

Applicability Results of a Nonlinear Model-Based Robust Blood Glucose Control Algorithm

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Abstract

Introduction:

Generating optimal control algorithms for an artificial pancreas is an intensively researched problem. The available models are all nonlinear and rather complex. Model predictive control or run-to-run-based methodologies have proven to be efficient solutions for individualized treatment of type 1 diabetes mellitus (T1DM). However, the controller has to ensure safety and stability under all circumstances. Robust control methods seek to provide this safety and guarantee to handle even the worst-case situations and, hence, to generalize and complement results obtained by individualized control algorithms.

Methods:

Modern robust (e.g., H_{inf}) control is a linear model-based methodology that we have combined with the nonlinear model-based linear parameter varying technique. The control algorithm was designed on the high-complexity modified nonlinear glucose–insulin model of Sorensen, and it was compared step-by-step with linear model-based H_{inf} control results published in the literature. The applicability of the developed algorithm was tested first on a control cohort of 10 healthy persons' oral glucose tolerance test results and then on a large meal absorption profile adapted from the literature. In the latter case, two preliminary virtual patients were generated based on 1–1 week real continuous glucose monitor measurements.

Results:

We have found that the algorithm avoids hypoglycemia (not caused by physical activity or stress) independently from the considered absorption profiles.

Conclusion:

Use of hard constraints proved their efficiency in fitting blood glucose level within a defined interval. However, in the future, more data of different T1DM patients will be collected and tested, including dynamic absorption model and *in silico* tests on validated simulators.

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Abbreviations: (AP) artificial pancreas, (CGM) continuous glucose monitor, (CHO) carbohydrate, (LPV) linear parameter varying, (LTI) linear time invariant, (MPC) model predictive control, (OGTT) oral glucose tolerance test, (RDS) rapidly digestible starch, (RS) resistant starch, (SDS) slowly digestible starch, (T1DM) type 1 diabetes mellitus

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Introduction

According to data provided by the World Health Organization, the diabetes population is predicted to double from 2000 to 2030,¹ and the trend is maintained in a 2010 prognosis as well.² Regarding type 1 diabetes mellitus (T1DM), the statistics of the International Diabetes Federation show that the European Region has the highest number and the highest incidence rate of T1DM in children compared with any other region worldwide.³ Uncontrolled T1DM (characterized by complete pancreatic β -cell insufficiency) results in acute events and chronic diseases, e.g., cardiovascular disease and kidney disease.⁴

Technological advances have enabled development of (i) continuous glucose monitors (CGMs) for subcutaneous measurement of glucose concentration and (ii) insulin pumps for subcutaneous delivery of insulin.⁵ Sensor-augmented pump therapy seems to improve glycemic control compared with traditional therapeutic schemes.⁶ Furthermore, automatic regulation of the glucose profile using a controller that closes the loop between CGM and pump will make the realization of an artificial pancreas (AP) feasible.⁷⁻⁹

To design an appropriate control, an adequate model is necessary. Different mathematical models of the human blood glucose system have appeared.⁵ The minimal model¹⁰ proved to be the simplest one, but a lot of components of the glucose–insulin interaction were neglected in its formulation. Therefore, other general but more complicated models emerged.¹¹⁻¹⁴

Although different control algorithms have been proposed in the literature,^{5,8,15} only four main control strategies have been used for AP prototype systems: proportional-integral-derivative-based controllers,¹⁶ model predictive control (MPC),¹⁷⁻¹⁹ run-to-run,²⁰ and fuzzy logic.²¹ The majority of the mentioned algorithms are able to achieve nocturnal glucose regulation. The MPC-based approaches resulted in less hypoglycemic events and increased time in normoglycemia, while the run-to-run- and fuzzy-logic-based controllers had good performance during closed loop.

Due to insulin sensitivity differences and patient variability, hard constraints should also be beneficial in handling model uncertainties.^{12,22} Modern robust control theory is suitable for these purposes²³ by maintaining stability and performance level despite uncertainties in system dynamics. Although they represent linear control methods providing systematic design procedures of robust controllers, extension into nonlinear cases is an actively researched topic nowadays. A promising candidate is represented by the linear parameter varying (LPV) methodology, where—by adequately choosing variables—the nonlinearity can be hidden.²⁴

The aim of this article is to briefly summarize the developed nonlinear model-based LPV robust controller and to prove its applicability and robustness on different preliminary scenarios taken into account.

Methods

Linear Parameter Varying System Definition

The LPV system is a class of nonlinear systems, where the parameter could be an arbitrary time-varying, piecewise-continuous, vector-valued function denoted by $\rho(t)$, defined on a compact set P . In order to evaluate the system, the parameter trajectory is requested to be known either by measurement or by computation.²⁴⁻²⁶

An n th-order LPV system can be written in the form of

$$\begin{aligned} \dot{x}(t) &= A(\rho)x(t) + B(\rho)u(t) \\ y(t) &= C(\rho)x(t) + D(\rho)u(t) \end{aligned} \quad (1)$$

where $A = \mathbf{R}^S \rightarrow \mathbf{R}^{n \times n}$, $B = \mathbf{R}^S \rightarrow \mathbf{R}^{n \times n_u}$, $C = \mathbf{R}^S \rightarrow \mathbf{R}^{n_y \times n}$, and $D = \mathbf{R}^S \rightarrow \mathbf{R}^{n_y \times n_u}$ are continuous functions.²⁷

Hence, LPV systems provide a model paradigm that goes beyond the classical representation of nonlinear and linear systems.²⁸ Basically, LPV systems can be seen as an extension of linear time invariant (LTI) systems, where the relations are considered to be linear, but model parameters are assumed to be functions of a time-varying signal that is available for measurement. By choosing parameter variables, the system’s nonlinearity can be hidden, as the measured parameters describe the whole working domain of the designed controller. This methodology is used in different control solutions.²⁹

Linear Parameter Varying Modeling of the Type 1 Diabetes Mellitus Problem

There are different descriptions of the LPV systems.²⁸ In the affine description possibility, a part of the $x(t)$ states are equal with the $\rho(t)$ parameters.

The control problem was considered on the modified version of the 19th-order Sorensen model,¹² which is one of the most complex glucose–insulin models in the literature. The compartmental structure of the model is presented in **Figure 1**, while its detailed description can be found elsewhere.²⁴

However, due to the complexity of the modified Sorensen model, it is difficult or nearly impossible to capture the dynamics with affine-type LPV representation. Hence, polytopic representation was investigated, in which case the validity of the model is caught inside a polytopic region, and the model is built up by a linear combination of the linearized models derived in each polytopic point:

$$\Sigma_i = \begin{bmatrix} A_i & B_i \\ C_i & D_i \end{bmatrix}$$

The polytopic LPV model can be thought of as a set of linear models on a vertex (a convex envelope of LTI systems), where the grid points of the description are LTI systems. The LPV polytopic model is valid only in a restricted domain, characterized by the range of the polytope.^{24,25}

The validity of the modified Sorensen model was captured by a set of 48 points,^{24,26} where, in each point, the system was linearized. The created LPV model was proven to fit the original system.²⁶

The Linear-Parameter-Varying-Based Robust Controller

The LPV-based robust controller was developed to minimize the meal disturbance level over the performance output for all possible variation of the parameter within the created polytope:^{24,25}

$$\min_K \|G\| = \min_K \sup_{\rho \in F_p} \sup_{\|d\| \neq 0} \frac{\|z_y\|}{\|d\|}, \tag{2}$$

where d denotes the meal disturbance input and z describes the glucose variation. K represents the H_{inf} controller in question. F_p denotes the set of all piecewise continuous functions mapping the positive real number set R^+ (time) into the compact set P with a finite number of discontinuities in any interval. *A priori* information is injected to the controller throughout the augmentation of the nominal plant with extra dynamics, called weight functions.²³

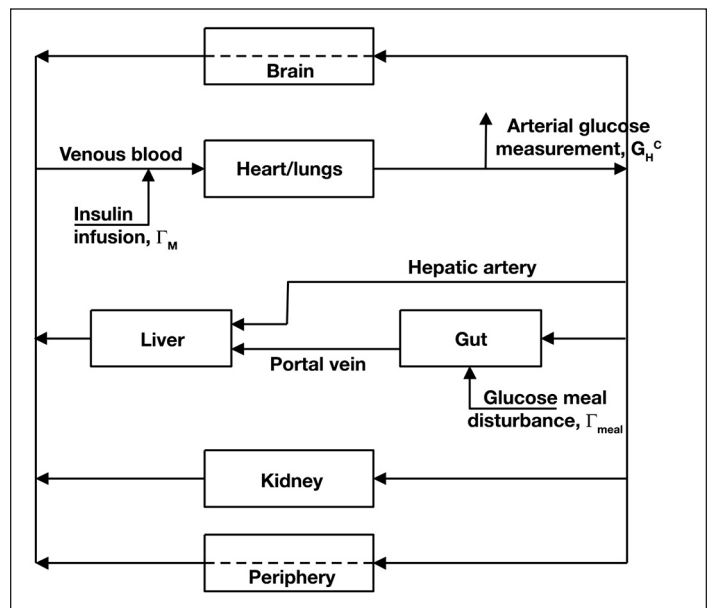


Figure 1. Compartmental representation of the modified Sorensen model.¹²

The augmented system and the controller are presented in **Figure 2**. In order to reproduce the same results obtained by Parker and coauthors,¹² the system was designed for the same absorption profile³⁰ used by Parker and coauthors.¹² This step represented the starting point in our robust controller design procedure.²⁴

Additionally, we have extended the constraint set of our robust structure with two multiplicative uncertainty weighting functions: output (see W_o in **Figure 2**), being considered negligible by Parker and coauthors¹² (used as $1/10000$), and input (see W_i and W_{im} in **Figure 2**). The reason for using output uncertainty is to reduce low-frequency glucose parameter errors (possible from CGM measurements) but also to consider neglected dynamics. Input multiplicative uncertainty was used on both glucose and insulin pathways of the model in order to model high-frequency dynamics. The weighting functions introduced were determined by sensitivity analysis using a similar procedure as Parker and coauthors.¹² Moreover, worst-case meal disturbance was considered in our case [i.e., 60 g carbohydrate (CHO) intake)], whereas only 50 g CHO was considered by Parker and coauthors.¹²

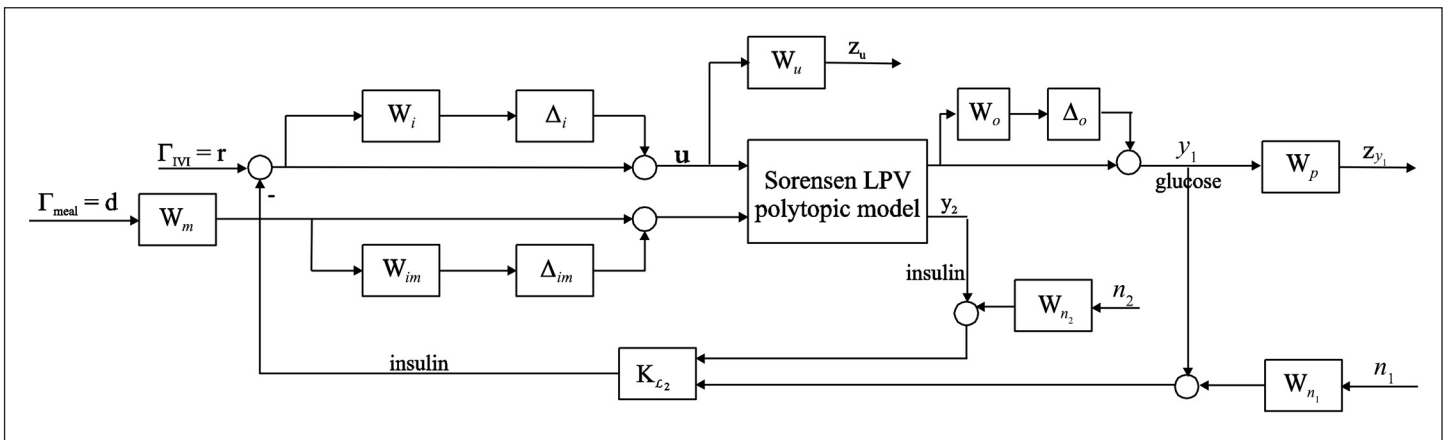


Figure 2. The augmented system and the controller.²⁴ The model is extended with the uncertainty weighting functions ($W_i, W_{im}, W_m, W_o, W_p, W_{n1}, W_{n2}$) and the uncertainty blocks ($\Delta_i, \Delta_{im}, \Delta_o$). K_{L2} represents the controller, while the signals are as follows: disturbance (d), reference signal (r), control input (u), system outputs (y_1, y_2), weighting function outputs (z_u, z_{y1}), and inputs (n_1, n_2).

Results

During the H_{inf} control design and using γ -iteration algorithm, $\gamma = 1.0096$ solution was obtained (the tolerance for the algorithm was set to 0.01).²⁴ The obtained value represents the upper limit of the robust performance criterion, which means that the formulated system requirements are quite severe. However, this could be an advantage in the validation process. Simulations on the reference value of Lehmann and Deutsch³⁰ were tested and prove that hyperglycemia is avoided (**Figure 3**). Additionally, it should be highlighted that simulation results are better in the case of the original nonlinear system than on the LPV model, which is explained by the fact that the built polytopic region is more general than the validity interval of the original nonlinear process.²⁴

Healthy Subjects' Absorption Profile

In order to test other absorption profiles, we collected data from a cohort of 10 healthy subjects (7 females and 3 males), body mass index = 23.9 ± 3.9 kg/m², age = 27.4 ± 2.5 years.

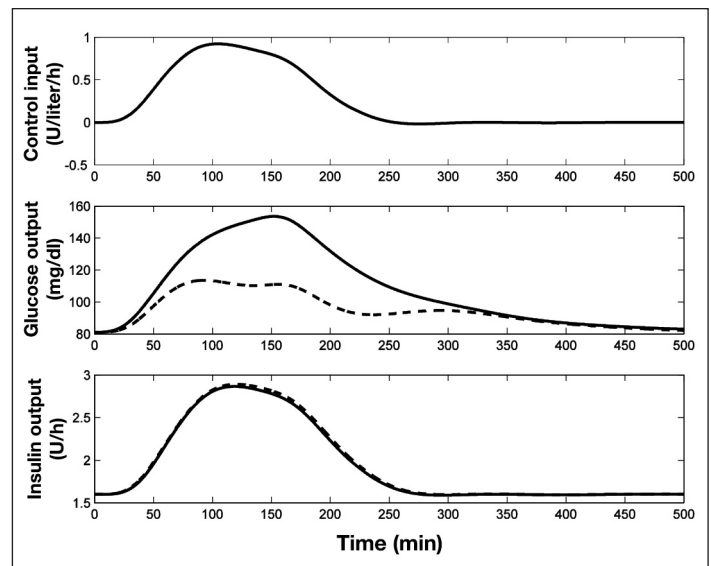


Figure 3. The LPV-based robust controller in case of the original modified nonlinear Sorensen model¹² (solid) and the considered polytopic region (dashed).²⁴ Absorption CHO profile is taken from Lehmann and Deutsch.³⁰

Oral glucose tolerance tests (OGTTs) were performed using a strict protocol: subjects arrived all on foot to the measurement place, in fasting condition, and they had eaten the same dinner prior to the measurement. During 2 days, two different 60 g CHO meal types were given to them. First, an OGTT was performed on bread intake that was composed by 67% rapidly digestible starch (RDS), 30% slowly digestible starch (SDS), and 3% resistant starch (RS). On day 2, pasta was used for breakfast composed of 50% RDS, 46% SDS, and 4% RS. In both test scenarios, the meal had to be consumed within 15 min with 250 ml water.

The rationale for this protocol was twofold. By generating different meal profiles (on rapidly and slowly digestible CHO absorptions³¹), we investigated the validity of the created LPV region but also tested the robust controller. Namely, we built up the polytope region for the LPV model to capture the whole working domain of the original nonlinear model. However, due to the model's characteristics, the created convex polytope is a more general region than the modified Sorensen's model working domain. As a result, the designed linear-model-based robust controller works on a more general domain, and hence, using the same control input could produce a worse output than the original model.

These theoretical assumptions were verified for all the 10 tested healthy subjects. The LPV-based robust controller kept the output of the system (glucose) in the healthy 70–140 mg/dl interval and followed the measured OGTT profile.³² Hence, the physiological background of the measured data set is covered by the constructed model. The differences of the glucose output between the LPV model and the original nonlinear model were maintained (similar to **Figure 3**), while the same insulin output has been calculated in both cases. Hence, it was demonstrated that, from an applicability point of view, there is no difference in insulin injection (as a control input) determination. Simulation results are shown in **Figure 4** on one subject's absorption profile from the measured cohort (for the two meal types separately).³²

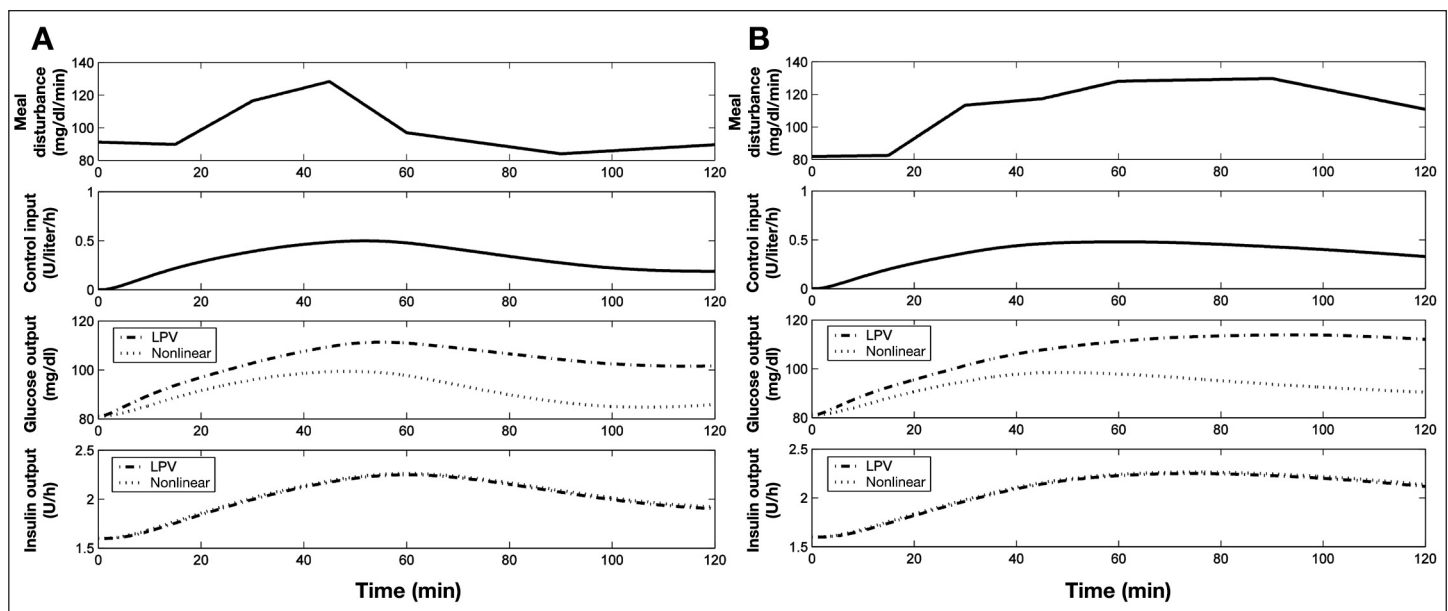


Figure 4. Simulation results of one subject's absorption profiles from the measured healthy cohort. (A) Bread meal intake and (B) pasta meal intake absorption are considered.

Large Meal Absorption

The simulation results focused on the classical meal absorption curve of Lehmann and Deutsch,³⁰ however, in order to test the robustness of the developed algorithm, we referred to large meal absorptions. In normal individuals, it is known that 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.³³ The latter situation can be considered the worst case of meal intakes.

In order to test the effect of large meal intake (based on theoretical models of absorption³⁴), the concentration of glucose absorption rate (normalized by distribution volume) can be considered to follow a Weibull curve (**Figure 5**):

$$g = p_3 \tau e^{-\tau}, \quad (3)$$

$$\text{where } \tau = \left(\frac{t}{p_1} \right)^{p_2}.$$

Observing the role of parameters p_1 , p_2 and p_3 , it can be seen that

- p_1 corresponds to the input scaling, in other words, it scales the curve along the horizontal axis;
- p_2 determines the shape of the curve since it can be interpreted as a time constant of the system; and
- p_3 scales the curve along the vertical axis.

Therefore, the amount of the glucose input can be taken into account by p_3 , whereas patient variability can be modeled by p_2 .

Simulation results of the robust controller on the considered large meal absorption profile are presented in **Figure 6**. It can be seen again that simulation results are better with the original nonlinear system than with the LPV model, while the insulin output is again the same for the two considered models.

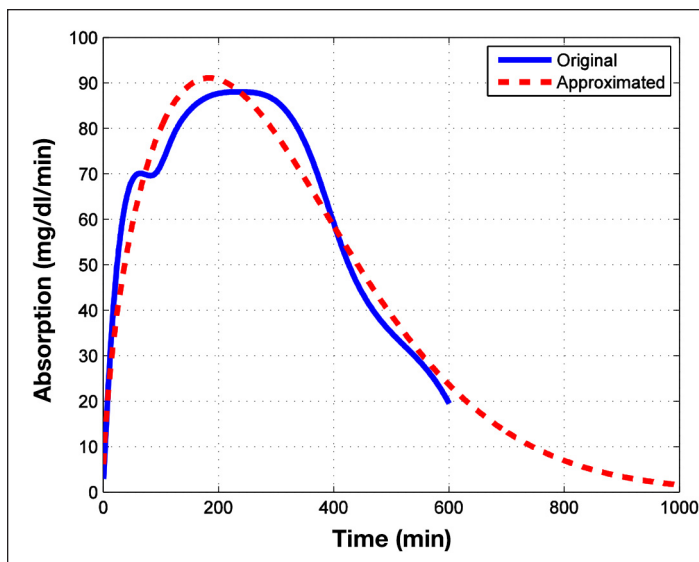


Figure 5. Large meal³³ and Weibull approximation of exogenous glucose absorption.

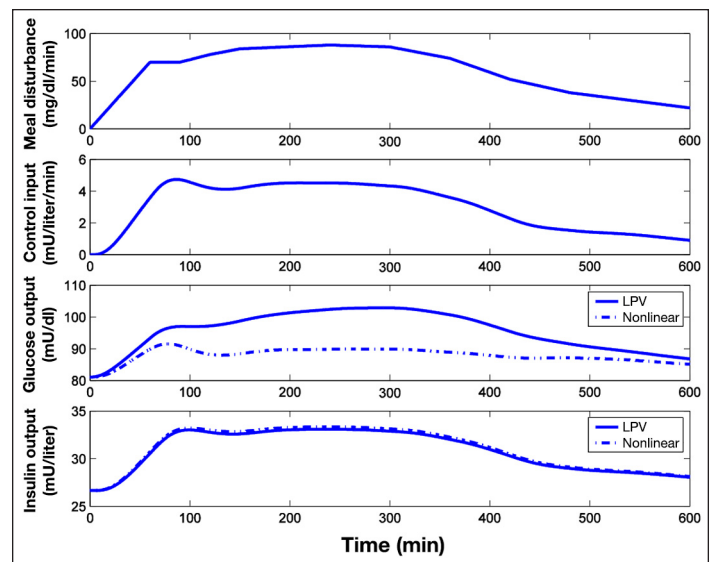


Figure 6. The LPV-based robust controller simulation results for large meal absorption profile taken from Korach-André and coauthors.³³

In conclusion, it can be mentioned that, after tuning, no information about meal occurrence is needed for the designed robust controller as long as meal amount does not exceed the expected maximum of the corresponding polytopic region.²⁵

Virtual Patient Generation

To start virtual patient generation in the case of the modified Sorensen model, the same sensitivity analysis was used as reported by Parker and coauthors.¹² The complexity, however, was a disadvantage regarding the identification method since the problem was numerically badly conditioned and had various local optima; furthermore, the stability of the model was difficult to assure or even to determine.²⁵ Two T1DM patients' 1-week-long real data were collected to perform the first tests: patient 1 was a 17-year-old boy (he has used an insulin pump for half a year and has an

active lifestyle and good compliance), while patient 2 was a 43-year-old woman (she has used an insulin pump for 3 years and is characterized with moderate compliance). Both patients used a Medtronic Paradigm 522 pump and followed their usual lifestyle. The only control in the system was that their daily plan was discussed a day before by their doctor, and the following day, the doctor checked if corresponding data were registered correctly (CHO intake and physical activity); consequently, the patients did not follow specific meal protocol.

Every CHO amount was modeled in the system as a large meal with a Weibull curve absorption profile presented in **Equation (3)**.

Figure 7 presents results of 3 of 7 days total for patient 1 using the large absorption scenario (worst-case test). In this case, every CHO intake of the patient was adjusted as a large meal absorption presented in **Equation (3)**

Figure 8 presents results of 3 of 7 days total for patient 2 using the large absorption scenario (worst-case test). In this case, every CHO intake of the patient was again adjusted as a large meal absorption presented in **Equation (3)**.

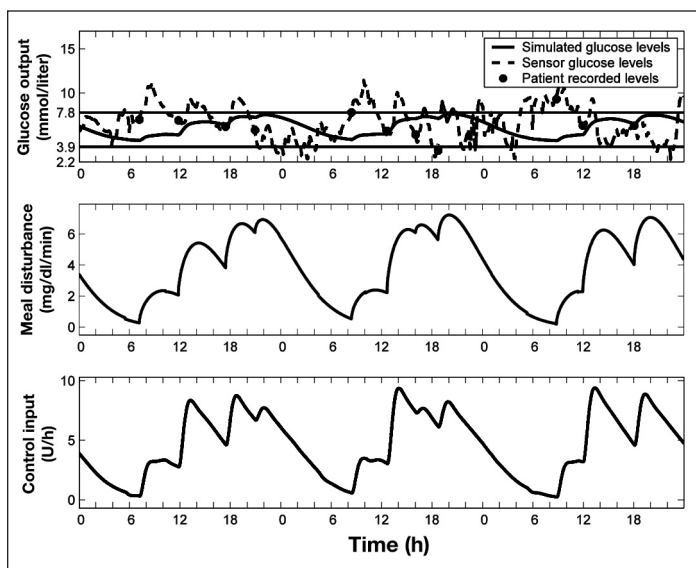


Figure 7. Comparison of robust controller output (solid) and collected CGM data (dashed) using large meal absorption scenario in case of patient 1. The dots represent the real fingertip measurements. The middle figure shows the absorption profiles of CHO intakes considered as large meal absorptions. The lower figure represents the insulin control input.

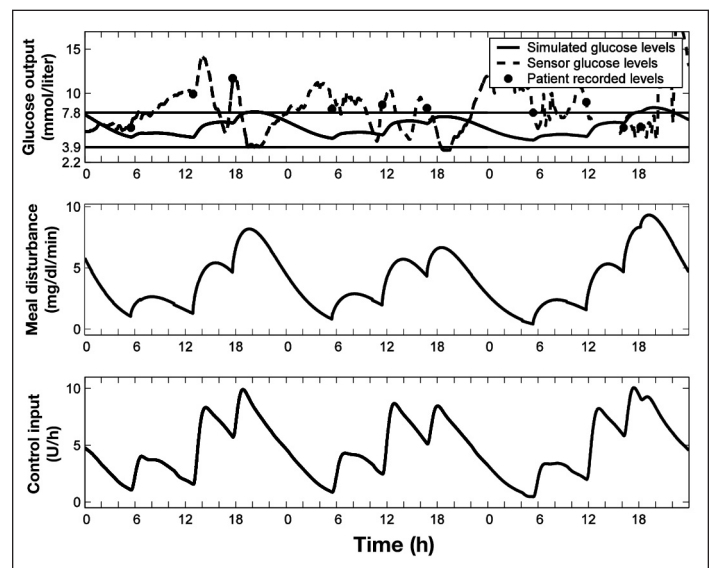


Figure 8. Comparison of robust controller output (solid) and collected CGM data (dashed) using large meal absorption scenario in case of patient 2. The dots represent the real fingertip measurements. The middle figure shows the absorption profiles of CHO intakes considered as large meal absorptions. The lower figure represents the insulin control input.

Discussion

Results of both patients (**Figures 7** and **8**) show that the output of the controller fit the blood glucose level almost all the time in the normal 3.9–7.8 mmol/liter (70–140 mg/dl) range, and a hypoglycemic episode was avoided. In the case of the control input, only the controller's calculated input (insulin) is presented.

It can be seen that the patients' physiology is followed, but variation of the blood glucose levels is much lower. Due to worst-case design and uncertainties taken into account and included in the control design, hypoglycemic events were avoided and hyperglycemic episodes are lower in most of the cases than those exhibited in the patients' real data.

Investigating the control algorithm (without any recalibration) on the model presented by Kovács and coauthors,²⁵ two remarks should be highlighted. First, it can be seen that the blood glucose level could be again stabilized in a

better range than the real data of the patients, and also, hypoglycemia events can be avoided. Hence, the presented preliminary results demonstrate the robustness capability of the developed algorithm; however, more simulation results are required.

Investigating the individualized control strategies (e.g., MPC) presented in the literature, it can be concluded that individual protocols have given better results per patient than the developed robust controller. However, in our case, this is much more an advantage than a disadvantage. It is known that MPC strategies have better results in the case of individual control problems.^{14,35,36} However, robustness is much harder to guarantee in these cases. In contrast, modern robust control could give a generalized solution, but examined on individual cases, it leaves space for improvement.

Conclusions

This article summarized a nonlinear model-based LPV robust controller and proved by preliminary results its applicability and robustness with different scenarios taken into account. Hence, it has the potential to handle patient groups and—in this way—efficiently support and complement individualized control (e.g., MPC-based) protocols.

This article is the first part of a series of three publications (presenting Hungarian AP research results). The second paper aims to deal with *in silico* tests, while the third paper should give a summary of the work done.

Furthermore, we plan to extend the robust framework with hard constraints regarding physical activity and stress and test the results on other patients' data as well. We also plan to investigate model-free approaches³⁷ by implementing the same controller structure to different models, preferably based on the ones used most frequently in AP research by the international community.^{13,14} Finally, the capabilities of these controllers will be tested on either the modified Sorensen model or any model not used for the controller design. Our further aim is to test our results on the Food and Drug Administration-approved simulator³⁸ as well and to combine our framework with individualized control protocols.

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