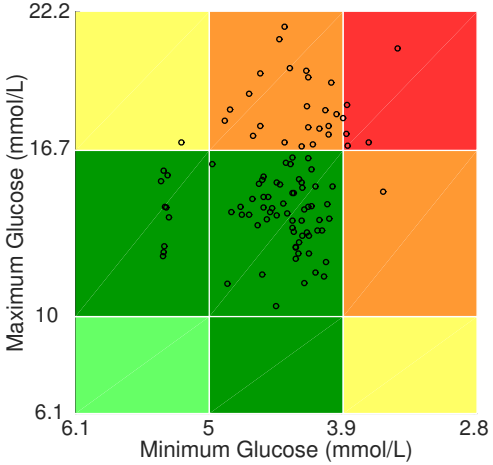


Figure 3: Verification of the insulin MPC. CVGA plot [90] for 100 virtual patients generated using the Hovorka model [50].

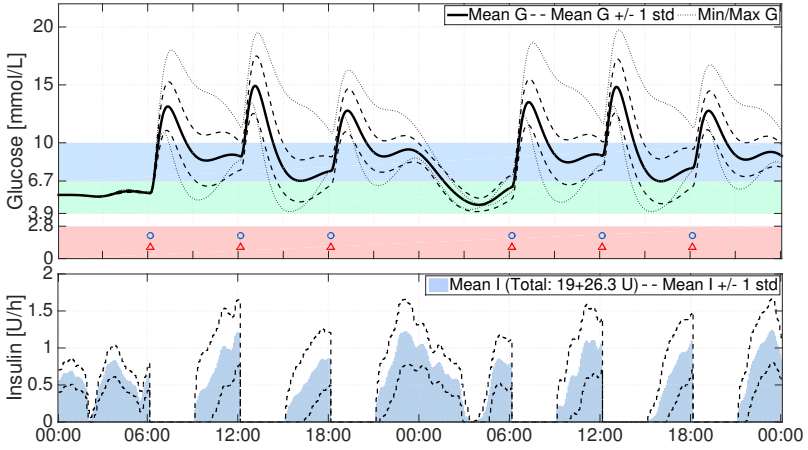


Figure 4: Verification of the insulin MPC. Mean glucose trace +/- 1 standard deviation for 100 virtual patients along with traces for patients with the lowest and highest mean glucose level, followed by the mean insulin infusion profile +/- 1 standard deviation. Red and blue markers represent the meals and the mealtime insulin boluses, respectively. Legend reports the mean value of the total insulin administered continuously + in the form of mealtime boluses.

induced hypoglycemia. From 100 virtual patients only 3 patients encounter mild hypoglycemia (G<3.9 mmol/L) with the lowest observed glucose level $G_{min} = 3.5$ mmol/L and 3 other patients are at the boundary of normo- and hypoglycemic range.

4.3 Glucagon MPC with Predictive Activation and Insulin Suspension after Bolus

Simulated scenarios include insulin-only, dual-hormone with relay switching and dual-hormone with predictive switching strategies tested when the insulin sensitivity of the patients is 40% larger compared to the model used in the MPC. Fig. 5 reports performance of the dual-hormone controller with relay and predictive switching in the scenario with increased insulin sensitivity. Results for all considered strategies, summarized in Table 1, suggest that a combination of the predictive switching between insulin and glucagon controllers together with the insulin suspension after mealtime bolus is very effective in avoiding insulin induced postprandial hypoglycemia, even when there is a substantial patient-model mismatch.

Simulations are in a good agreement with the previously obtained results. On average, across the 3 virtual patients and all glucagon infusion episodes, the predictive switching leads to approximately 33 minute earlier initiation of the glucagon administration. This results in a significant reduction of time spent in hypoglycemia (G<3.9 mmol/L) in the scenario with increased insulin sensitivity in case of virtual patient 1. The relative decrease exceeds 50% - from 9.67% to 4.67% of the total simulation time, as reported in Table 1. However, difference in the minimal glucose level observed is insignificant with $G_{min} = 3.7$ mmol/L in case of the predictive switching vs. $G_{min} = 3.6$ mmol/L in case of the relay switching.

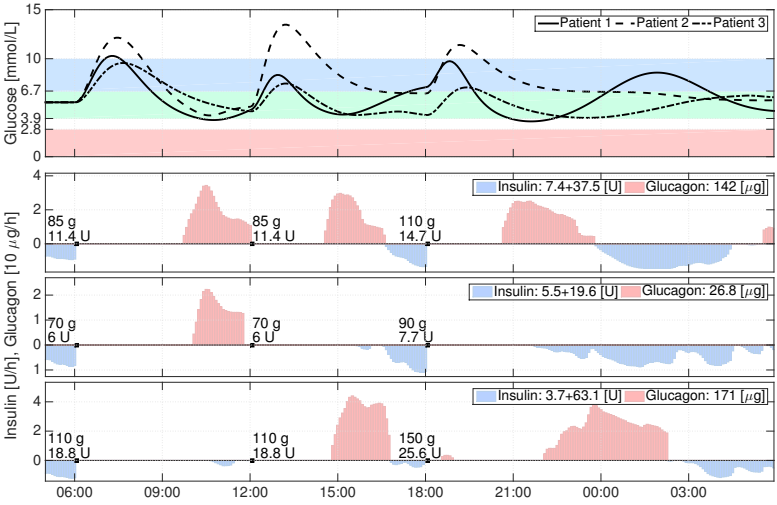
It is also important to note that the 50% reduction of time spent in hypoglycemia in virtual patient 1 is achieved at the cost of only 14% increase in the total amount of glucagon administered. This is consistent with the results of Bakhtiani et al. [91] that proper administration is an important factor determining the glucagon efficiency and injecting glucagon too late may compromise its action.

4.4 Comparison of Adaptive and Non-Adaptive Dual-Hormone AP

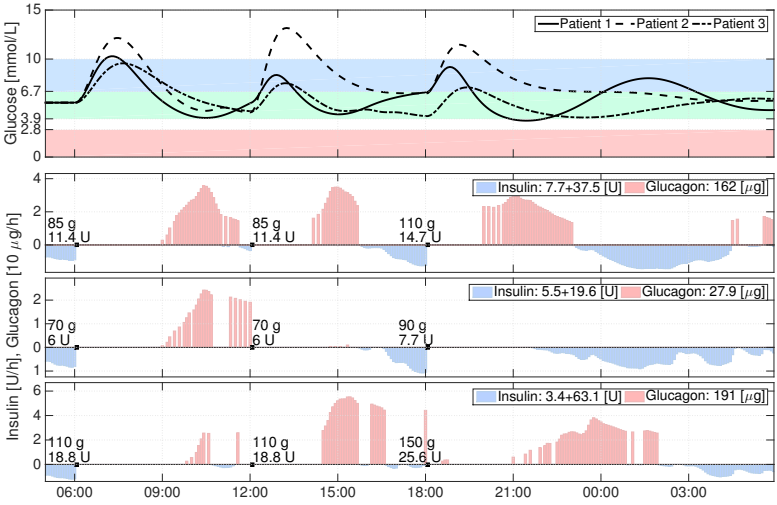
We test the adaptive algorithm presented in subsection 3.4 using the predictive switching between insulin and glucagon controller and the insulin suspension after mealtime bolus. The simulation scenario is based on a meal plan identical to the meal plan used in simulations in subsection

Table 1: Summary of the experiment - insulin only (I), dual-hormone with relay switching (IG/R) and dual-hormone control with predictive switching (IG/P). The table reports percentage of time spent in different glucose ranges, min / max / mean glucose level and total insulin / glucagon administration. The amount of administered insulin does not include the mealtime bolus insulin.

		Normal IS			Increased IS		
	$[G]$ = mmol/L	I	IG/R	IG/P	I	IG/R	IG/P
P1	$G > 10$ (%)	4.00	4.00	4.00	2.00	2.00	2.00
	$8 \leq G \leq 10$ (%)	10.33	12.33	12.00	8.00	17.67	11.67
	$3.9 \leq G \leq 8$ (%)	85.67	83.67	84.00	73.33	70.67	81.66
	$G < 3.9$ (%)	0.00	0.00	0.00	16.67	9.67	4.67
	mean G	6.21	6.31	6.32	5.70	6.11	6.07
	min G	4.06	4.30	4.47	3.47	3.60	3.71
	max G	10.96	10.96	10.96	10.28	10.28	10.28
	Insulin (U)	7.26	7.22	7.75	6.81	7.37	7.72
	Glucagon (μg)	0.00	31.78	50.84	0.00	141.72	162.47
P2	$G > 10$ (%)	23.67	24.33	24.67	17.67	19.00	18.33
	$8 \leq G \leq 10$ (%)	14.00	14.00	14.00	12.33	11.67	12.34
	$3.9 \leq G \leq 8$ (%)	62.33	61.67	61.33	64.67	69.33	69.33
	$G < 3.9$ (%)	0.00	0.00	0.00	5.33	0.00	0.00
	mean G	7.95	8.03	8.04	7.36	7.54	7.52
	min G	4.04	4.49	4.58	3.46	4.21	4.53
	max G	13.17	13.76	13.64	12.22	13.47	13.17
	Insulin (U)	5.12	5.15	5.18	5.47	5.54	5.55
	Glucagon (μg)	0.00	10.05	12.25	0.00	26.77	27.89
P3	$G > 10$ (%)	2.67	2.67	2.67	0.00	0.00	0.00
	$8 \leq G \leq 10$ (%)	13.33	14.00	14.00	7.67	7.67	7.67
	$3.9 \leq G \leq 8$ (%)	84.00	83.33	83.33	77	92.33	92.33
	$G < 3.9$ (%)	0.00	0.00	0.00	15.33	0.00	0.00
	mean G	6.18	6.28	6.25	5.40	5.69	5.70
	min G	4.30	4.49	4.61	3.57	3.97	4.03
	max G	10.22	10.22	10.22	9.56	9.56	9.57
	Insulin (U)	2.92	3.85	4.40	2.41	3.74	3.42
	Glucagon (μg)	0.00	48.09	50.66	0.00	170.71	191.45



(a) Relay switching



(b) Predictive switching

Figure 5: Dual-hormone AP with a) relay switching, b) predictive switching and insulin suspension after mealtime bolus. The IS is 40% larger compared to the nominal case when the model used in the MPC was estimated [72].

4.3. The simulation time is 5 days, where after day 2 the insulin sensitivity is increased by 40%.

The simulation results indicate that adaptation of the prediction model noise term further reduces time spent in hypoglycemia. In all 3 virtual patients, the adaptive control algorithm eliminated hypoglycemia completely with 0% of the time spent in the hypoglycemic range. On the other hand, the reduction is accompanied with slightly elevated mean glucose levels and glucagon delivery. While the increase in glucose level is minimal, the increase in glucagon delivery is more significant - 11% in patient 1, 4% in patient 2 and 53% in patient 3.

The comparison reveals that the adaptive control algorithm performs slightly better, mainly due to the elimination of hypoglycemia. The difference from non-adaptive control is very small, though. This finding supports the results from [73], that in the closed-loop setup the quality of prediction model is not as critical as expected. The most important aspect seems to be the presence of feedback.

Conclusion

The proposed dual-hormone control algorithm implements an innovation form state-space model realization of a relatively simple ARMAX model. The ARMAX model is based on second-order linear models describing the glucose-insulin and glucose-glucagon dynamics, and the effects of other unknown factors. Identification of the linear models requires only basic patient-specific data that is either a priori known or easy to obtain in clinical practice. The data includes insulin sensitivity factor, peak insulin action time and corresponding parameters of the glucagon action. Carbohydrate intake represents the major disturbance acting on the blood glucose. Due to large uncertainty in the carbohydrate absorption, we do not model the meal dynamics explicitly. Instead, we use the noise term of the ARMAX model to account for all unknown factors, including the meals. In the non-adaptive version, we use the noise term parameters identified previously by Duun-Henriksen et al. [75]. In the adaptive version, the parameters are continuously identified using the recursive least squares algorithm.

The dual-hormone control algorithm consists of a Kalman filter and separated insulin and glucagon controllers. The insulin infusion is controlled by an MPC, which is a commonly used approach. We compare a PD controller and an MPC for glucagon manipulation. The switching between the insulin and glucagon controllers is performed either using a threshold of certain glucose level with hysteresis or using the Kalman filter predictions. The control algorithm is designed to focus mainly on insulin and use glucagon

only as a safety feature. Therefore, large emphasis is put on the safety of the insulin controller.

We can conclude from the simulation results that the best performance, in terms of the tradeoff between hyperglycemia compensation and hypoglycemia prevention, is obtained with both insulin and glucagon infusion manipulated by MPCs and their switching governed by the Kalman filter glucose predictions. The MPCs are equipped with with hard input constraints limiting the maximal allowed infusion rates, soft output constraints imposing heavy penalization (if violated) of glucose excursions into hyper- and hypoglycemic range. Additional safety modifications include asymmetric reference signal and modifying the allowed infusion rates according to the current glucose level estimate. In addition, we implement a bolus calculator with a 3-hour insulin suspension following the bolus to reduce the risk of a late postprandial hypoglycemia.

Verification of the insulin controller performed on a cohort of randomly generated virtual patients using the Hovorka model confirms that the controller meets the design goals. During a challenging simulation scenario, no episode of severe hypoglycemia occurs. The dual-hormone control algorithm proves to be able to regulate glucose safely even in the simulation scenarios, where the insulin sensitivity increases unexpectedly or if the mealtime insulin boluses are overestimated.

Thesis Contribution

We can summarize the thesis contribution as follows

- Introduction of a control oriented dual-hormone model for glucose prediction, which can be identified only from basic, commonly known patient-specific data or, if the data is not available for a particular patient, using a simple experiment;
- Implementation of a dual-homorne control algorithm with the focus on the insulin controller safety and using glucagon as a safety feature in a non-aggressive way. The algorithm consists of a Kalman filter, separated insulin and glucagon model predictive controllers with hard and soft safety constraints, and a bolus calculator;
- a control structure allowing both dual- and single-hormone (insulin-only) control without any modifications needed thanks to the separation of the controllers;
- Comparison of the glucagon MPC and PD controllers;

- Evaluation of a controller switching strategy based on a certain glucose level threshold with hysteresis and a strategy using the Kalman filter glucose predictions;
- Comparison of a standard bolus calculator and a bolus calculator with insulin suspension following the bolus;
- Introduction of a dual-hormone adaptive control using a continuous identification of the model with ARMAX structure using the recursive least squares algorithm.

The presented work is a result of collaboration with the Technical University of Denmark, which lead, among others, to publications presented at IEEE and IFAC conferences including IEEE American Control Conference (ACC 2015), IEEE European Control Conference (ECC 2015), IEEE Conference on Control Applications (CCA 2014), IFAC Symposium on Biomedical Systems (IFAC BMS 2015), and a journal paper submitted to IEEE Transactions on Control Engineering Technology, which is currently under review.

List of author's publications

[A1] V. Bátora, M. Tárník, J. Murgaš, S. Schmidt, K. Nørgaard, N. K. Poulsen, H. Madsen, D. Boiroux, and J. B. Jørgensen, "Glucagon administration strategies for people with type 1 diabetes," *Control Engineering Technology*, vol. submitted, 2016.

[A2] V. Bátora, M. Tárník, J. Murgaš, S. Schmidt, K. Nørgaard, N. K. Poulsen, H. Madsen, D. Boiroux, and J. B. Jørgensen, "The contribution of glucagon in an artificial pancreas for people with type 1 diabetes," in *2015 American Control Conference (ACC 2015)*, Chicago, IL, USA, July 2015, pp. 5097–5102.

[A3] V. Bátora, M. Tárník, J. Murgaš, S. Schmidt, K. Nørgaard, N. K. Poulsen, H. Madsen, D. Boiroux, and J. B. Jørgensen, "Bihormonal control of blood glucose in people with type 1 diabetes," in *2015 European Control Conference (ECC 2015)*, Linz, Austria, July 2015, pp. 25–30.

[A4] V. Bátora, M. Tárník, J. Murgaš, S. Schmidt, K. Nørgaard, N. K. Poulsen, H. Madsen, and J. B. Jørgensen, "Bihormonal model predictive control of blood glucose in people with type 1 diabetes," in *2014 IEEE Conference on Control Applications (CCA)*, 2014, pp. 1693 – 1698.

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