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Maximizing performance of linear model predictive control of glycemia for T1DM subjects

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The primary objective of this paper is the custom design of an effective, yet relatively easy-to-implement, predictive control algorithm to maintain normoglycemia in patients with type 1 diabetes. The proposed patient-tailorable empirical model featuring the separated feedback dynamics to model the effect of insulin administration and carbohydrate intake was proven to be suitable for the synthesis of a high-performance predictive control algorithm for artificial pancreas. Within the introduced linear model predictive control law, the constraints were applied to the manipulated variable in order to reflect the technical limitations of insulin pumps and the typical nonnegative nature of the insulin administration. Similarly, inequalities constraints for the controlled variable were also assumed while anticipating suppression of hypoglycemia states during the automated insulin treatment. However, the problem of control infeasibility has emerged, especially if one uses too tight constraints of the manipulated and the controlled variable concurrently. To this end, exploiting the Farkas lemma, it was possible to formulate the helper linear programming problem based on the solution of which this infeasibility could be identified and the optimality of the control could be restored by adapting the constraints. This adaptation of constraints is asymmetrical, thus one can force to fully avoid hypoglycemia at the expense of mild hyperglycemia. Finally, a series of comprehensive in-silico experiments were carried out to validate the presented control algorithm and the proposed improvements. These simulations also addressed the control robustness in terms of the intersubject variability and the meal announcements uncertainty.

Key words: diabetes mellitus, artificial pancreas, glycemia control, predictive control, constrained optimization, control feasibility

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1. Introduction

A technology capable of fully automatic control of blood glucose concentration in diabetic patients was a subject to intense scientific endeavor in the last decades, and it still remains an active research interest nowadays [1–3]. However, the artificial pancreas (abbr. AP) can be seen rather a general concept than a particular device or apparatus. Thanks to the advent of novel rapid-acting insulin forms [4, 5], the intrinsic delay in the insulin-glucose interaction, additionally emphasized by turning to the fully subcutaneous route [6], appears to be partially suppressed. Moreover, continuous glucose monitoring devices (abbr. CGM) are capable of relatively accurate and dense readings of glycemia required by the closed control loop of the artificial pancreas [7, 8]. The current major obstacle to wider deployment and commercial availability of such a device is actually the absence of an effective and safe control algorithm capable of operating in demanding free-living conditions [9, 10].

The paper is organized as follows. In Section 2 the basic structure of the discrete-time linear empirical model of type 1 diabetes is proposed. Section 3 comprises the derivation of the essential predictive equations. The constrained predictive control algorithm together with the control feasibility problem formulation and the proposed constraints adaptation algorithm are presented in Section 4. Finally, in Section 5, the results of multiple different simulation-based experiments are discussed.

1.1. State of the art

So far, the problem of glycemia control has been addressed in a respectable number of papers, while exploiting various more or less sophisticated strategies starting from simple PID controllers [11–13], adaptive approaches [14–16], robust control [17], and concluding with the predictive control as perhaps the most promising one [18]. Some of the most significant and closely related works will be briefly examined in this section.

In [19] the authors exploited a simple ARX model hand in hand with the generalized predictive control algorithm. However, without involving the meal announcements, so neither the crucial disturbance prediction or the feed-forward disturbance compensation were featured at all. In addition, only the unconstrained closed-form control law was applied, implying that the manipulated variable was simply saturated, ultimately resulting in loss of the control optimality. It is worth noting that although the carbohydrate counting itself and the subsequent strict adherence to the meal schedule may be inconvenient or even annoying for the patient, the actual qualitative benefits of doing so are indisputable.

A traditional model predictive control assuming the ARX model with disturbance input, manipulated variable constraints, and state estimation using the conventional Kalman filter was reported in [20]. Another typical application of

the unconstrained model predictive control for the state-space model obtained by transforming the nonparametric impulse-response model along with the state estimation based on the steady-state Kalman filter was presented in [21]. However, due to the demand of control law in the closed form, the insulin administration rate constraints were implemented by clipping, and the output constraints were treated by carefully tuning the penalty weights. The unconstrained saturated MPC with meal announcing was compared to the PID control in [22], but due to the input–output MPC scheme and the non-minimal state-space model, the state estimator was not needed.

One of the few applications of the constrained MPC was presented in [23] where the finite-horizon optimization problem was converted to the equivalent quadratic programming problem and the artificial pancreas with the application of combined pump, maximum input variation and ketone bodies constraints was compared to the traditional saturated MPC, reporting significant performance improvements. The authors also suggested possible future improvements by constraining the state of the system.

Interesting in-silico [24] and in-vivo [25] studies focused on using the ARMAX and ARIMAX models without disturbance submodel nor disturbance compensation. The closed-loop control was performed only overnight when no meal disturbance could occur, whereas the standard insulin bolus therapy was applied during the daytime to compensate for meal intake. In both aforementioned papers, the MPC algorithm was exploited while the hard constraints were assumed only for the manipulated variable. Concerning the controlled variable, soft constraints were implemented as a special penalty term using slack variables, so this MPC formulation used an asymmetric objective function that penalized low glucose levels more heavily.

The paper [26] presented algorithms based on neural and fuzzy models together with quadratic programming for the MPC problem. In detail, the single-input single-output multi-layer perceptron neural model with one hidden layer was used. Also in this case, slack variables were involved to implement the asymmetric soft constraints of the controlled variable.

In [27], the nonlinear model predictive control using the individualized complex simulation model was experimentally applied on real diabetic subjects. Such an interesting feature was the Bayesian parameter estimation with online re-estimation proposed primarily in order to adapt the model parameters due to presence of intra-subject time-variability.

Another remarkable contribution to the state of the art in this field was made in [28]. Firstly, the linear model predictive control with disturbance compensation for the two-input ARX model transformed to an equivalent non-minimal state-space representation was performed as a part of the in-silico trial there. The authors experimented with both unconstrained and constrained control, concluding that involving the constraints did not show any significant performance

improvement but recommended more detailed research on this problem. Secondly, fully nonlinear predictive control was applied exploiting the individualized complex simulation model. But in general, the application of predictive control based on complex nonlinear models may struggle with the problem of correct model individualization or even with a priori identifiability and will increase the computational load needed to solve the control optimization problem. Moreover, non-linear optimization is likely to converge to a local minimum, so there is no guarantee that the algorithm will find the global optimal solution.

2. System model

In this paper, the two-input transfer function-based discrete-time empirical model is proposed for the MPC synthesis. This model comprises three terms representing the control submodel for the insulin administration effect, the measurable disturbance submodel for the carbohydrate intake effect, and the unmeasurable disturbance submodel, respectively. The featured separate feedback (autoregressive) dynamics for each of the submodels makes possible to capture distinctly different dynamic responses of the control and the disturbance input. It also reflects the actual physiological response of the human body, particularly the delayed effect of insulin admission compared to the faster and shorter lasting effect of carbohydrate intake. Hereby more realistic modeling of the glycemia dynamics can be theoretically achieved, especially if compared to the ordinary ARX model [29, 30]. In addition, the model is extended by the constant output term due to which the basal state of the subject can be directly integrated into the model structure.

The dynamic equation of the proposed model is presented below:

$$y_{(k)} = \frac{B^u(z)}{A^u(z)} u_{(k)} + \frac{B^d(z)}{A^d(z)} d_{(k)} + \frac{C(z)}{D(z)} \epsilon_{(k)} + y_0 \,, \tag{1}$$

where $y(t)$ [mmol/l] represents the controlled variable, that is, the blood glucose concentration, $u(t)$ [U/min] denotes the manipulated variable i.e. the insulin infusion rate, and $d(t)$ [g/min] stands for the measurable disturbance i.e the carbohydrate intake rate. The signal of an unmeasurable disturbance $\epsilon(t)$ represents the combined effect of the measurement noise as the stochastic term and the correlated plant-model mismatch. Since the real diabetic subject is generally considered a complex time-varying non-linear system, the presence of plant-model mismatch is anticipated. Additionally, patients are likely to be affected by various hard-to-quantify disturbances such as physical activity [31].

The polynomials of the model (1) are defined as

$$A^{u/d}(z) = 1 + a_1^{u/d} z^{-1} + a_2^{u/d} z^{-2} + \ldots a_{n_{A^{u/d}}}^{u/d} z^{-n_{A^{u/d}}} , \tag{2a}$$

$$B^{u/d}(z) = b_1^{u/d} z^{-1} + b_2^{u/d} z^{-2} + \ldots b_{n_{B^{u/d}}}^{u/d} z^{-n_{B^{u/d}}}, \tag{2b}$$

$$D(z) = 1 + d_1 z^{-1} + d_2 z^{-2} + \ldots d_{n_D} z^{-n_D}, \tag{2c}$$

$$C(z) = 1 + c_1 z^{-1} + c_2 z^{-2} + \ldots c_{n_C} z^{-n_C}, \tag{2d}$$

where n_{A^u}, n_{A^d}, n_{B^u}, n_{B^d}, n_D and n_C denote the model orders.

The constant term y_0 can be associated with the basal state of the subject as follows:

$$y_0 = G_b - \left(v_b \frac{\sum b_i^u}{\sum a_i^u} \right), \tag{3}$$

where G_b [mmol/l] is the basal glycemia and v_b [U/min] is the basal insulin administration rate.

We can also decompose the model output as the sum of its internal states x^u, x^d and x^ϵ:

$$y_{(k)} = x_{(k)}^u + x_{(k)}^d + x_{(k)}^\epsilon + y_0 \,. \tag{4}$$

The single-step-ahead predictions of internal variables can be written as follows:

$$\hat{x}_{(k|k-1)}^u = (1 - A^u(z))\, x_{(k)}^u + B^u(z) u_{(k)} \,, \tag{5a}$$

$$\hat{x}_{(k|k-1)}^d = \left(1 - A^d(z)\right) x_{(k)}^d + B^d(z) d_{(k)} \,, \tag{5b}$$

$$\hat{x}_{(k|k-1)}^\epsilon = (1 - D(z))\, x_{(k)}^\epsilon + (C(z) - 1)\, \hat{\epsilon}_{(k)} \,. \tag{5c}$$

The output single-step-ahead prediction will be:

$$\hat{y}_{(k|k-1)} = \hat{x}_{(k|k-1)}^u + \hat{x}_{(k|k-1)}^d + \hat{x}_{(k|k-1)}^\epsilon + y_0 \,. \tag{6}$$

However the internal variables x^u, x^d and x^ϵ are unmeasurable in practice, so only their estimates are available. Since the model structure (1) postulates the control x^u and the disturbance term x^d as theoretically undistorted by noise, the pure simulation $\hat{x}^u$ and $\hat{x}^d$ can be considered equal to the actual signals. The unmeasurable disturbance can be estimated as the error of the output single-step-ahead prediction such that:

$$\hat{\epsilon}_{(k|k)} = y_{(k)} - \hat{y}_{(k|k-1)} \,. \tag{7}$$

In order to perform the measurement-compensated prediction, the single-step-ahead prediction of $\hat{x}^\epsilon$ should be corrected by the current estimate $\hat{\epsilon}_{(k|k)}$ according to (7):

$$\hat{x}_{(k|k)}^\epsilon = \hat{x}_{(k|k-1)}^\epsilon + \hat{\epsilon}_{(k|k)} \,. \tag{8}$$

3. Predictive equations

The explicit predictive equations for the model (1) have to be introduced before the control algorithm itself. The output prediction can be decomposed into the free and the forced response:

$$\hat{y}_f = \hat{y}_f^{\text{free}} + \hat{y}_f^{\text{forc}}. \tag{9}$$

For the free response estimation, no future changes of the manipulated variable are assumed. On the other hand, the forced response represents the effect of future control changes Δu_f, while the vector $\hat{y}_f^{\text{forc}}$ $[n_e \times 1]$ gets the following linear form:

$$\hat{y}_f^{\text{forc}} = H_f \Delta u_f\,, \tag{10}$$

where H_f $[n_e \times n_u]$ is the step-response matrix. The prediction horizon representing the length of the $\hat{y}_f$ vector is denoted n_e.

The vector of future control changes Δu_f $[n_u \times 1]$ is defined as:

$$\Delta u_f = \left[\Delta u_{(k)} \;\; \Delta u_{(k+1)} \;\; \ldots \;\; \Delta u_{(k+n_u-1)}\right]^T, \tag{11}$$

where n_u is the control horizon representing the number of assumed changes of the manipulated variable.

The vectors of the past input signals u_p $[n_{B^u} - 1 \times 1]$, d_p $[n_{B^d} - 1 \times 1]$, $\hat{\epsilon}_p$ $[n_C - 1 \times 1]$ and future input signals u_f $[n_e \times 1]$, d_f $[n_e \times 1]$, $\hat{\epsilon}_f$ $[n_e + 1 \times 1]$ are defined as follows:

$$u_f = \left[u_{(k)} \;\; u_{(k+1)} \;\; \ldots \;\; u_{(k+n_e-1)}\right]^T, \tag{12a}$$

$$u_p = \left[u_{(k-1)} \;\; u_{(k-2)} \;\; \ldots \;\; u_{(k-n_{B^u}+1)}\right]^T, \tag{12b}$$

$$d_f = \left[d_{(k)} \;\; d_{(k+1)} \;\; \ldots \;\; d_{(k+n_e-1)}\right]^T, \tag{12c}$$

$$d_p = \left[d_{(k-1)} \;\; d_{(k-2)} \;\; \ldots \;\; d_{(k-n_{B^d}+1)}\right]^T, \tag{12d}$$

$$\hat{\epsilon}_f = \left[\hat{\epsilon}_{(k|k)} \;\; \hat{\epsilon}_{(k+1|k)} \;\; \ldots \;\; \hat{\epsilon}_{(k+n_e|k)}\right]^T, \tag{12e}$$

$$\hat{\epsilon}_p = \left[\hat{\epsilon}_{(k-1)} \;\; \hat{\epsilon}_{(k-2)} \;\; \ldots \;\; \hat{\epsilon}_{(k-n_C+1)}\right]^T. \tag{12f}$$

Equation (12c) implies that not only the amount of carbohydrates just consumed must be announced, but also their future values have to be provided to with relatively high accuracy. In the context of the artificial pancreas, this feature is also called meal announcing [18, 28]. However, it is worth noting that some recent studies show no need of explicit meal announcing if the intraperitoneal insulin delivery is applied [32] or even propose to use the meal size estimation algorithm [33].

Concerning the prediction of the ϵ term, the current estimate $\hat{\epsilon}_{(k|k)}$ is assumed in the future while representing the best prediction of the integrated white noise:

$$\hat{\epsilon}_f = \begin{bmatrix} 1 & 1 & \dots & 1 \end{bmatrix}^T \hat{\epsilon}_{(k|k)} \,. \tag{13}$$

The vectors of the past $\hat{x}_p^u$ $[n_{A^u} \times 1]$, $\hat{x}_p^d$ $[n_{A^d} \times 1]$, $\hat{x}_p^\epsilon$ $[n_D \times 1]$ and the future $\hat{x}_f^u$ $[n_e \times 1]$, $\hat{x}_f^d$ $[n_e \times 1]$, $\hat{x}_f^\epsilon$ $[n_e \times 1]$ estimates of the internal variables are defined as:

$$\hat{x}_p^{u/d} = \begin{bmatrix} \hat{x}_{(k)}^{u/d} & \hat{x}_{(k-1)}^{u/d} & \dots & \hat{x}_{(k-n_{A^{u/d}}+1)}^{u/d} \end{bmatrix}^T, \tag{14a}$$

$$\hat{x}_f^{u/d} = \begin{bmatrix} \hat{x}_{(k+1)}^{u/d} & \hat{x}_{(k+2)}^{u/d} & \dots & \hat{x}_{(k+n_e)}^{u/d} \end{bmatrix}^T, \tag{14b}$$

$$\hat{x}_p^{\epsilon} = \begin{bmatrix} \hat{x}_{(k)}^{\epsilon} & \hat{x}_{(k-1)}^{\epsilon} & \dots & \hat{x}_{(k-n_D+1)}^{\epsilon} \end{bmatrix}^T, \tag{14c}$$

$$\hat{x}_f^{\epsilon} = \begin{bmatrix} \hat{x}_{(k+1)}^{\epsilon} & \hat{x}_{(k+2)}^{\epsilon} & \dots & \hat{x}_{(k+n_e)}^{\epsilon} \end{bmatrix}^T. \tag{14d}$$

To derive the predictive form of the model (1), the matrix calculations method [34] was adopted and enhanced in this paper. The following matrix equation can be formed for prediction of the control submodel:

$$\hat{x}_f^u = M_f^y (A^u)^{-1} \left(-M_p^y (A^u) \hat{x}_p^u + M_f^u (B^u) u_f + M_p^u (B^u) u_p \right). \tag{15}$$

The corresponding matrices M_f^y, M_p^y, M_f^u and M_p^u are valid for a general transfer function-based model.

For an arbitrary denominator polynomial $A(z)$, the matrices M_f^y $[n_e \times n_e]$ and M_p^y $[n_e \times n_A]$ hold:

$$M_f^y(A) = \begin{pmatrix} 1 & 0 & \cdots & 0 & \cdots & 0 \\ a_1 & 1 & \cdots & 0 & \cdots & 0 \\ \vdots & \vdots & \ddots & \vdots & \ddots & \vdots \\ a_{n_A} & a_{n_A-1} & \cdots & 1 & \cdots & 0 \\ \vdots & \vdots & \ddots & \vdots & \ddots & \vdots \\ 0 & 0 & \cdots & a_{n_A} & \cdots & 1 \end{pmatrix}, \tag{16}$$

$$M_p^y(A) = \begin{pmatrix} a_1 & a_2 & \cdots & a_{n_A-1} & a_{n_A} \\ a_2 & a_3 & \cdots & a_{n_A} & 0 \\ \vdots & \vdots & \ddots & \vdots & \vdots \\ a_{n_A} & 0 & \cdots & 0 & 0 \\ \vdots & \vdots & \ddots & \vdots & \vdots \\ 0 & 0 & \cdots & 0 & 0 \end{pmatrix}. \tag{17}$$

The matrices $M_f^u\ [n_e \times n_e]$ and $M_p^u\ [n_e \times n_B - 1]$ for a numerator polynomial $B(z)$ are defined as:

$$M_f^u(B) = \begin{pmatrix} b_1 & 0 & \cdots & 0 & \cdots & 0 \\ b_2 & b_1 & \cdots & 0 & \cdots & 0 \\ \vdots & \vdots & \ddots & \vdots & \ddots & \vdots \\ b_{n_B} & b_{n_B-1} & \cdots & b_1 & \cdots & 0 \\ \vdots & \vdots & \ddots & \vdots & \ddots & \vdots \\ 0 & 0 & \cdots & b_{n_B} & \cdots & b_1 \end{pmatrix}, \tag{18}$$

$$M_p^u(B) = \begin{pmatrix} b_2 & b_3 & \cdots & b_{n_B-1} & b_{n_B} \\ b_3 & b_4 & \cdots & b_{n_B} & 0 \\ \vdots & \vdots & \ddots & \vdots & \vdots \\ b_{n_B} & 0 & \cdots & 0 & 0 \\ \vdots & \vdots & \ddots & \vdots & \vdots \\ 0 & 0 & \cdots & 0 & 0 \end{pmatrix}. \tag{19}$$

The predictive equation (15) can be modified to analogously represent the predictions of the remaining terms of the model (1).

The forced response is equal to:

$$\hat{y}_f^{\text{forc}} = H_f \Delta u_f = M_f^y (A^u)^{-1} M_f^u (B^u) M_\Sigma \Delta u_f \tag{20}$$

and the free response gets the following form:

$$\begin{aligned} \hat{y}_f^{\text{free}} = {} & M_f^y (A^u)^{-1} \left(-M_p^y (A^u) \hat{x}_p^u + M_f^u (B^u) \begin{bmatrix} 1 & 1 & \dots & 1 \end{bmatrix}^T u_{(k)} + M_p^u (B^u) u_p \right) \\ & + M_f^y (A^d)^{-1} \left(-M_p^y (A^d) \hat{x}_p^d + M_f^u (B^d) d_f + M_p^u (B^d) d_p \right) \\ & + M_f^y (D)^{-1} \left(-M_p^y (D) \hat{x}_p^\epsilon + \left(M_f^u (C) \begin{bmatrix} I & \mathbf{0} \end{bmatrix} + \begin{bmatrix} \mathbf{0} & I \end{bmatrix} \right) \hat{\epsilon}_f + M_p^u (C) \hat{\epsilon}_p \right) \end{aligned} \tag{21}$$

whence $I\ [n_e \times n_e]$ is the unit matrix, $\mathbf{0}\ [n_e \times 1]$ is the zeros vector and matrix $M_\Sigma\ [n_e \times n_u]$ is defined as lower triangular:

$$M_\Sigma = \begin{pmatrix} 1 & 0 & \cdots & 0 \\ 1 & 1 & \cdots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ 1 & 1 & \cdots & 1 \\ \vdots & \vdots & \ddots & \vdots \\ 1 & 1 & \cdots & 1 \end{pmatrix}. \tag{22}$$

The output prediction $\hat{y}_f$ is finally calculated as:

$$\hat{y}_f = \hat{x}_f^u + \hat{x}_f^d + \hat{x}_f^\epsilon + \begin{bmatrix} 1 & 1 & \dots & 1 \end{bmatrix}^T y_0 \,, \tag{23}$$

where $\hat{y}_f$ $[n_e \times 1]$ can be unwind as:

$$\hat{y}_f = \begin{bmatrix} \hat{y}_{(k+1)} & \hat{y}_{(k+2)} & \dots & \hat{y}_{(k+n_e-1)} & \hat{y}_{(k+n_e)} \end{bmatrix}^T . \tag{24}$$

4. Control algorithm

The artificial pancreas is a quite complex problem in the general context, but there are actually two particular issues that make the automatic control of glycemia exceptionally difficult to master. The first is the presence of significant lag (delay) in the insulin action dynamics, and the second is the nonnegative nature of the insulin administration that limits the possible control actions of the artificial pancreas [9, 10].

The rationale for using the predictive control is its potential for effective rejection of meal disturbances, as insulin can be applied in the optimal time advance. However, making a really powerful compensation of the disturbance is kind of questionable because even if the meal is effectively compensated and no hyperglycemia occurs, the relatively long-lasting effect of the administered insulin may subsequently cause a severe hypoglycemic event. Therefore, a perfect disturbance compensation is practically unachievable, so a reasonable trade-off between mild hyper or hypoglycemia must always be made. The basic block diagram of the closed loop of the artificial pancreas is depicted in Fig. 1.

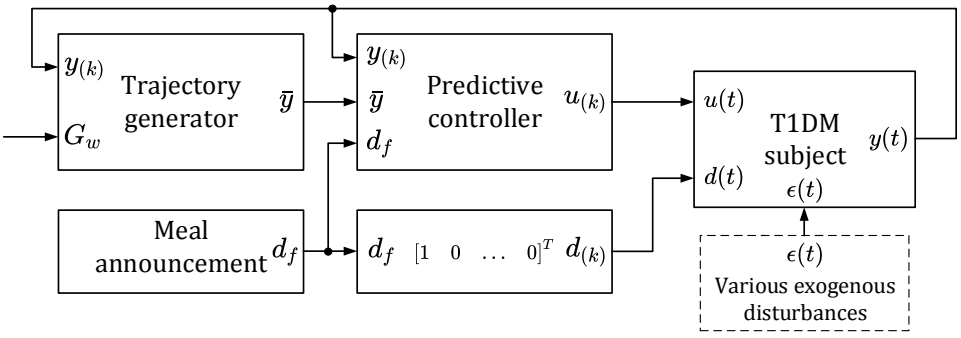


Figure 1: Closed loop of the artificial pancreas utilizing the predictive control

The predictive control algorithm minimizes the quadratic cost function of the model-based predictions of the controlled variable through the appropriate

changes in the manipulated variable. For the assumed incremental control law, the decision vector of the future control changes Δu_f is related to the vector of the future manipulated variable u_f using the M_Σ matrix (22) as:

$$u_f = \begin{bmatrix} 1 & 1 & \dots & 1 \end{bmatrix}^T u_{(k-1)} + M_\Sigma \Delta u_f \,. \tag{25}$$

The general cost function of the predictive control can be written as [35]:

$$J(\Delta u_f) = \sum_{i=1}^{n_e} \lambda_i^y \left[\bar{y}_{(k+i)} - \hat{y}_{(k+i)} \right]^2 + \sum_{j=1}^{n_u} \lambda_j^u \Delta u_{(k+j-1)}^2 \,. \tag{26}$$

The weighting vector λ^u $[n_u \times 1]$ for penalizing the squared changes of the manipulated variable can be interpreted as the factor affecting the aggressiveness of control:

$$\lambda^u = \begin{bmatrix} \lambda_1^u & \lambda_2^u & \dots & \lambda_{n_u-1}^u & \lambda_{n_u}^u \end{bmatrix}^T . \tag{27}$$

The vector λ^y $[n_e \times 1]$ is the counter-weighting vector for the control error penalty:

$$\lambda^y = \begin{bmatrix} \mathbf{0} & \lambda_{n_e^\star}^y & \lambda_{n_e^\star+1}^y & \dots & \lambda_{n_e-1}^y & \lambda_{n_e}^y \end{bmatrix}^T , \tag{28}$$

where $\mathbf{0}$ $[1 \times n_e^\star]$ is the zeros vector and the parameters $n_e^\star$ and n_e represent the beginning and the end of the optimized prediction horizon, respectively.

The elements of the future reference vector $\bar{y}$ $[n_e \times 1]$ can be assumed to be equal to constant G_t (representing the target glycemia) or can be dynamically generated by the trajectory generator.

$$\bar{y} = \begin{bmatrix} \bar{y}_{(k+1)} & \bar{y}_{(k+2)} & \dots & \bar{y}_{(k+n_e-1)} & \bar{y}_{(k+n_e)} \end{bmatrix}^T . \tag{29}$$

The target glycemia G_t can be chosen according to the physician's recommendation, from the relatively narrow interval $5.0 < G_t < 6.0$ mmol/l.

The generic cost function (26) can be reshaped into the equivalent quadratic form:

$$J(\Delta u_f) = \left(\bar{y} - \hat{y}_f \right)^T \Lambda^y \left(\bar{y} - \hat{y}_f \right) + \Delta u_f^T \Lambda^u \Delta u_f \,, \tag{30}$$

where Λ^u $[n_u \times n_u]$ and $\Lambda^y [n_e \times n_e]$ are positive definite diagonal matrices with diagonal vectors λ^u (27) and λ^y (28), respectively [36].

$$\Lambda^u = \mathrm{diag}(\lambda^u), \tag{31}$$

$$\Lambda^y = \mathrm{diag}(\lambda^y). \tag{32}$$

Substituting the output prediction (9) and the forced response in the linear form (10) into the cost function (30), the quadratic form with respect to the decision variable Δu_f can be derived [37]:

$$J(\Delta u_f) = \Delta u_f^T \mathbf{A} \Delta u_f + 2\mathbf{b}^T \Delta u_f + c, \tag{33}$$

where matrix $\mathbf{A}$ $[n_u \times n_u]$, vector $\mathbf{b}$ $[n_u \times 1]$, and scalar c are defined as:

$$\mathbf{A} = H_f^T \Lambda_y H_f + \Lambda_u \,, \tag{34a}$$

$$\mathbf{b}^T = -\left(\bar{y} - \hat{y}_{\text{free}}\right)^T \Lambda_y H_f \,, \tag{34b}$$

$$c = \left(\bar{y} - \hat{y}_{\text{free}}\right)^T \Lambda_y \left(\bar{y} - \hat{y}_{\text{free}}\right) . \tag{34c}$$

The above cost function can be minimized either analytically for the unconstrained case or using numerical methods of the quadratic programming if linear inequalities constraints are assumed. The unconstrained optimal solution of the predictive control problem (33), (34) can be derived assuming the optimality condition $\nabla_{\Delta u_f} J(\Delta u_f) = \mathbf{0}$ in the closed form as:

$$\Delta u_f = -\mathbf{A}^{-1}\mathbf{b} \,. \tag{35}$$

Using the receding-horizon strategy, only the first element of the solution Δu_f is actually applied:

$$u_{(k)} = u_{(k-1)} + \begin{bmatrix} 1 & 0 & \dots & 0 \end{bmatrix} \Delta u_f \,. \tag{36}$$

4.1. Constraining the manipulated variable

The greatest weakness of the traditional concept of the artificial pancreas is the apparent non-negative nature of insulin administration. As a consequence, the artificial pancreas is virtually unable to actively raise glycemia, so extra attention must be paid to the management of hypoglycemia. It is also worth noting that some studies focused on a promising strategy of using glucagon as an insulin antagonist and counterregulatory hormone, thus the desired glycemia-raising effect could be initiated by the artificial pancreas [38, 39]. However, in this paper, we will stick to the conservative strategy of solely insulin application.

In addition to the lower bound, insulin pumps also have technological limits for the maximal insulin delivery rate, so the manipulated variable lies within the interval:

$$u_{\min} \leqslant u \leqslant u_{\max} \,. \tag{37}$$

The minimal infusion rate $u_{\min}$ is zero while the typical value of $u_{\max}$ was reported in [27] or [21]:

$$u_{\min} = 0 \text{ U/min}, \qquad u_{\max} = \frac{1}{15} \text{ U/min} \,. \tag{38}$$

A simple but not optimal solution to involve these constraints in the predictive control algorithm is to use the saturation operation, as reported in [21, 22, 28] and [19]. For true constrained optimization, it is desired to express the manipulated

value constraints (37) as an equivalent set of linear inequalities with respect to the decision vector Δu_f using the M_Σ matrix (22) as [36]:

$$-M_\Sigma \Delta u_f \leqslant -\begin{bmatrix}1 & 1 & \dots & 1\end{bmatrix}^T \left(u_{\min} - u_{(k-1)}\right), \tag{39}$$

$$+M_\Sigma \Delta u_f \leqslant +\begin{bmatrix}1 & 1 & \dots & 1\end{bmatrix}^T \left(u_{\max} - u_{(k-1)}\right). \tag{40}$$

4.2. Constraining the controlled variable

Constraining the controlled variable is especially fundamental for the artificial pancreas, since it could be the clue to reduce the risk of hypo and hyperglycemia during the automated insulin treatment.

Formally, the controlled variable is supposed to be within the interval:

$$y_{\min} \leqslant y \leqslant y_{\max}. \tag{41}$$

The relatively safe interval of glycemia is roughly:

$$y_{\min} = 4.5 \text{ mmol/l}, \qquad y_{\max} = 9 \text{ mmol/l}. \tag{42}$$

In order to include the constraints (41) to the optimization problem, the corresponding linear inequalities with respect to the decision vector Δu_f have to be derived. Based on the output prediction decomposition theorem (9) and the linear form of the forced response (10), one can write [36]:

$$-H_f \Delta u_f \leqslant -\begin{bmatrix}1 & 1 & \dots & 1\end{bmatrix}^T y_{\min} + \hat{y}^{\text{free}}, \tag{43}$$

$$+H_f \Delta u_f \leqslant +\begin{bmatrix}1 & 1 & \dots & 1\end{bmatrix}^T y_{\max} - \hat{y}^{\text{free}}. \tag{44}$$

Unfortunately, this approach has some practical limitations, as will be analyzed in the next section.

4.3. Control feasibility

Concerning the a priori existence of the constrained solution of the predictive control problem, one may suppose that the constraints of the manipulated and the controlled variable have mutually contradictory effect on their feasibility. Under some specific circumstances, particularly if applying too strict constraints concurrently, it may happen that there is no feasible solution for all the assumed inequalities (39), (40), (43), (44), whereas this phenomenon was already marginally mentioned in [21] and [26]. In fact, the constraints of the manipulated variable basically cannot be violated since these are physically grounded, so it is the controlled variable, the constraints of which have to be corrupted after all.

Accordingly, the proposed strategy is to detect the infeasibility during the control, generate the corresponding alarm, and adapt the constraints of the controlled variable (43), (44) in order to recover the feasibility and optimality of the control. For a rigorous analysis of this problem, one can harness the Farkas lemma [40]:

Theorem 1 (Farkas lemma) *Either the linear inequalities system* $Ax \leqslant b$ *has a solution with* $x \in \mathbb{R}^n$*, or the equalities system* $A^T y = 0$ *subject to constraints* $y \geqslant 0$ *has a solution such that* $b^T y < 0$

The following linear programming problem has to be solved, and the minimum checked for meeting the feasibility condition defined by the Farkas lemma.

$$\begin{gathered} \min b^T y \\ \text{subj. to: } A^T y = 0 \quad \text{and} \quad y \geqslant 0. \end{gathered} \tag{45}$$

The solution of the joint linear inequalities system formed by (39), (40), (43), (44) is feasible if the corresponding optimization problem (45) has a non-negative optimum i.e. $\min b^T y \geqslant 0$. If there is no feasible solution, then the controlled variable constraints (41) have to be adapted according to the Algorithm 1.

Algorithm 1 Controlled variable constraints adaptation

Assume tuning parameters β and γ:

$\beta \in \langle 0.01, 0.1 \rangle$

$\gamma \in \langle 0.01, 0.1 \rangle$

$A = \begin{bmatrix} -M_\Sigma{}^T & M_\Sigma{}^T & -H_f{}^T & H_f{}^T \end{bmatrix}^T$

repeat

$$b = \begin{bmatrix} -\begin{bmatrix} 1 & 1 & \dots & 1 \end{bmatrix}^T \left(u_{\min} - u_{(k-1)} \right) \\ +\begin{bmatrix} 1 & 1 & \dots & 1 \end{bmatrix}^T \left(u_{\max} - u_{(k-1)} \right) \\ -\begin{bmatrix} 1 & 1 & \dots & 1 \end{bmatrix}^T y_{\min} + \hat{y}^{\text{free}} \\ +\begin{bmatrix} 1 & 1 & \dots & 1 \end{bmatrix}^T y_{\max} - \hat{y}^{\text{free}} \end{bmatrix}$$

$J \leftarrow \min b^T y$ to constraints $A^T y = 0$ and $y \geqslant 0$

if $J < 0$ **then**

$y_{\max} \leftarrow y_{\max} (1 + \beta)$

$y_{\min} \leftarrow y_{\min} (1 - \gamma)$

end if

until $J \geqslant 0$

This algorithm allows to choose either the upper or the lower bound of the controlled variable has to be preserved via tuning the parameters β and γ. In the case of glycemia control, due to the serious consequences of hypoglycemia, the lower bound is much more important not to be violated, so we can choose

$\beta = 0.1$ and $\gamma = 0.01$ to reflect this demand. Hence, restoring the feasibility and correcting the constraints can be considered non-symmetrical.

It should be mentioned that checking the control feasibility is absolutely essential to be carried out before solving the optimization problem, since otherwise the numerical solution of the quadratic program would fail. We suppose that this kind of selective adaptation of the hard constraints is a better alternative to the pure symmetrical penalizing of the controlled variable deviations from the reference value because the physiology-involved asymmetry of the span of the controlled variable is taken into account this way. A comparable result could potentially be achieved using the soft constraints implemented as the asymmetric cost function with the slack variables representing the constraints violations, as was presented in [24] and [25].

5. In-silico experiment

In order to evaluate the presented improvements and assess the actual effectiveness of the proposed control algorithm, comprehensive in-silico, i.e. simulation-based experiments, were carried out. The main advantage of the in-silico approach is the elimination of potential health risks that may occur during this early stage of the artificial pancreas testing. In addition, the financial and time burden of this kind of experiment is reduced compared to regular clinical trials.

As a virtual diabetic subject, the complex nonlinear simulation model originally presented in [41] and [42] was adopted. It should be mentioned that this model was accepted by the *Food and Drug Administration* agency as a substitute to animal trials for the preclinical testing of control strategies in artificial pancreas studies [7]. However, the model needs to be correctly parameterized, so the available mean-population parameters published in [42] were assumed. Since this parameters set represents an average healthy subject, some modifications had to be made in order to make it compliant with type 1 diabetes [22, 43]. The basal state was adjusted according to the basal glycemia $G_b = 7$ mmol/l and the corresponding basal insulin delivery rate $v_b = 0.01$ U/min. The virtual CGM measurements were distorted by the additive white noise with the variance $\sigma^2 = 0.01$ mmol/l.

5.1. Meal plan

The experiment was designed to emulate the regular behavior of a subject with type 1 diabetes during the two-day period. The applied meal plan included one major meal for lunch, two minor meals for breakfast and dinner, and a few little snack-like portions for each day. The overnight meal-free gap was also assumed in order to address the potential risk of nocturnal hypoglycemia. Notice that there are two slightly different scenarios present in Table 1.

Table 1: Meal plans for the control experiments

		Day 1						Day 2					
Scenario 1	t [h:min]	5:00	10:00	13:20	15:00	18:20	20:00	7:30	9:10	10:50	16:40	19:10	21:40
	CHO [g]	15	5	45	10	30	15	20	10	50	15	20	5
Scenario 2	t [h:min]	5:50	8:20	12:30	16:40	19:10	21:40	6:40	8:20	11:40	15:50	17:30	20:50
	CHO [g]	25	10	60	20	50	5	20	15	65	25	30	10

5.2. Controller parameters

Since the controlled system model is an essential part of the proposed predictive controller, its accuracy and validity significantly affects the control performance. Note that problems related to the estimation of physiology-compliant model parameters from diabetic datasets are not in the scope of this paper, so for more comprehensive details on this topic, see our recent work [44].

The orders of the empirical model (1) were chosen as $n_{A^u} = n_{B^u} = 4$, $n_{A^d} = n_{B^d} = 3$ and $n_C = 1$, $n_D = 2$ and the model polynomial coefficients were estimated as follows:

$$A^u(z) = 1 - 3.4546z^{-1} + 4.4641z^{-2} - 2.5572z^{-3} + 0.5479z^{-4}, \tag{46a}$$

$$B^u(z) = -0.0078z^{-1} - 0.0133z^{-2} - 0.0065z^{-3} - 0.0008z^{-4}, \tag{46b}$$

$$A^d(z) = 1 - 2.3887z^{-1} + 1.8778z^{-2} - 0.4857z^{-3}, \tag{46c}$$

$$B^d(z) = 0.0439z^{-1} + 0.0313z^{-2} + 0.0048z^{-3}, \tag{46d}$$

$$D(z) = 1 - 0.5269z^{-1} - 0.3574z^{-2}, \tag{46e}$$

$$C(z) = 1 - 0.3217z^{-1}. \tag{46f}$$

In order to assess the control performance obtained using the proposed model (1) compared to the traditional approaches, the following parameters of the two-input ARX model with orders $n_A = n_{B^u} = n_{B^d} = 4$ were identified:

$$A(z) = 1 - 1.9515z^{-1} + 0.3865z^{-2} + 1.1245z^{-3} - 0.5584z^{-4}, \tag{47a}$$

$$B^u(z) = -0.3617z^{-1} + 0.1660z^{-2} - 0.0254z^{-3} + 0.0013z^{-4}, \tag{47b}$$

$$B^d(z) = 0.0943z^{-1} + 0.1038z^{-2} - 0.0746z^{-3} - 0.0841z^{-4} \tag{47c}$$

and the following assumption holds for the polynomials of model (1) in this case:

$$A^u(z) = A(z), \qquad A^d(z) = A(z), \qquad C(z) = D(z) = 1. \tag{48}$$

The design of the predictive controller is primarily based on empirical tuning rules. First, $n_e^\star$ and n_e parameters have to be chosen, as they represent the beginning and the end of the optimized horizon, respectively (see (28)). The parameter

$n_e^\star$ should be equal to the approximate input-output delay, so based on the impulse response of the identified control submodel (refer to [44]), the effect of insulin appears in about 50 minutes, implying that for the sample time $T_s = 10$ min one gets $n_e^\star = 5$.

However, n_e is actually the crucial one, as it defines the overall length of the optimized prediction horizon. Extending this horizon can potentially lead to a desired reduction in hypoglycemia risk because the controller can cut off insulin dosing soon enough before hypoglycemia develops. On the other hand, increasing n_e puts the demand for higher predictive performance of the identified empirical model (1) and the patient's burden to provide the correct announcement of meals as well. Regarding both factors, the length of the prediction horizon was chosen as $n_e = 20$. Finally, the control horizon was set as $n_u = 10$.

The weighting vector of the manipulated variable changes penalty λ^u affects the control aggressiveness as well as it makes the control more or less noise prone. This vector was chosen as:

$$\lambda^u = \begin{bmatrix} 1 & 1 & \dots & 1 \end{bmatrix}^T 25 \, \frac{1}{n_u} \, . \tag{49}$$

The counter-weighting vector λ^y was designed as:

$$\lambda^y = \begin{bmatrix} 1 & 1 & \dots & 1 \end{bmatrix}^T \frac{1}{n_e - n_e^\star} \, . \tag{50}$$

5.3. Inter-subject variability

To assess the robustness of the artificial pancreas with respect to the inter-subject variability, the so-called *Control Variability Grid Analysis* (abbr. CVGA) is typically used [45]. The CVGA interprets the control performance on a single subject as a point in the plane, while its coordinates represent the minimal and maximal measured glycemia during a finite time period. By experimenting on a group of diabetic subjects, the set of CVGA points can be obtained such that:

$$CVGA_i = [\min(G_i(t)), \, \max(G_i(t))] \, . \tag{51}$$

The CVGA plane can be divided into nine zones rated from the best control performance (A) to the worst (E). Needless to say that to achieve truly unbiased results, the disturbance conditions must be same for all the experimented subjects, and for each of these virtual patients, individual identification of the empirical model (1) has to be carried out first.

The virtual diabetic subjects population was randomly generated assuming the normal distribution of all model parameters with the available mean-population value μ_i and the standard deviation σ_i determined according to the strategy

uniform coefficient of variation. The coefficient of variation c_v is defined as the fixed ratio for all the model parameters:

$$c_v = \frac{\sigma_i}{\mu_i} = 0.15. \tag{52}$$

5.4. Results

The results for several distinct control scenarios and controller setups are discussed in this section. For each of the experiments, the control performance has been quantified by the maximal $G_{\max}$ and the minimal $G_{\min}$ observed glycemia, as well as by the basic quadratic criterion defined for the experiment with N samples as:

$$Q = \sum_{i=0}^{N} \left[y_{(i)} - G_t \right]^2. \tag{53}$$

The first experiment representing the unconstrained control according to the closed-form solution (35) with simply saturated manipulated variable, as the prevailing control strategy in the literature, is depicted in Fig. 2. Applying the true constraints to the manipulated variable in the terms of (39), (40) with bounds (38) noticeably improved the control performance, as can be observed in Fig. 3.

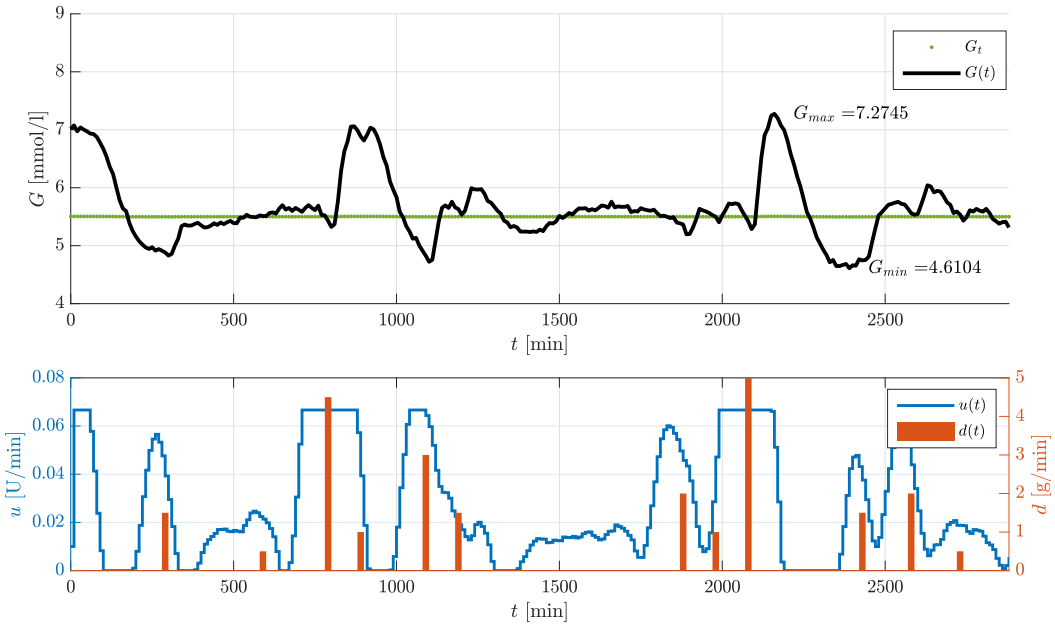


Figure 2: Predictive control in-silico experiment with unconstrained control – meal scenario 1, $Q = 99.04$

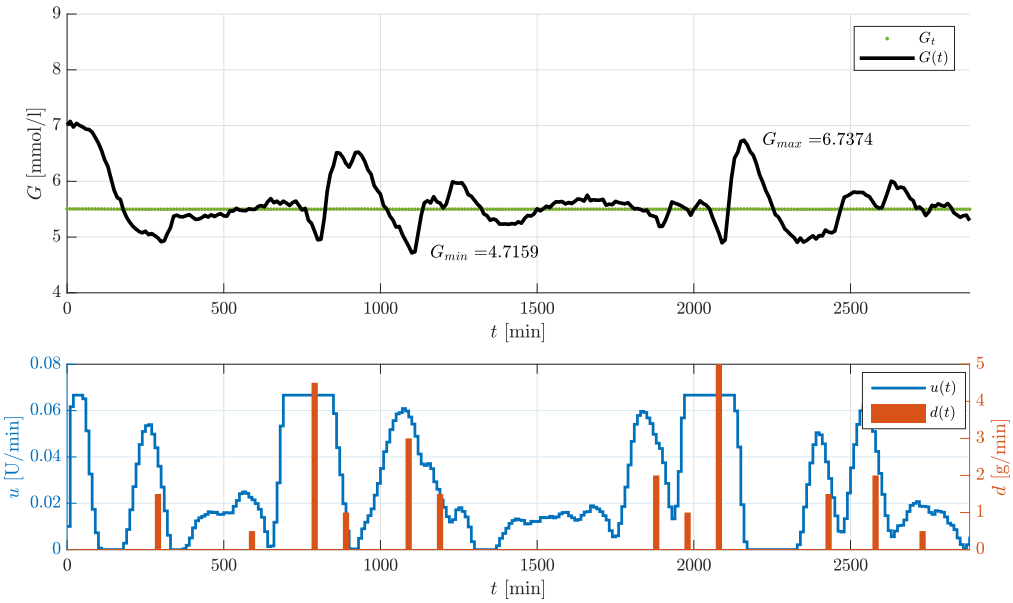


Figure 3: Predictive control in-silico experiment with constrained manipulated variable – meal scenario 1, Q = 63.48

It is also quite important to assess the control performance under assumption (48) of the ARX model simplification with the corresponding model parameters (47). In Fig. 4, it can be seen a much worse management of glycemia concerning its maximal and minimal value, as well as a higher value of the metric Q indicating a poorer control performance compared to the control with the proposed model (1) having separate feedback dynamics for the insulin administration submodel and the carbohydrate intake submodel.

Another simulation concerns the control with no disturbance prediction, i.e. only the current meal is announced. In this case, notable poor control performance can be seen in Fig. 5, since meal-compensating insulin administration occurs after the corresponding meal intake.

The next scenario represents the same controller setup as in Fig. 3 but for a different meal scenario number 2 from Table 1. Due to more demanding disturbance conditions, one can observe slightly deteriorated control performance in Fig. 6.

Now the constraints are also applied to the controlled variable according to equations (43), (44) with bounds (42). In Fig. 7 one can notice improved hypoglycemia management although it was apparently achieved at the expense of higher maximal glycemia and worse performance metric Q than in the previous case. However, constraining the controlled variable yields another degree of freedom in the controller tuning procedure, primarily affecting the strategy of

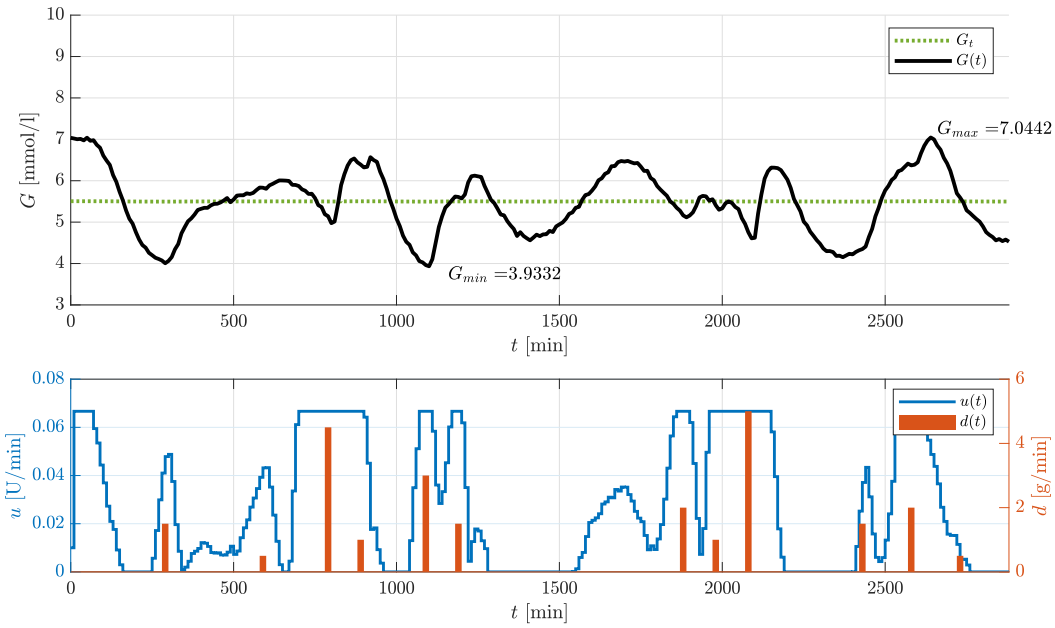


Figure 4: Predictive control in-silico experiment with the ARX model and constrained manipulated variable – meal scenario 1, Q = 169.92

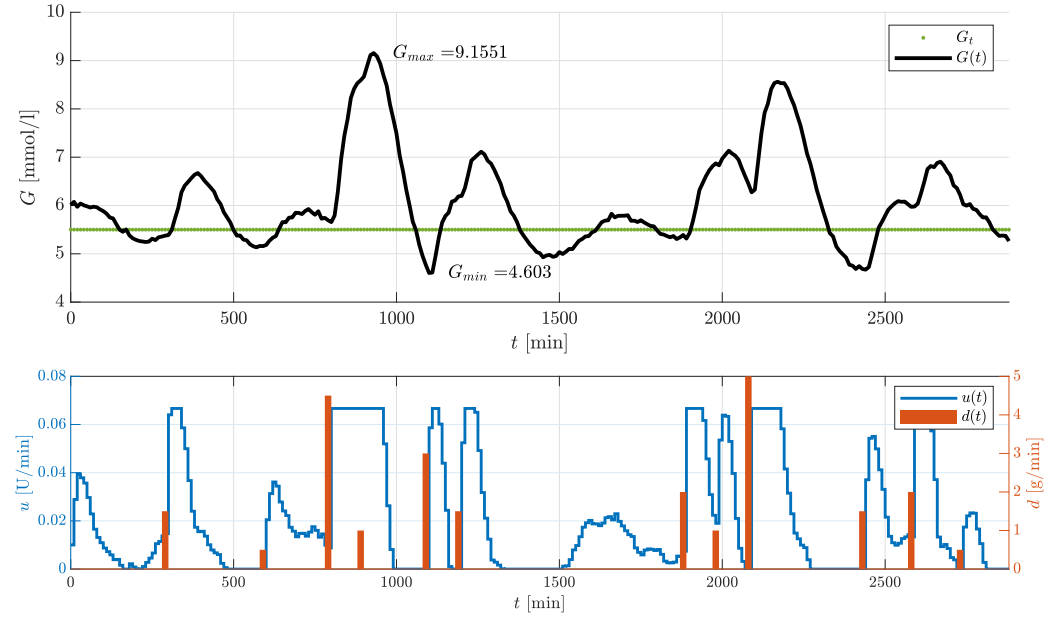


Figure 5: Predictive control in-silico experiment with constrained manipulated variable and no meal announcing – meal scenario 1, Q = 371.53

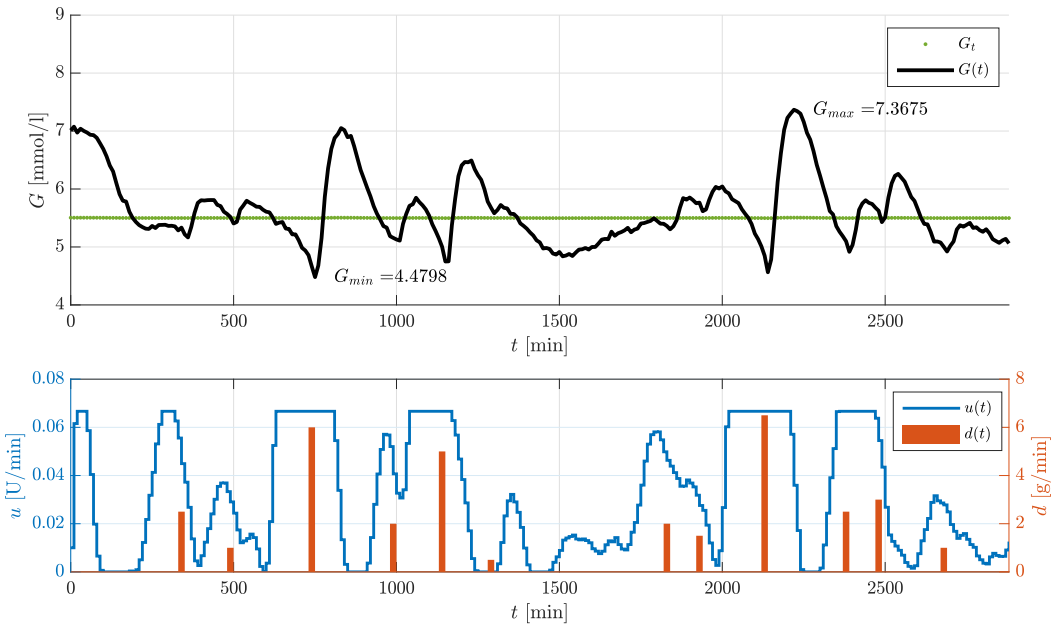


Figure 6: Predictive control in-silico experiment with constrained manipulated variable – meal scenario 2, Q = 109.22

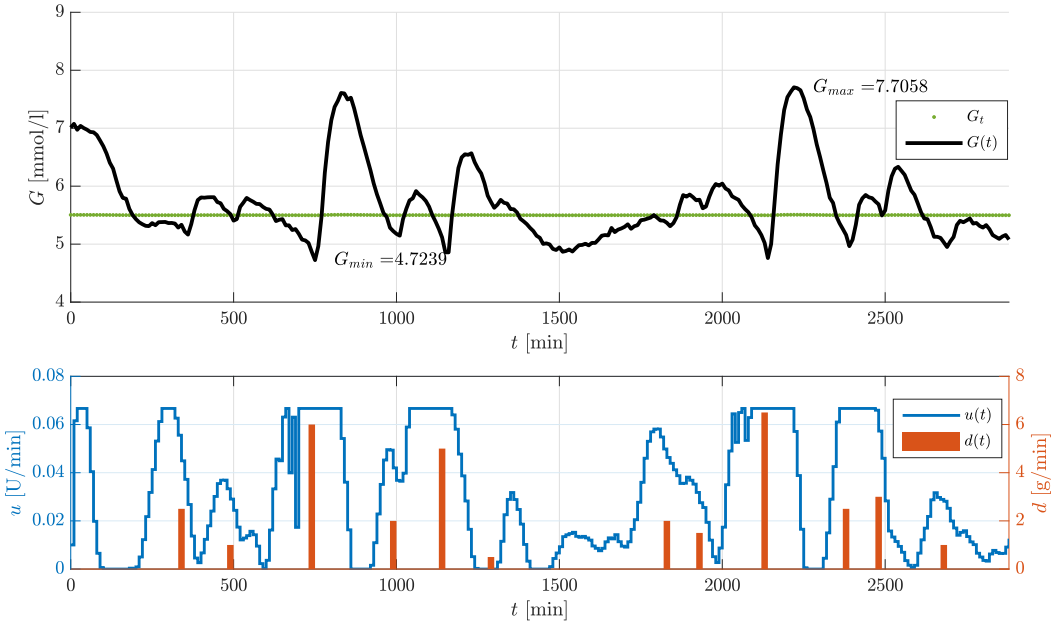


Figure 7: Predictive control in-silico experiment with constrained manipulated and controlled variable – meal scenario 2, Q = 143.07

hypoglycemia and hyperglycemia management and their trade-off. It is also worth noting that the controlled variable may appear as it was not constrained since the lower bound 4.5 mmol/l is actually never reached, but this bias was caused by nothing but the presence of plant-model mismatch.

Another interesting experiment concerns the problem of control feasibility, as was theoretically analyzed in Section 4.3. Choosing too strict constraints on the controlled variable, for instance $y_{\min} = 5.0$ mmol/l, $y_{\max} = 6.5$ mmol/l, caused the control to be infeasible, resulting in an inevitable violation of the constraints. In order to avoid the more dangerous hypoglycemia state, the upper constraint was adapted during the control to recover the control feasibility and optimality. Thanks to the asymmetric constraints adaptation, the lower bound of the controlled variable remained virtually untouched. This case is demonstrated in Fig. 8, where the infeasibility alarm is also plotted (refer to equation (45) and Algorithm 1).

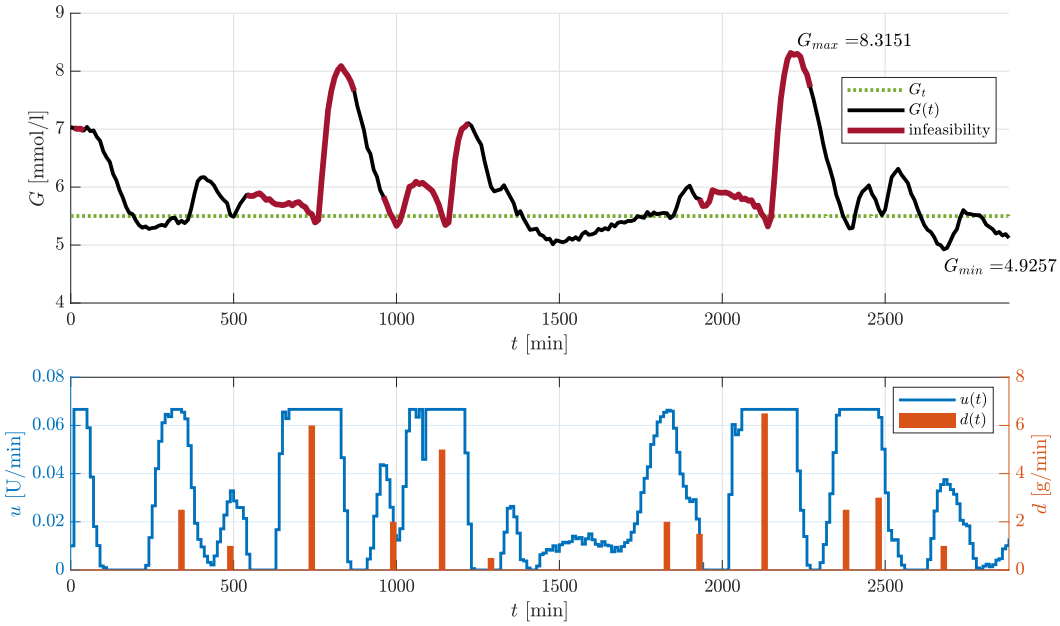


Figure 8: Predictive control in-silico experiment with controlled variable constraints infeasibility – meal scenario 2, $Q = 212.20$

In practice, the meal announcing will probably not be very reliable and accurate, so the robustness of the artificial pancreas also needs to be addressed from this perspective. One can expect to receive biased input from the patient, including unannounced yet consumed meals, deviations in the amount and the time of carbohydrate intake, and the false meal announcement as the most dan-

gerous phenomenon. The announced but unconsumed meal can lead to a severe and potentially unrecoverable hypoglycemia state, as the effect of predictively administered insulin would be totally inadequate and irreversible in that case. In order to involve this meal announcement mismatch to our experiments, two distinct disturbance signals are assumed: the real one $d_r(t)$, which is actually applied, and the announced one $d(t)$, which is passed to the control algorithm (see Table 2). An obvious deterioration of the control performance can be observed in Fig. 9 as well as infeasibility of the original constraints of the controlled variable if the meal-announcing mismatch is present, yet no severe hyperglycemia or hypoglycemia occurred, so the controller was capable to maintain relatively safe values of glycemia under the condition of disturbance uncertainty.

Table 2: Mismatch between the real and the announced carbohydrate intake

		Day 1						Day 2					
Announced	t [h:min]	5:00	10:00	13:20	15:00	18:20	20:00	7:30	8:50	10:50	16:40	19:10	21:40
	CHO [g]	15	5	40	10	30	15	20	0	45	15	20	5
Real	t [h:min]	5:10	10:00	13:20	15:30	18:20	20:00	7:10	8:50	10:20	16:40	19:10	21:40
	CHO [g]	12.5	3.5	60	10	25	10	20	10	60	25	22.5	0

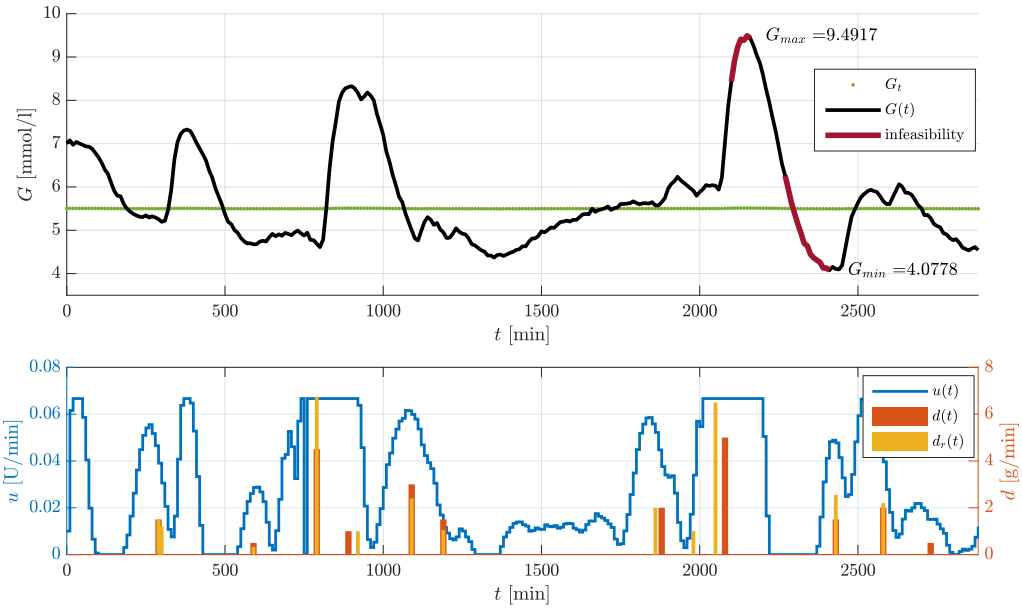
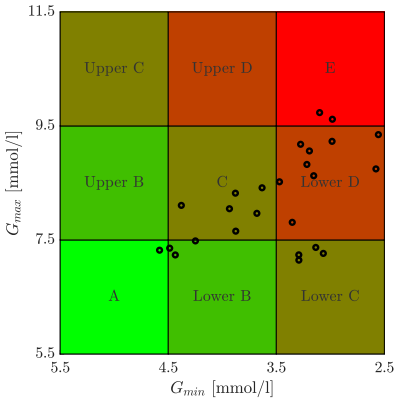
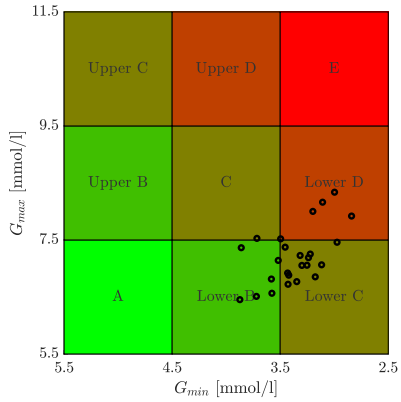


Figure 9: Predictive control in-silico experiment – disturbance mismatch of meal scenario from Table 2, Q = 417.40

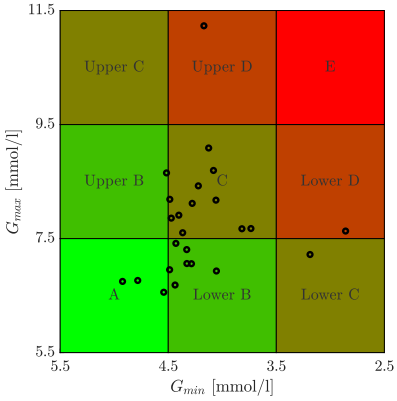
Finally, the CVGA evaluated for 25 virtual subjects assuming various controller setups concludes this section. Simple unconstrained control with saturated manipulated variable yields quite poor control performance as documented in Fig. 10a. Moreover, unacceptable results were obtained using the traditional ARX model, while severe hypoglycemia states can be observed in Fig. 10b, showing the superiority of the proposed model (1). In Figs. 10c and 10d one can notice a significant bias in minimum and maximum glycemia if hard constraints of the controlled variable are applied, which implies that by their appropriate selection, the risk of hypoglycemia can be significantly reduced and a reasonable trade-off between the hypoglycemia and hyperglycemia can be tuned intuitively.



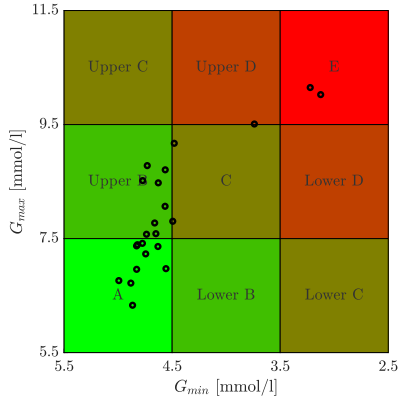
(a) Unconstrained (saturated) manipulated variable and unconstrained controlled variable



(b) Constrained manipulated variable and unconstrained controlled variable, ARX model



(c) Constrained manipulated variable and unconstrained controlled variable



(d) Constrained manipulated variable and constrained controlled variable

Figure 10: Control Variability Grid Analysis for the meal scenario 2

The overall performance comparison for all experiments carried out is summarized in Table 3.

Table 3: Experiments control performance summary

Experiment	Q	$G_{\max}$	$G_{\min}$
unconstrained control and saturated u, sc. 1	99	7.2	4.6
constrained u, meal scenario 1	63	6.7	4.7
constrained u, ARX model, meal scenario 1	170	7.0	3.9
constrained u, no disturbance prediction, meal scenario 1	371	9.1	4.6
constrained u, meal scenario 2	109	7.3	4.4
constrained u and y, meal scenario 2	143	7.7	4.7
constrained u and y, strict constraints, meal scenario 2	212	4.9	8.3
constrained u and y, disturbance mismatch	417	9.5	4.0

6. Conclusions

In this paper, the practical performance limits of the linear model predictive control were tested in such a complex and demanding application as the artificial pancreas that maintains normoglycemia in subjects with type 1 diabetes. An empirical model featuring separate feedback dynamics for control and disturbance input turned out to be a better alternative to the traditional two-input ARX or ARMAX models. In contrast to the traditional unconstrained predictive control law, linear inequalities were assumed for the constraints of the manipulated and controlled variable. The emerging problem of control infeasibility was rigorously addressed by exploiting the properties of the Farkas lemma. In order to recover the feasibility and optimality of the control, an iterative algorithm was proposed to adapt the constraints of the controlled variable. However, this adaptation can be asymmetrical, what allowed to force the suppression of hypoglycemia while tolerating mild hyperglycemia.

At the end of this paper, a series of in-silico experiments were carried out while analyzing various disturbance scenarios and different controller setups. The proposed model and the control algorithm have been proven to be superior to conventional solutions, while constraining the controlled variable turned out to be an effective strategy for the suppression of hypoglycemia states. Additionally, the control robustness was assessed with respect to the inter-subject variability and the meal announcement mismatch, obtaining quite satisfying results. Even if the observed good in-silico control performance may seem encouraging, it does not guarantee the same results to be obtained in vivo, so the computer simulation can not be considered as a full substitute to clinical trials, but is a prerequisite.

The possible future enhancements should involve better unmeasurable disturbance prediction as well as design of the adaptive version of controller in order to address the time-variability of subject physiology.

References

[1] R. Sánchez-Peña and D. Chernavvsky: *Artificial Pancreas: Current Situation and Future Directions*. Academic Press, 2019.

[2] C. Cobelli, E. Renard and B. Kovatchev: Artificial Pancreas Past, Present, Future. *Diabetes*, **60**(11), (2011), 2672–2682. DOI: 10.2337/db11-0654.

[3] C.K. Boughton and R. Hovorka: Advances in artificial pancreas systems. *Science Translational Medicine*, **11**, (2019). DOI: 10.1126/scitranslmed.aaw4949.

[4] S.R. Mudaliar, F.A. Lindberg, M. Joyce, P. Beerdsen, P. Strange, A. Lin and R.R. Henry: Insulin aspart (B28 asp-insulin): a fast-acting analog of human insulin: absorption kinetics and action profile compared with regular human insulin in healthy nondiabetic subjects. *Diabetes Care*, **22**(9), (1999), 1501–1506. DOI: 10.2337/diacare.22.9.1501.

[5] E.W.T. Braak, J.R. Woodworth, R. Bianchi, B. Cerimele, D.W. Erkelens, J.H.H. Thijssen and D. Kurtz: Injection site effects on the pharmacokinetics and glucodynamics of insulin lispro and regular insulin. *Diabetes Care*, **19**(12), (1996), 1437–1440. DOI: 10.2337/diacare.19.12.1437.

[6] C. Cobelli, M. Schiavon, C. Dalla Man, A. Basu and R. Basu: Interstitial fluid glucose is not just a shifted-in-time but a distorted mirror of blood glucose: Insight from an in silico study. *Diabetes technology & therapeutics*, **18** (2016). DOI: 10.1089/dia.2016.0112.

[7] C. Cobelli, C. Dalla Man, G. Sparacino, L. Magni, G. De Nicolao and B.P. Kovatchev: Diabetes: Models, signals, and control. *IEEE Reviews in Biomedical Engineering*, **2** (2009), 54–96. DOI: 10.1109/RBME.2009.2036073.

[8] C. Fabris and B. Kovatchev: *Glucose Monitoring Devices: Measuring Blood Glucose to Manage and Control Diabetes*. Academic Press, 2020.

[9] B.W. Bequette: A critical assessment of algorithms and challenges in the development of a closed-loop artificial pancreas. *Diabetes Technology & Therapeutics*, **7**(1), (2005), 28–47. DOI: 10.1089/dia.2005.7.28.

[10] B.W. Bequette: Challenges and recent progress in the development of a closed-loop artificial pancreas. *Annual Reviews in Control*, **36**(2), (2012), 255–266. DOI: 10.1016/j.arcontrol.2012.09.007.

[11] G. Steil, A. Panteleon and K. Rebrin: Closed-loop insulin delivery—the path to physiological glucose control. *Advanced Drug Delivery Reviews*, **56**(2), (2004), 125–144. DOI: 10.1016/j.addr.2003.08.011.

[12] G. M. Steil, K. Rebrin, C. Darwin, F. Hariri and M. F. Saad: Feasibility of automating insulin delivery for the treatment of type 1 diabetes. *Diabetes*, **55**(12), (2006), 3344–3350. DOI: 10.2337/db06-0419.

[13] G. Marchetti, M. Barolo, L. Jovanovic, H. Zisser and D. E. Seborg: An improved PID switching control strategy for type 1 diabetes. *IEEE Transactions on Biomedical Engineering*, **55**(3), (2008), 857–865. DOI: 10.1109/TBME.2008.915665.

[14] R. Hovorka: Management of diabetes using adaptive control. *International Journal of Adaptive Control and Signal Processing*, **19**(5), (2005), 309–325. DOI: 10.1002/acs.851.

[15] M. Tárník, J. Murgaș, E. Miklovičová and L. Farkas: Adaptive control of time-delayed systems with application for control of glucose concentration in type 1 diabetic patients. *IFAC Proceedings Volumes, 11th IFAC Workshop on Adaptation and Learning in Control and Signal Processing*, **46**(11), (2013), 452–457. DOI: 10.3182/20130703-3-FR-4038.00033.

[16] M. Tárník, E. Miklovičová, J. Murgaș, I. Ottinger and T. Ludwig: Model reference adaptive control of glucose in type 1 diabetics: A simulation study. *IFAC Proceedings Volumes, 19th IFAC World Congress.*, **47**(3), (2014), 5055–5060. DOI: 10.3182/20140824-6-ZA-1003.00321.

[17] A. Ilka, I. Ottinger, T. Ludwig, M. Tárník, V. Veselý, E. Miklovičová and J. Murgaș: Robust controller design for T1DM individualized model:gain-scheduling approach. *International Review of Automatic Control (IREACO)*, **8**(2), (2015). DOI: 10.15866/ireaco.v8i2.5554.

[18] G. De Nicolao, L. Magni, C.D. Man and C. Cobelli: Modeling and control of diabetes: Towards the artificial pancreas. *IFAC Proceedings Volumes, 18th IFAC World Congress*, **44**(1), (2011), 7092–7101. DOI: 10.3182/20110828-6-IT-1002.03036.

[19] E. Miklovičová and M. Tárník: GPC for diabetes control without meal annoucement – control loop design and control performance study. In *Recent*

Advances in Mechanical Engineering and Automatic Control, Proceedings of the 3rd European Conference of Control (ECC '12), Paris, France, WSEAS Press, **12** (2012), 58–63.

[20] H. Kirchsteiger and L. del Re: A model based bolus calculator for blood glucose control in type 1 diabetes. In *2014 American Control Conference*, (2014), 5465–5470. DOI: 10.1109/ACC.2014.6858980.

[21] R.S. Parker, F.J. Doyle and N.A. Peppas: A model-based algorithm for blood glucose control in type i diabetic patients. *IEEE Transactions on Biomedical Engineering*, **46**(2), (1999), 148–157. DOI: 10.1109/10.740877.

[22] L. Magni, D.M. Raimondo, L. Bossi, C.D. Man, G.D. Nicolao, B. Kovatchev and C. Cobelli: Model predictive control of type 1 diabetes: An in silico trial. *Journal of Diabetes Science and Technology*, **1**(6), (2007), 804–812. DOI: 10.1177/193229680700100603.

[23] M. Messori, E. Fornasiero, C. Toffanin, C. Cobelli and L. Magni: A constrained model predictive controller for an artificial pancreas. *IFAC Proceedings Volumes*, **47**(3), (2014), 10 144–10 149. DOI: 10.3182/20140824-6-ZA-1003.01880.

[24] D. Boiroux, A.K. Duun-Henriksen, S. Schmidt, K. Norgaard, S. Madsbad, N.K. Poulse, H. Madsen and J.B. Jorgensen: Overnight glucose control in people with type 1 diabetes. *Biomedical Signal Processing and Control*, **39**, (2018), 503–512. DOI: 10.1016/j.bspc.2017.08.005.

[25] D. Boiroux, S. Schmidt, A. Duun-Henriksen, L. Frøssing, K. Nørgaard, S. Madsbad, O. Skyggebjerg, N. Poulsen, H. Madsen and J. Jørgensen: Control of blood glucose for people with type 1 diabetes: an in vivo study. *17th Nordic Process Control Workshop* Kongens Lyngby, Denmark, (2012), 133–140. http://npcw17.imm.dtu.dk.

[26] M. Ławryńczuk, P. Marusak and P. Tatjewski: Efficient predictive control algorithms based on soft computing approaches: Application to glucose concentration stabilization. In *Technological Developments in Education and Automation*, (2010), 425–430. DOI: 10.1007/978-90-481-3656-8.

[27] 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**(4), (2004), 905–920. DOI: 10.1088/0967-3334/25/4/010.

[28] L. Magni, D. Raimondo, C.D. Man, G. De Nicolao, B. Kovatchev and C. Cobelli: Model predictive control of glucose concentration in subjects with type 1 diabetes: an in silico trial. *IFAC Proceedings Volumes, 17th IFAC World Congress*, **41**(2), (2008), 4246–4251. DOI: 10.3182/20080706-5-KR-1001.00714.

[29] M. Cescon and R. Johansson: Linear modeling and prediction in diabetes physiology. Ser. *Lecture Notes in Bioengineering, Marmarelis, V and Mitsis, G*, Springer, 2014, 187–222. DOI: 10.1007/978-3-642-54464-4_9.

[30] H. Kirchsteiger, J. Jørgensen, E. Renard and L. del Re, Eds.: Prediction methods for blood glucose concentration: Design, use and evaluation. Ser. *Lecture Notes in Bioengineering*, Springer, 2016.

[31] D. Romeres, M. Schiavon, A. Basu, C. Cobelli, R. Basu and C. D. Man: Exercise effect on insulin-dependent and insulin-independent glucose utilization in healthy and type 1 diabetes individuals. a modeling study. *American Journal of Physiology. Endocrinology and Metabolism*, **321**(1), (2021), E122–E129. DOI: 10.1152/ajpendo.00084.2021.

[32] C. Toffanin, L. Magni and C. Cobelli: Artificial pancreas: In silico study shows no need of meal announcement and improved time in range of glucose with intraperitoneal vs. subcutaneous insulin delivery. *IEEE Transactions on Medical Robotics and Bionics*, **3**(2), (2021), 306–314. DOI: 10.1109/TMRB.2021.3075775.

[33] H. Lee, B.A. Buckingham, D.M. Wilson and B.W. Bequette: A closed-loop artificial pancreas using model predictive control and a sliding meal size estimator. *Journal of Diabetes Science and Technology*, **3**(5), (2009), 1082–1090. DOI: 10.1177/193229680900300511.

[34] R. Haber, R. Bars and U. Schmitz: *Predictive Equations of Linear SISO Models*. John Wiley & Sons, Ltd, 2011, ch. 3, 55–101.

[35] P. Tatjewski: Effectiveness of dynamic matrix control algorithm with Laguerre functions. *Archives of Control Sciences*, **31**(4), (2021), 795–814. DOI: 10.24425/acs.2021.139731.

[36] R. Nebeluk and P. Marusak: Efficient MPC algorithms with variable trajectories of parameters weighting predicted control errors. *Archives of Control Sciences*, **30**(2), (2020), 325–363. DOI: 10.24425/acs.2020.133502.

[37] R. Haber, R. Bars and U. Schmitz: *Generalized Predictive Control of Linear SISO Processes*. John Wiley & Sons, Ltd, 2011, ch. 5, 135–220.

[38] V. Bátora, M. Tárnik, J. Murgaş, 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), 1693–1698. DOI: 10.1109/CCA.2014.6981556.

[39] F.H. El-Khatib, S.J. Russell, D.M. Nathan, R.G. Sutherlin and E.R. Damiano: A Bihormonal Closed-Loop Artificial Pancreas for Type 1 Diabetes. *Science Translational Medicine*, **2**(27), (2010). DOI: 10.1126/scitranslmed.3000619.

[40] J. Matousek and B. Gärtner: *Understanding and Using Linear Programming*. Ser. Universitext, Springer Berlin Heidelberg, 2006.

[41] C. Dalla Man, R. Rizza and C. Cobelli: Mixed meal simulation model of glucose-insulin system. In *28th Annual International Conference of the IEEE Engineering in Medicine and Biology Society, EMBS'06*. Ser. Annual International Conference of the IEEE Engineering in Medicine and Biology – Proceedings, (2006), 307–310. DOI: 10.1109/IEMBS.2006.260810.

[42] C. Dalla Man, R. A. Rizza and C. Cobelli: Meal simulation model of the glucose-insulin system. *IEEE Transactions on Biomedical Engineering*, **54**(10), (2007), 1740–1749. DOI: 10.1109/TBME.2007.893506.

[43] C.D. Man, D.M. Raimondo, R.A. Rizza and C. Cobelli: GIM, simulation software of meal glucose-insulin model. *Journal of Diabetes Science and Technology*, **1**(3), (2007), 323–330. DOI: 10.1177/193229680700100303.

[44] M. Dodek and E. Miklovičová: Physiology-compliant empirical model for glycemia prediction. *International Review of Automatic Control (IREACO)*, **14**(6), (2021). DOI: 10.15866/ireaco.v14i6.21283.

[45] L. Magni, D.M. Raimondo, C.D. Man, M. Breton, S. Patek, G.D. Nicolao, C. Cobelli and B.P. Kovatchev: Evaluating the efficacy of closed-loop glucose regulation via control-variability grid analysis. *Journal of Diabetes Science and Technology*, **2**(4), (2008), 630–635. DOI: 10.1177/193229680800200414.