Computer Methods and Programs in Biomedicine 236 (2023) 107568

Contents lists available at ScienceDirect

Computer Methods and Programs in Biomedicine

journal homepage: www.elsevier.com/locate/cmpb

Intermittent closed-loop blood glucose control for people with type 1 diabetes on multiple daily injections

Ernesto Estremera[a], Aleix Beneyto[a], Alvis Cabrera[a], Iván Contreras[a], Josep Vehí[a,b,*]

[a] Department of Electrical, Electronic and Automatic Engineering, University of Girona, 17004 Girona, Spain
[b] Centro de Investigación Biomédica en Red de Diabetes y Enfermedades Metabólicas Asociadas, Instituto de Salud Carlos III, Spain

ARTICLE INFO

Article history:
Received 1 February 2023
Revised 13 April 2023
Accepted 24 April 2023

Keywords:
Event-triggered control
Hypoglycemia
Hyperglycemia
Model predictive control
Multiple daily injection therapy
Type 1 diabetes

ABSTRACT

Background and objectives: Recent advances in Automated Insulin Delivery systems have been shown to dramatically improve glycaemic control and reduce the risk of hypoglycemia in people with type 1 diabetes. However, they are complex systems that require specific training and are not affordable for most. Attempts to reduce the gap with closed-loop therapies using advanced dosing advisors have so far failed, mainly because they require too much human intervention. With the advent of smart insulin pens, one of the main constraints (having reliable bolus and meal information) disappears and new strategies can be employed. This is our starting hypothesis, which we have validated in a very demanding simulator. In this paper, we propose an intermittent closed-loop control system specifically intended for multiple daily injection therapy to bring the benefits of artificial pancreas to the application of multiple daily injections.

Methods: The proposed control algorithm is based on model predictive control and integrates two patient-driven control actions. Correction insulin boluses are automatically computed and recommended to the patient to minimize the duration of hyperglycemia. Rescue carbohydrates are also triggered to avoid hypoglycemia episodes. The algorithm can adapt to different patient lifestyles with customizable triggering conditions, closing the gap between practicality and performance. The proposed algorithm is compared with conventional open-loop therapy, and its superiority is demonstrated through extensive in silico evaluations using realistic cohorts and scenarios. The evaluations were conducted in a cohort of 47 virtual patients. We also provide detailed explanations of the implementation, imposed constraints, triggering conditions, cost functions, and penalties for the algorithm.

Results: The in-silico outcomes combining the proposed closed-loop strategy with slow-acting insulin analog injections at 09:00 h resulted in percentages of time in range (TIR) (70–180 mg/dL) of 69.5%, 70.6%, and 70.4% for glargine-100, glargine-300, and degludec-100, respectively, and injections at 20:00 h resulted in percentages of TIR of 70.5%, 70.3%, and 71.6%, respectively. In all the cases, the percentages of TIR were considerably higher than those obtained from the open-loop strategy, being only 50.7%, 53.9%, and 52.2% for daytime injection and 55.5%, 54.1%, and 56.9% for nighttime injection. Overall, the occurrence of hypoglycemia and hyperglycemia was notably reduced using our approach.

Conclusions: Event-triggering model predictive control in the proposed algorithm is feasible and may meet clinical targets for people with type 1 diabetes.

1. Introduction

Type 1 diabetes (T1D) is a chronic disease in which the beta cells of the pancreas fail to produce enough insulin. Insulin is a hormone that helps glucose enter cells as a supply of energy. Without sufficient insulin, excess glucose remains in the blood, causing high blood glucose (BG) levels (i.e., hyperglycemia). If this disease is not treated correctly, it derives in acute complications such as retinopathy, neuropathy, nephropathy, coronary heart disease, and cerebrovascular disease [1,2]. Therefore, the lack of insulin should be compensated by the administration of exogenous insulin to maintain healthy BG levels. To this end, multiple daily injection (MDI) therapy and continuous subcutaneous insulin infu-

* Corresponding author.
E-mail addresses: ernesto.estremera@udg.edu (E. Estremera), aleix.beneyto@udg.edu (A. Beneyto), alvita.cabrera@udg.edu (A. Cabrera), ivan.contreras@udg.edu (I. Contreras), josep.vehi@udg.edu (J. Vehí).

https://doi.org/10.1016/j.cmpb.2023.107568

sion, or insulin pump therapy, are commonly used for a patient to stay in normoglycemia (i.e., BG levels of 70–180 mg/dL).

Over the last years, insulin pumps have attracted interest, especially with the development of artificial pancreas (AP) and closed-loop (CL) insulin technology [3]. Nevertheless, MDI therapy remains the most widely used treatment for people with T1D to satisfy their daily insulin needs [4]. The MDI therapy usually involves the subcutaneous administration of long-acting insulin to ensure basal insulin requirements along with the infusion of rapid-acting insulin boluses to minimize postprandial hyperglycemia [5]. The physician adjusts the therapy regularly according to the characteristics of the patient, who should execute it daily. The benefits of MDI therapy over other approaches, such as AP, are the freedom for patients from wearing insulin pumps or needing an external device permanently attached to the body [6]. In MDI therapy, the patient is the controller and should make many daily decisions depending on their lifestyle. Consequently, there is a high risk of forgetting or miscalculating an insulin dose.

The control performance is evaluated following current clinical targets for continuous glucose monitoring (CGM). The consensus guidelines define good performance being when the BG levels are below 54 mg/dL $< 1\%$, below 70 mg/dL $< 4\%$, time in range (TIR) $70-180$ mg/dL $> 70\%$, above 180 mg/dL $< 25\%$, and above 250 mg/dL $< 5\%$ [7]. Therefore, people with T1D aim to maximize the TIR. However, the performance is often exchanged to ensure zero low BG levels (i.e., hypoglycemia) [8]. Hypoglycemia can occur due to an imbalance between the administered insulin doses, exercise, diet, or other physiological phenomena [9]. Failure to correctly manage hypoglycemia can lead to severe complications [10], thus motivating more conservative control strategies. People with T1D only have a handful of options to treat hypoglycemia symptoms in free-living conditions to increase the BG concentrations to the normal level: 1) administration of exogenous glucagon or 2) consumption of fast-acting rescue carbohydrates (CHO). Regarding hyperglycemia, the most effective treatment is giving insulin boluses to correct the excess glucose in blood.

Multiple control schemes and strategies have been utilized for designing artificial pancreas systems for diabetes management, with the primary ones being proportional-integral-derivative control [11–13] and model predictive control (MPC), [14–17]. These studies not only explore the pure form of the strategy but also its multiple variants such as PD, zone MPC, adaptive MPC, etc. This assertion is supported by examining some of the leading AP systems in the market. For instance, the Minimed 770G system uses a PID algorithm with insulin feedback and adaptive insulin restrictions, while the 780G combines this strategy with an adaptive MPC. On the other hand, the CamAPS FX, Control IQ, Diabeloop, and Omnipod 5 systems use adaptive MPC algorithms [18–20].

These strategies have not been applied to conventional MDI therapy owing to the inherent therapy limitations: 1) a fully CL system is unreachable owing to a lack of a commanded actuator; and 2) appropriate sensors and actuators for the therapy are unavailable. In the last few years, smart insulin pens have been developed, and CGM approaches have become readily available to most people with T1D regardless of the adopted therapy. Compared with traditional syringes and vials, smart pens are more convenient, discreet in use, accurate for dosing, and suitably adherent [21]. Many of these marketed devices allow to keep track of the actions performed by the patient because they communicate in real time with external devices that obtain information from CGM. These developments have motivated the transition from AP algorithms to MDI therapies, which may enhance the glycemic performance by using newly available information in controllers and supervision tools.

In this study, we aimed to minimize hypoglycemic and hyperglycemic episodes in patients with T1D receiving MDI therapy. For this purpose, we designed a CL system with two event-triggered MPC schemes. By introducing a CL strategy, the proposed system can dramatically reduce the daily decisions that people with T1D make while increasing the TIR. The first controller is responsible for suggesting CHO intake to minimize the occurrence of hypoglycemia. The second controller suggests corrective insulin boluses to decrease hyperglycemic exposure. The user can customize the controller constraints and values defined as hypoglycemic and hyperglycemic limits according to their lifestyle and the number of daily control actions they are willing to handle. The controllers do not run continuously but are triggered by conditions that can be configured by a physician based on the therapy goals and cost–benefit to the patient.

To validate the designed therapy, a cohort of 47 virtual patients and the simulation scenario presented in [22] were used to compare the reported open-loop (OL) results with the CL results obtained with the proposed MPC approach. By analyzing the in silico results, the proposed therapy obtained a notable decrease in hyperglycemic and hypoglycemic events and considerable increase in TIR. A reduction in the coefficient of variation (CV) was also a remarkable result when few control actions were performed daily. The proposed MDI therapy may meet the clinical targets established in [7] most of the time.

2. MPC schemes

2.1. Preliminaries

We designed two event-triggered MPC schemes. Both controllers use an autoregressive model with exogenous input and sampling period $t_s = 5$ min (see Section 2.2). The first controller (see Section 2.3) is aimed at suggesting rescue CHO to minimize hypoglycemic events. To this end, we penalize BG levels below a hypoglycemic threshold and the BG level derivative. The second controller (see Section 2.4) determines insulin boluses to minimize hyperglycemic excursions. Similarly, we penalize BG levels above a hyperglycemic threshold and BG variations. The controllers also impose constraints on control signals u_{cho} and u_{bolus}: they cannot be negative because insulin or CHO removal from the system is unfeasible. Figure 1 shows the CL scheme implemented with the controllers.

CL MPC is achieved by applying the first element, U_1^{opt}, of the optimal and predicted control input trajectory $\{U_1^{opt}, \ldots, U_M^{opt}\}$ at timestep k. The elements are determined by solving the following cost function J:

$$\{U_1^{opt}, \ldots, U_M^{opt}\} := arg\min J(y_k, \{U_1, \ldots, U_M\}) \tag{1}$$

2.2. Prediction model

An autoregressive model with exogenous input for BG level prediction is used for both controllers using MPC, as expressed in Eq. (2) [23].

$$A(q)y(t) = B(q)u(t) \tag{2}$$

where $A(q)$ and $B(q)$ are model polynomials. To identify the values of the parameter vector in Eq. (2), we use the recursive least squares algorithm [23]. For the controllers, we use a fourth-order autoregressive model with exogenous input (i.e., $n_a = 4$ and $n_b = 3$). We use the following exogenous inputs (see Eq. (3)): basal insulin (u_{basal}), bolus insulin (u_{bolus}), and CHO on board (COB).

$$\begin{aligned}\varphi(k) = [&-y(k-1) \ \ldots \ -y(k-n_a) \ u_{basal}(k-1) \\ &u_{bolus}(k-1) \ COB(k-1)]^T\end{aligned} \tag{3}$$

The initial values of φ, H_p, and $\widehat{\theta}$ are defined as indicated in [13]. $\widehat{\theta}$ is not recalculated for the prediction horizon, that is, at

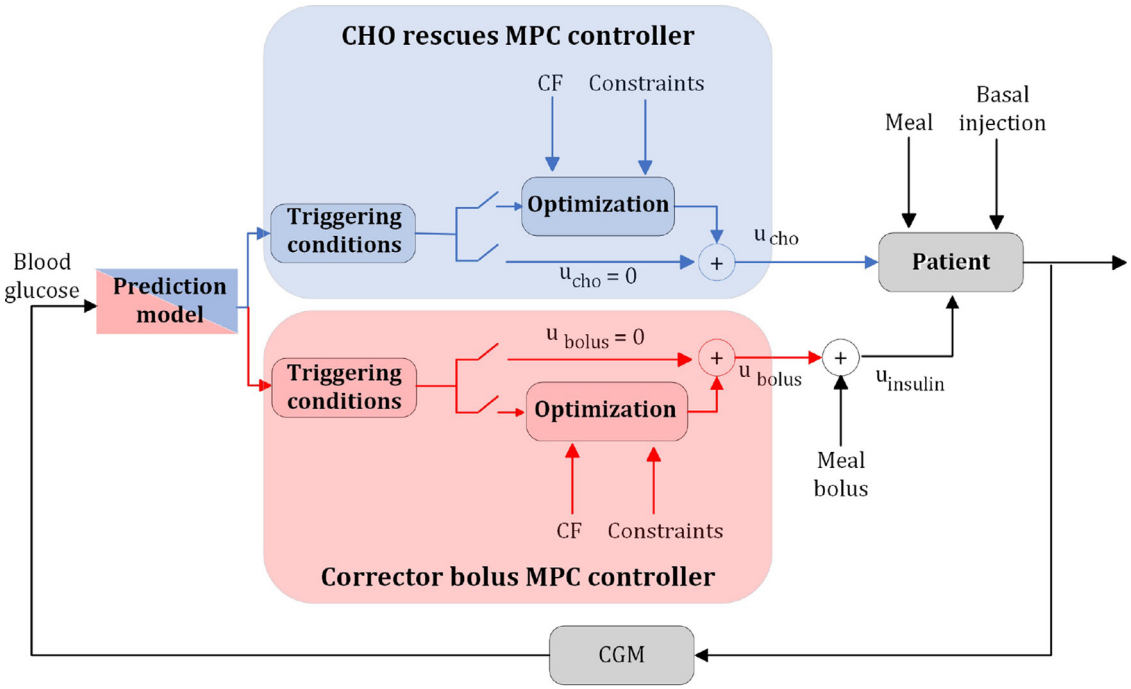

Fig. 1. Diagram of closed loop control scheme.

each timestep k after calculating $\widehat{\theta}$, it does not vary within the prediction loop (see Eq. (4)).

$$\widehat{\theta}(k+i|k) = \widehat{\theta}(k) \quad for \;\; i = 1, 2, \ldots, H_p \tag{4}$$

2.3. MPC for CHO rescue

MPC for recue CHO uses cost function J_{CHO} given by

$$J_{CHO} = \sum_{k=1}^{P} \left[Q_1(y_k)\widehat{Z}_k^{\,2} + Q_2\left(\frac{dy_k}{dt}\right)\widehat{V}_k^{\,2} \right] + \sum_{k=1}^{M} R u_{cho}^{\,2} \tag{5}$$

subject to

$$\widehat{Z}_k := \min(y_k - Z_{\min}, 0)$$
$$\widehat{V}_k := \min(V_k, 0)$$
$$u_{cho} = \begin{cases} \underline{u}_{cho} \le u_{cho} \le \overline{u}_{cho} & \text{if } y \le 54 \;||\; y \le 70 \,\&\, [\widehat{y}_{k+1}, \cdots, \widehat{y}_{k+4}] \le 54 \\ 0 \le u_{cho} \le \overline{u}_{cho} & otherwise \end{cases} \tag{6}$$

where $\widehat{Z}_k$ is the glucose excursion below $Z_{\min}$ (by default, $Z_{\min} = 70$ mg/dL), $\widehat{V}_k$ is the negative glucose derivative at timestep k, and Q_1, Q_2, and R are weights for optimization. Like in [15], we set the weights of Eq. (5). Weight $Q_1(y)$ applies to $\widehat{Z}_k$ and depends on the BG level at timestep k (see Eq. (7)). A level closer to $Z_{\min}$ implies a higher weight. On the other hand, weight Q_2 applies to $\widehat{V}_k$ and depends on glucose change rate at timestep k, as shown in Eq. (8) (see Fig. 2). In addition, $R := 1$ is the weight of the control action, and $H_p = 30$ min and $H_c = 25$ min.

$$Q_1(y) = \begin{cases} 60 & \text{if } y < 80 \; mg/dL \\ 20 & \text{if } y > 120 \; mg/dL \\ 20 * \sin\left(\frac{\pi}{40}(y+20)\right) + 40 & otherwise \end{cases} \tag{7}$$

$$Q_2\left(\frac{dy}{dt}\right) = \begin{cases} 20 & \text{if } \frac{dy}{dt} < -1 \; mg/dL/min \\ 0 & \text{if } \frac{dy}{dt} > 0 \; mg/dL/min \\ 5 * \sin\left(\frac{\pi}{5}(\triangle y - 2.5)\right) + 15 & otherwise \end{cases} \tag{8}$$

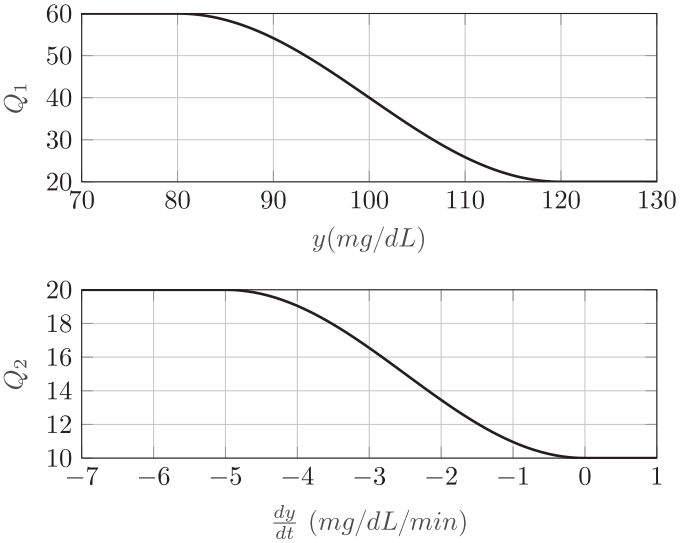

Fig. 2. Weights $Q_1(y)$ and $Q_2(\frac{dy}{dt})$ defined in Eqs. (7) and (8), respectively.

Equation (6) includes constraints on control action u_{cho}. Specifically, the suggested amount (in grams) of CHO cannot be negative. Variables $\underline{u}_{cho}$ and $\overline{u}_{cho}$ represent the minimum amount of CHO to suggest if severe hypoglycemia is present or expected in the next 20 min and the maximum amount accepted by the patient, respectively. Both parameters can be customized to the patient.

Once the optimization problem is solved, the CHO control action is penalized by subtracting the CHO on board (COB), as shown in Eq. (9). Finally, u_{cho} is quantified as shown in Eq. (10).

$$u_{cho} = \max(0, u_{cho} - COB) \tag{9}$$

Table 1
Controller suggestion for 20 g of CHO 2 h after last meal and at BG level of 69 mg/dL.

Type of food	Usual portion	Recommended serving
Glucose	Sport gel (40 g)	1/2 portion
Tonic	Glass (200 cm^3)	1 portion
Dried date	Unit (10 g)	3 portions
Drink cola or flavors	Glass (200 cm^3)	1 portion
Maria cookie type	Cookie (7 g)	4 portions
Prince cookie type	Cookie (15 g)	2 portions
White bread	Muffin (60 g)	2/3 portion
Toast	Unit (10 g)	3 portions
Bread stick	Unit (5 g)	6 portions

$$u_{cho} = \begin{cases} 0 & \text{if } u_{cho} < 7.5\ g \\ 10\ g & \text{if } 7.5\ g \le u_{cho} < 12.5\ g \\ 15\ g & \text{if } 12.5\ g \le u_{cho} < 17.5\ g \\ 20\ g & \text{if } 17.5\ g \le u_{cho} < 22.5\ g \\ 25\ g & \text{if } 22.5\ g \le u_{cho} < 27.5\ g \\ 30\ g & otherwise \end{cases} \tag{10}$$

Food library for rescue CHO

The MPC scheme suggests the amount (in grams) of CHO that the patient should ingest to minimize the risk of hypoglycemia. For practical control, the patient should receive notifications indicating different rescue CHO options and the recommended servings. To this end, we provide a food library constructed with data retrieved from [24], which contains information on the glycemic index (GI) of multiple foods along with their usual servings and CHO contents.

The GI is a measure of how quickly a food can raise the BG levels. Foods with a high GI tend to increase the BG level faster than those with a low value. The food library is classified according to high, medium, and low GIs, as listed in Table A.1 in Appendix A. Considering the dynamics of the GI, Eq. (11) is proposed for rescue CHO selection from the food library.

$$GI = \begin{cases} High & \text{if } y \le 80 \ \ || \ \ 80 < y \le 85 \& \triangle y \le -3 \\ Medium & \text{if } 80 < y \le 85 \& \triangle y > -3 \ \ || \ \ 85 < y \le 95 \& \triangle y \le -4 \\ Low & otherwise \end{cases} \tag{11}$$

Once the controller determines a CHO suggestion, various types of foods are available from the CHO MPC. First, the GI value is determined according to Eq. (11), and foods with similar GI are selected from the library (Table A.1). Second, the serving of each selected food is calculated according to the CHO control action. Finally, the timespan from the previous meal is considered. Table 1 illustrates a result received by a user after the controller is triggered and a CHO control action is generated. In this example, the controller recommends 20 g of CHO, the BG level is 69 mg/dL, and more than 2 h have passed since the last meal of the user.

2.4. MPC for hyperglycemia minimization

MPC for corrector insulin boluses uses cost function J_{CB} given by

$$J_{CB} = \sum_{k=1}^{H_p} \left[Q_3 \check{Z}_k^{\,2} + Q_4 \check{V}_k^{\,2} \right] + \sum_{k=1}^{H_c} R_1 u_{bolus}^{\,2} \tag{12}$$

subject to

$$\begin{aligned} &\check{Z}_k := \max(y_k - Z_{\max}, 0) \\ &\check{V}_k := \max(V_k, 0) \\ &0 \le [u_{bolus}] \le \overline{u}_{bolus} \\ &-\triangle u \le \triangle u_{bolus} \le \triangle u \\ &\widehat{y}_{(45\ min)} \ge \bar{y} \end{aligned} \tag{13}$$

where $\check{Z}_k$ is the glucose excursion above $Z_{\max}$ (by default, $Z_{\max} = 180$ mg/dL), $\check{V}_k$ is the positive glucose derivative at timestep k, and Q_3, Q_4, and R_1 are weights for optimization set to 40, 20, and 1, respectively. We also set $H_p = 45$ min and $H_c = 25$ min.

This controller can be customized by setting $\overline{u}_{bolus}$ and $\bar{y}$, which are part of the imposed constraints and allow users to define a less aggressive strategy when the risk of hypoglycemia increases. Once the optimization problem is solved, the correction bolus control action is penalized by the currently estimated insulin on board (IOB) (see Eq. (14)).

$$u_{bolus} = \max(0, u_{bolus} - IOB) \tag{14}$$

3. Event-triggered MPC

In this section, we address the design of the event-triggering conditions for aperiodic MPC. The events are compliant with physiological responses and clinical safety. Each MPC scheme is triggered by different events, enabling the independent execution of both control actions. The designed physiological conditions and events for triggering control can be applied to any other control algorithm for MDI therapy.

Event $\mathbf{E}$ is defined as a conditional statement of the form If..., Then..., where the activation of the if statement may trigger the solving of the MPC problem. We implement six types of events according to the daytime and occurrence of hypoglycemia or hyperglycemia.

$$\begin{aligned} &\mathbf{E}_1: \text{ if daytime\&} y_k \le BG_{CHO}^{day} \& r > 0 \text{ then } u_{cho} \longleftarrow U_{1|k}^{opt} \\ &\mathbf{E}_2: \text{ if nighttime\&} y_k \le BG_{CHO}^{night} \& \triangle y \le BG_{CHO}^{change} \text{ then } u_{cho} \longleftarrow U_{1|k}^{opt} \\ &\mathbf{E}_3: \text{ if } y_k \le BG_{hypo} \text{ then } u_{cho} \longleftarrow U_{1|k}^{opt} \\ &\mathbf{E}_4: \text{ if daytime\&} y_k \ge BG_{bolus}^{day} \& s > 0 \text{ then } u_{bolus} \longleftarrow U_{1|k}^{opt} \\ &\mathbf{E}_5: \text{ if nighttime\&} y_k \ge BG_{bolus}^{night} \& \triangle y \ge BG_{bolus}^{change} \text{ then } u_{bolus} \longleftarrow U_{1|k}^{opt} \\ &\mathbf{E}_6: \text{ if } y_k \ge BG_{hyper} \text{ then } u_{bolus} \longleftarrow U_{1|k}^{opt} \\ &\mathbf{E}_7: \text{ if } !\mathbf{E}_1 \& !\mathbf{E}_2 \& !\mathbf{E}_3 \text{ then } u_{cho} \longleftarrow 0 \\ &\mathbf{E}_8: \text{ if } !\mathbf{E}_4 \& !\mathbf{E}_5 \& !\mathbf{E}_6 \text{ then } u_{bolus} \longleftarrow 0 \end{aligned}$$

where BG_{CHO}^{day}, BG_{CHO}^{night}, BG_{CHO}^{change}, BG_{hypo}, BG_{bolus}^{day}, BG_{bolus}^{night}, BG_{bolus}^{change}, and BG_{hyper} are tuning parameters, and r and s are given by:

$$r = \sum_{j=2}^{H_p+1} I\{\mathbf{Y}_j - \mathbf{Y}_{j-1} < 0\} \tag{15}$$

$$s = \sum_{j=2}^{H_p+1} I\{\mathbf{Y}_j - \mathbf{Y}_{j-1} > 0\} \tag{16}$$

with $\mathbf{Y} = y_k \cup \widehat{\mathbf{Y}} = \begin{bmatrix} y_k & \hat{y}_{k+1} & \cdots & \hat{y}_{k+H_p} \end{bmatrix}$ being the measured and predicted glucose values at timestep k. r and s are defined using the notation $I\{\}$ which refers to the indicator function. This mathematical function takes the value of 1 when its argument satisfies a certain condition and 0 otherwise. Basically, r and s monitor the predicted glucose trend and will be greater than one if at least one increase in the prediction horizon is negative or positive, respectively. Events 1–3 are designed to trigger MPC for CHO ingestion, whereas events 4–6 are designed to trigger MPC for correction bolus. Events 7 and 8 represent cases where MPC is not triggered. Figure 3 shows the flowchart of event-triggered MPC.

The conditions with the highest priority in terms of performance and clinical and patient safety are aimed to prevent prolonged hypoglycemia. We impose a terminal condition for the hypoglycemia trigger as $\mathbf{E}_3$. The events $\mathbf{E}_4$ and $\mathbf{E}_5$ must also be designed to mitigate the aggressiveness of the strategy, for this, it is important to carefully assess the selection of the thresholds because the lower these are, the more risk of there will be hypo-

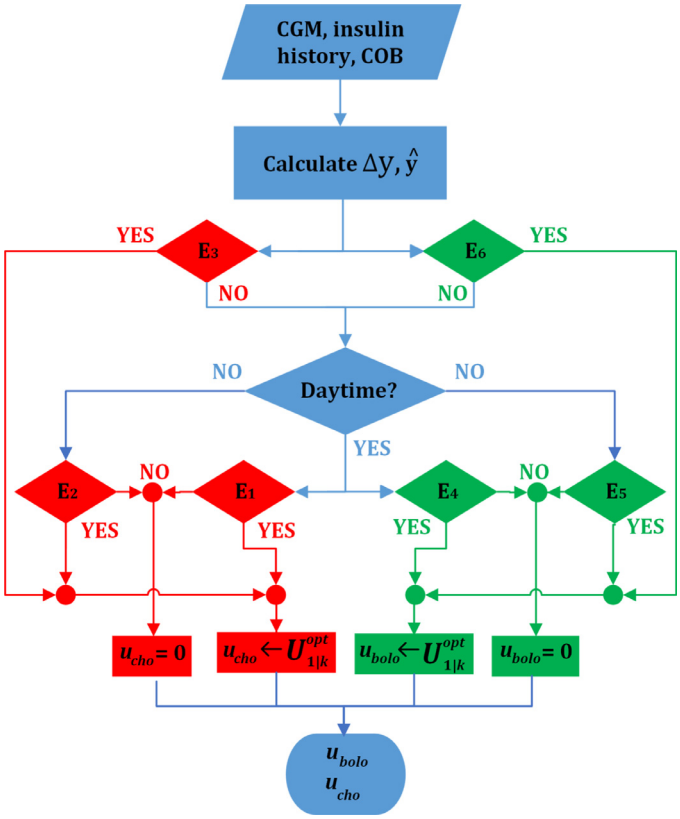

Fig. 3. Flowchart of event-triggered MPC.

glycemia after a corrective bolus. Specific events for day and night are also defined owing to the nature of the control problem. Hence, the user can customize the triggering of events by setting different BG thresholds according to their specific needs or willingness to receive recommendations for tight control.

4. Scenario

Different simulation environments for T1D have been reported [25–28]. However, they are mainly intended to test continuous subcutaneous insulin infusion instead of MDI. In [22], a simulator was presented with realistic and challenging scenarios for virtual patients with T1D undergoing continuous subcutaneous insulin infusion and MDI therapies. This simulator includes virtual patient generation and long-acting insulin analog models including glargine 100 U/mL (Gla-100), glargine 300 U/mL (Gla-300), and degludec 100 U/mL (Deg-100). In this study, we used the virtual cohort and simulated scenario from Estremera et al. [22].

The scenario in this study, different for each patient, consists of a 60-day simulation protocol with 3 daily meals of between 40 and 60 g of CHO administered randomly between 06:30-11:30, 11:30-16:30 and 16:30-21:30 h, respectively. A random misestimation in the CHO count is included in the range of ± 20% at all meals. For the MDI simulation, we adjusted the therapy settings from [22] (CHO ratios and basal slow-acting insulin for injections at 09:00 and 20:00 h). Table 2 lists the parameters defined in each controller for the in silico test.

The implementation of the controllers and in silico tests were carried out in MathWorks MATLAB R2021a running in a computer equipped with an Intel(R) Core(TM) i7-4770 CPU at 3.40 GHz with 16 GB of RAM. The YALMIP MATLAB Toolbox [29] was used along with the Gurobi solver [30] for MPC execution.

Table 2
Parameters used for in silico simulation.

Controller	Parameter	Value
Hypoglycemia MPC	$\overline{u}_{cho}$	30 g
	$\underline{u}_{cho}$	20 g
	BG^{day}_{CHO}	110 mg/dL
	BG^{night}_{CHO}	85 mg/dL
	BG^{change}_{CHO}	-1 mg/dL/min
	BG_{hypo}	70 mg/dL
	$\overline{u}_{bolus}$	4 u
	$\triangle U$	0.5 u
Hyperglycemia MPC	BG^{day}_{bolus}	165 mg/dL
	BG^{night}_{bolus}	200 mg/dL
	BG^{change}_{bolus}	1 mg/dL/min
	BG_{hyper}	220 mg/dL

5. Results

The proposed CL MDI therapy was simulated using three of the most used slow-acting insulin analogs (i.e., Gla-100, Gla-300, and Deg-100) and compared with the OL therapy presented in [22]. Tables 3, 4, and 5 show the standardized CGM metrics [7] as the median (25th–75th percentiles).

Tables 3 and 4 list the results for the three analogs with injection times of 09:00 h and 20:00 h, respectively. Table 5 shows performance data for both controllers. In addition, instances of rescue CHO and correction boluses are detailed for all simulated cases. Combining the proposed CL strategy with slow-acting insulin analog injections at 09:00 h resulted in TIRs of 69.5%, 70.6%, and 70.4% for Gla-100, Gla-300, and Deg-100, respectively, and injections at 20:00 h resulted in TIRs of 70.5%, 70.3%, and 71.6%, respectively. In all cases, the TIRs were considerably higher than those obtained from the OL strategy of 50.7%, 53.9%, and 52.2% for daytime injection and 55.5%, 54.1%, and 56.9% for nighttime injection. Hypoglycemia occurrence was minimized after the introduction of MPC for rescue CHO, as listed in Tables 3 and 4. In most cases, the reported performance satisfied the clinical targets. The reduction of hypoglycemia by the CHO MPC stands out. Glycemic variability was also reduced with the introduction of the CL controllers compared to the OL sham results.

Tables 3 and 4 also present the glycemic risk index (GRI) [31]. The GRI for the CL scheme is lower than that for the conventional OL scheme. In most cases, the 75th percentile of therapy with CL control is lower than the 25th percentile of therapy with OL control. Figure 4 show GRI grids of hyperglycemia and hypoglycemia components for the cohort, OL, and CL CGM profiles.

Figure 5 shows representative CGM trajectories, injection times, and meals for 2 days of the cohort for one of the three analogs and both OL control and CL MPC. The figures indicate the physiological plausibility of the glucose trajectories and allow visual comparison of the control effects.

6. Discussion

We introduce an event-triggered CL control strategy for MDI therapy comprising two MPC schemes, one for triggering suggestions of rescue CHO and the other for correction insulin boluses. The goal of this approach is minimizing the occurrence of hypoglycemia and hyperglycemia while overcoming inherent burdens of MDI therapy.

Despite their limitations, in silico simulations are necessary when testing algorithms before their deployment to patients in free-living conditions. To perform realistic simulations, we used an existing simulator developed by our group with highly realistic scenarios and virtual patient dynamics [22]. For a comprehensive comparison, we used the same cohort and scenario from [22].

Table 3
In silico OL and CL control results for MDI therapy with long-acting insulin Gla-100, Gla-300, and Deg-100 injected at 09:00 h.

Indicator	Gla-100		Gla-300		Deg-100	
	OL	CL	OL	CL	OL	CL
Median CGM (mg/dL)	168 (146–187)	154 (146–169)*	166 (143–192)	158 (145–167)*	157 (142–185)	152 (141–168)
CV (%)	46.4 (41.9–52.2)	35.9 (31.8–39.7)*	43.8 (38.6–49.9)	34 (31.2–38.8)*	46.7 (40.7–52.2)	35.2 (32.4–39.9)*
TAB>250 (%)	13.7 (7.2–21.3)	4.2 (2.4–8.8)*	10.9 (5.1–23.3)	3.9 (2.6–8.4)*	10 (5.4–20.4)	4.2 (2.1–8.2)*
180<TAB<250 (%)	23.7 (18.7–27.5)	24.3 (18.6–26.5)	24 (19.1–29.7)	23.1 (17.4–27.1)	23.3 (14.8–27.1)	22.3 (15.2–29.1)
70<TIR<180 (%)	50.7 (42.7–59.5)	70.2 (61.1–76.9)*	53.9 (42.1–63.4)	70.6 (61.6–77.2)*	52.2 (42.4–62.3)	70.4 (58.8–78.4)*
54<TBR<70 (%)	4.2 (3.1–6)	1.2 (0.8-1.9)*	3.8 (2.5-5.6)	0.9 (0.7-1.4)*	4.6 (3.4–7.1)	1.3 (0.7-1.9)*
TBR<54 (%)	4.4 (2.3–7)	0.2 (0-0.8)*	2.9 (2–6.2)	0.1 (0-0.6)*	5.1 (2.5–7.8)	0.2 (0-0.8) *
GRI	68.2 (57.9–81.5)	30.5 (24.7–43.2)*	60.9 (48.6–76.8)	29.6 (23.1–39.9)*	71.4 (51.8–85.8)	31.9 (21.3–43)*

Values are reported as median, interquartile range (25th–75th percentile). *$P < 0,05$ (Wilcoxon signed-rank test).

Table 4
In silico OL and CL control results for MDI therapy with long-acting insulin Gla-100, Gla-300, and Deg-100 injected at 20:00 h.

Indicator	Gla-100		Gla-300		Deg-100	
	OL	CL	OL	CL	OL	CL
Median CGM (mg/dL)	171 (148–187)	159 (147–177)*	165 (155–188)	158 (150–175)*	164 (150–197)	159 (149–176)*
CV (%)	41.1 (35.6–48.6)	34.2 (30.4–39.3)*	43.8 (37.1–48.9)	35.2 (30.7–39.2)*	39.8 (35.8–47.5)	34.3 (30.8–37.9)*
TAB>250 (%)	11.2 (6.2–22.1)	5 (3.2–11.1)*	11.1 (6.2–21.1)	4.7 (2.8–10.2)*	9.7 (5–19.9)	4.2 (2.7–10.6) *
180<TAB<250 (%)	24.7 (18.7–31.1)	22.7 (18.5–28.5)	25 (21.2–31.3)	24.4 (19.8–28.7)	24.7 (17–32.2)	22.6 (17.8–31.2)
70<TIR<180 (%)	55.5 (41.1–65.1)	70.5 (58.3–76.2)*	54.1 (38.2–60.7)	70.3 (55.8–74)*	56.9 (39.6–63.8)	71.6 (58–78.1) *
54<TBR<70 (%)	2.7 (1.4-4.4)	0.7 (0.3-1.2)*	3.4 (2–4.8)	0.8 (0.4-1.4)*	3.4 (1.6-5.7)	0.9 (0.4-1.5)*
TBR<54 (%)	1.4 (0.6-3.6)	0.1 (0-0.3)*	2.4 (1.1–4.2)	0.2 (0-0.6)*	1.8 (0.7-4.6)	0 (0-0.2) *
GRI	55 (41–75.5)	30.9 (23.9–45.4)*	58.7 (47.9–83.6)	30.6 (25.4–46.1)*	57.5 (46.3–82.1)	31.9 (22.4–40.9)*

Values are reported as median, interquartile range (25th–75th percentile). *$P < 0,05$ (Wilcoxon signed-rank test).

Table 5
Analysis of control action events.

	Indicator	Gla-100		Gla-300		Deg-100	
		09:00 h	20:00 h	09:00 h	20:00 h	09:00 h	20:00 h
Rescue CHO events	Instances	3917	1994	3125	2602	4696	2949
	CHO rescue (g/day)	18.9 (11.4–25)	10.1 (3.3–13)	15.1 (8–20.9)	12.7 (6.5–16.3)	22.8 (11.7–29.8)	15.6 (4.7–16.7)
	Instances per day	1.4 (0.7-1.8)	0.7 (0.3-0.9)	1.1 (0.7-1.5)	0.9 (0.5-1.2)	1.4 (0.9-2.2)	1 (0.3-1.2)
	Percentage night (%)	5.2	12.2	6	6.1	9.9	22.2
Correction bolus events	Instances	5120	5213	5120	5407	4983	5329
	Insulin (U/day)	4 (3–4.8)	3.5 (1.9-4.7)	3.7 (2.5-4.9)	3.9 (2.5-4.8)	3.6 (2.6-4.7)	3.4 (2–4.4)
	Instances per day	1.8 (1.4-2.2)	1.8 (1.2-2.5)	1.8 (1.2-2.3)	1.9 (1.3-2.5)	1.6 (1.3-2.2)	1.9 (1.2-2.2)
	Percentage night (%)	26.8	15	21.6	21.6	23.1	15.5
	Instances per day	3.1	2.6	2.9	2.8	3.2	2.9

Values are reported as median, interquartile range (25th–75th percentile).

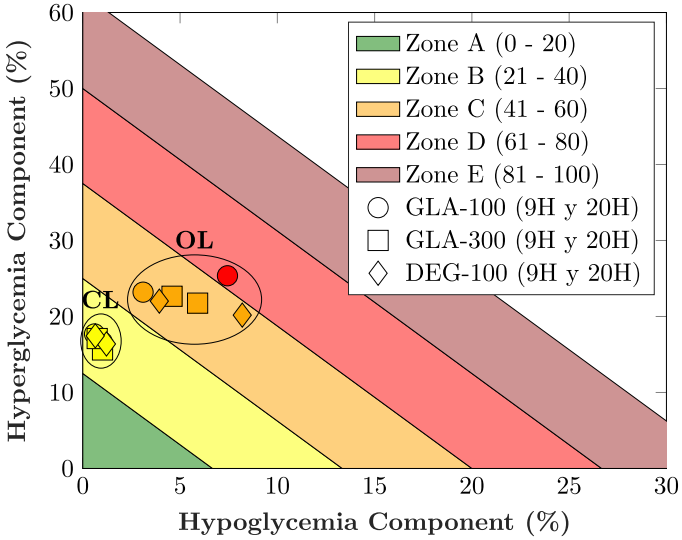

Fig. 4. GRI grid for cohort and all analogs in OL control and CL MPC.

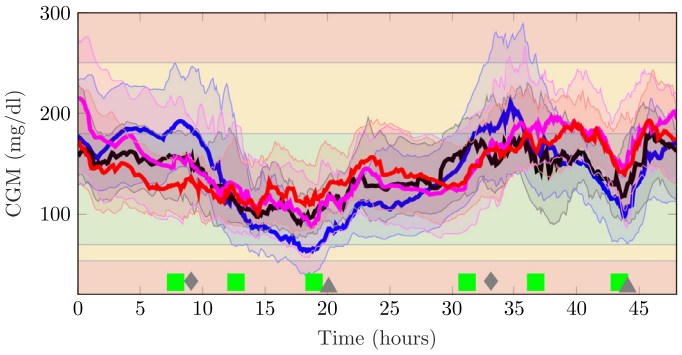

Fig. 5. CGM trajectories over 2 days of cohort generated for Deg-100 (median and interquartile range) for therapy with OL control and MPC: OL control (blue) and MPC (black) at 09:00 h and OL control (magenta) and MPC (red) at 20:00 h. The green squares represent meals. The gray rhombuses and triangles represent injection times of 09:00 h and 20:00 h, respectively.

Statistical tests considering the p-values showed statistical significance in most studied metrics when using our new approach. Hence, the current standard of care under MDI therapy may be greatly benefited from the introduction of CL control.

The proposed control actions led to a notable decrease in hypoglycemia and hyperglycemia occurrence while increasing the TIR. More importantly, the simulation results are in line with recommended clinical targets [7]. Additionally, Tables 3, 4, and 5 and Fig. 4 suggest that the injection time of the slow-acting insulin analog does not considerably affect the outcomes.

Constraints and cost functions were designed to achieve the clinical targets by minimizing the number of daily interventions. Table 5 shows that the median control effort required from the patient did not exceed three events per day. Therefore, the reported performance is achievable without an additional burden to the patient, and the patient can adapt the system to their needs. Depending on each patient's control goals and willingness to undergo more intense therapy, the parameters can be customized to increase the number of daily interventions and thus likely improve the CL control performance.

The sampling time used was 5 min, representing a total of 288 times per day to run both controllers. For the following analysis the values are reported as median. The CHO controller is activated

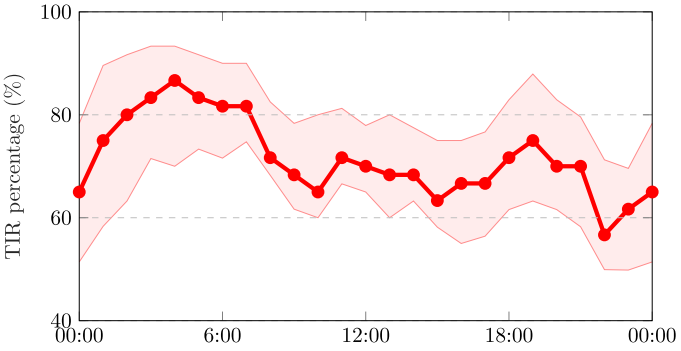

Fig. 6. TIR for CL MDI therapy with MPC.

8.3% of the time (24 times), suggesting CHO approximately 1.3 times daily. The corrective bolus controller is activated 12.1% of the time (35 times) and suggests boluses about 1.5 times daily. When the controllers are activated they use an average execution time of 0.4 s to solve the cost function. Given that they are executed about 59 times in total, this represents an approximate daily computational cost of 23.6 s. These data demonstrate that this approach implementation substantially reduces the total computational cost. This presents advantages such as: 1) the reduction of energy consumption, which means a decrease in the total energy consumption of the system since it makes less use of processing resources; 2) makes the controller more accessible for applications with limited budgets; 3) makes the controller more easily scalable to larger and more complex systems.

"In [32] and [33], a review of studies with AP systems is presented, which have demonstrated superiority over pump systems in OL. Both studies conclude that CL systems were superior to OL systems in terms of glycemic control, particularly during the night, where they have proven to be very effective and safe. Nighttime periods are characterized by not disturbing the system much. However, there are still significant barriers to achieving daytime glucose control equal to nighttime while also reducing the burden of diabetes management during the day. This is due to the fundamental limitations of the control problem. A disturbance in the glucose level is much faster than the response to control action, even if anticipatory control is used [32,33]. The proposed combination of CL control with MDI therapy may provide a balanced alternative with similar outcomes. While nighttime performance may decrease compared to that achieved with AP, daytime performance could be maintained in similar ranges. Additionally, limitations of AP such as cost or the patient being free from devices attached to the body could be addressed by using MDI, which may be attractive to many users, such as athletes."

To observe the behavior of the presented strategy and compare if it resembles what has been observed in the literature for APs systems, we will evaluate its average TIR curve in 24 h. Figure 6, shows the TIR over time of the day for the implemented CL MDI therapy, the behavior suggests that the proposed strategy may provide a balanced alternative with behavior similar to that observed for APs.

Despite not being a thorough comparison, the above mentioned results encourage further research and testing of CL control for MDI therapy. Additional clinical trials comparing both approaches in free-living conditions are required to assess the practical benefits of the proposed CL approach and identify the population group that would obtain the maximum benefit.

The in silico results of this study suggest that the proposed controllers can improve the outcomes of patients receiving MDI therapy. However, clinical trials on free-living conditions are required to validate these results in practice. The main limitations of this

study include 1) the non-inclusion of physical exercise, 2) non-inclusion of a meal bolus calculator to improve the bolus behavior, and 3) limitation on behavioral aspects of the patient as control actuator for administering correction boluses and eating the recommended dose of rescue CHO. On this last point, it is important to clarify that if the patient does not comply with or delays the control actions, the degradation of this therapy will not be affected beyond the performance of MDI therapy in OL.

7. Conclusion

We developed two event-triggered MPC schemes for MDI therapy in people with T1D. The proposed control algorithms translate technology from the AP to MDI therapy to exploit its benefits. The flexible and general framework provided by MPC allows to incorporate constraints and enables users to seamlessly adjust the daily intervention. In silico results indicate that if the control actions are followed, an improvement over conventional MDI therapy is guaranteed, even attaining clinical targets. Future work will involve clinical evaluations in free-living conditions of the proposed approach.

Funding

This work was partially supported by the Spanish Ministry of Science and Innovation under Grant number PID2019-107722RB-C22, by the Autonomous Government of Catalonia under Grant number 2017 SGR 1551, by the Spanish Ministry of Universities and European Union through the Next GenerationEU Plan (Margarita Salas), and by the program for researchers in training at the University of Girona (IFUdG2019).

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Ernesto Estremera: Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Data curation, Writing – original draft, Funding acquisition, Visualization. **Aleix Beneyto:** Conceptualization, Methodology, Software, Investigation, Resources, Writing – review & editing, Visualization, Supervision, Project administration, Funding acquisition. **Alvis Cabrera:** Software, Formal analysis, Investigation, Writing – review & editing, Funding acquisition. **Iván Contreras:** Writing – review & editing, Visualization, Supervision, Project administration, Funding acquisition. **Josep Vehí:** Conceptualization, Methodology, Investigation, Resources, Writing – review & editing, Visualization, Supervision, Project administration, Funding acquisition.

Appendix A. Rescue CHO food library

Table A.1
Rescue CHO food library.

Food	Usual portion	Serving with 5 g of CHO	GI
Liquid yogurt	Unit (200 mL)	1/6	Low
Orange	Medium unit (200 g)	1/4	Low
Banana	Small unit (100 g)	1/4	Low
Kiwi	Medium unit (100 g)	1/2	Low
Apple	Medium unit (200 g)	1/4	Low
Peach	Medium unit (100 g)	1/2	Low
Tangerine	Medium unit (100 g)	1/2	Low
Whole yogurt	Unit (125 mL)	1/3	Low
Whole milk	Glass or cup (200 mL)	1/2	Low
Natural yogurt	Unit (125 mL)	1	Low
Skimmed yogurt or fruit	Unit (125 mL)	1/2	Low
Natural or unsweetened fruit juice	Glass or brick (200 cm^3)	5/8	Low
Jam	Soup spoon (25 g)	2/5	Medium
Biscuit/ladyfingers	Individual commercial unit (25 g)	2/5	Medium
Ice Cream	Medium ball (100 g)	1/4	Medium
Condensed milk	Soup spoon (20 g)	1/2	Medium
Digestive biscuit	Unit (11 g)	5/7	Medium
Raisin	Handful closed hand (20 g)	3/8	Medium
Toasted chestnut	Unit (10 g)	5/4	Medium
Melon	Medium slice(200 g)	1/2	Medium
Commercial juice	Glass or brick(200 cm^3)	5/8	Medium
Glucose	Sport gel (40 g)	1/8	High
Tonic	Glass or bottle (200 cm^3)	1/4	High
Date	Unit (12 g)	5/8	High
Dried date	Unit (10 g)	3/4	High
Energy drink	Can (250 cm^3)	1/6	High
Soft drink (cola or flavors)	Glass (200 cm^3)	1/4	High
Maria cookie type	Cookie (7 g)	1	High
Prince cookie type	Cookie (15 g)	1/2	High
Potato chips	Small bag (30 g)	1/3	High
Isotonic drink	Can (330 cm^3)	1/5	High
Energy bar	Unit (20 g)	2/5	High
Sliced bread	Sliced (25 g)	2/5	High
White bread	Muffin (60 g)	1/6	High
Toast	Unit (10 g)	3/4	High
Bread sticks	Unit (5 g)	3/2	High

References

[1] Emerging Risk Factors Collaboration, et al., Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta–analysis of 102 prospective studies, The Lancet 375 (9733) (2010) 2215–2222.

[2] J.D. Steinmetz, R.R. Bourne, P.S. Briant, S.R. Flaxman, H.R. Taylor, J.B. Jonas, A.A. Abdoli, W.A. Abrha, A. Abualhasan, E.G. Abu-Gharbieh, et al., Causes of blindness and vision impairment in 2020 and trends over 30 years, and prevalence of avoidable blindness in relation to vision 2020: the right to sight: an analysis for the global burden of disease study, The Lancet Global Health 9 (2) (2021) e144–e160.

[3] F. León-Vargas, J.A. Arango Oviedo, H.J. Luna Wandurraga, Two decades of research in artificial pancreas: insights from a bibliometric analysis, J. Diabetes Sci. Technol. 16 (2) (2022) 434–445.

[4] L. Huo, W. Deng, L. Lan, W. Li, J.E. Shaw, D.J. Magliano, L. Ji, Real-world application of insulin pump therapy among patients with type 1 diabetes in china: a cross-sectional study, Front. Endocrinol. 13 (2022).

[5] J.B. McGill, A. Ahmann, Continuous glucose monitoring with multiple daily insulin treatment: outcome studies, Diabetes Technol. Ther. 19 (S3) (2017) S–3.

[6] R.I. Holt, J.H. DeVries, A. Hess-Fischl, I.B. Hirsch, M.S. Kirkman, T. Klupa, B. Ludwig, K. Nørgaard, J. Pettus, E. Renard, et al., The management of type 1 diabetes in adults. A consensus report by the american diabetes association (ADA) and the european association for the study of diabetes (EASD), Diabetes Care 44 (11) (2021) 2589–2625.

[7] G. Assessment, 6. Glycemic targets: standards of medical care in diabetes-2022, Diabetes Care 45 (2022) S83.

[8] J.H. Pettus, F.L. Zhou, L. Shepherd, K. Mercaldi, R. Preblick, P.R. Hunt, S. Paranjape, K.M. Miller, S.V. Edelman, Differences between patients with type 1 diabetes with optimal and suboptimal glycaemic control: a real-world study of more than 30 000 patients in a US electronic health record database, Diabetes Obesity Metab. 22 (4) (2020) 622–630.

[9] W.E. Winter, N.S. Harris, Evaluation of hypoglycemia, Handb. Diagn. Endocrinol. (2021) 203–235.

[10] B. Ahmed, M.N. Khan, Hypoglycemia: its effect on patients with diabetes, World Fam. Med. 17 (9) (2019) 18–23.

[11] A. Beneyto, A. Bertachi, J. Bondia, J. Vehi, A new blood glucose control scheme for unannounced exercise in type 1 diabetic subjects, IEEE Trans. Control Syst. Technol. 28 (2) (2018) 593–600.

[12] L. Cassany, D. Gucik-Derigny, J. Cieslak, D. Henry, R. Franco, A.F. De Loza, H. Rios, L. Olçomendy, A. Pirog, Y. Bornat, et al., A robust control solution for glycaemia regulation of type-1 diabetes mellitus, in: 2021 European Control Conference (ECC), IEEE, 2021, pp. 327–332.

[13] A. Beneyto, J. Vehi, Closed-loop blood glucose control using insulin and carbohydrates in front meals and exercise, IFAC-PapersOnLine 50 (1) (2017) 2058–2063.

[14] B. Grosman, E. Dassau, H. Zisser, L. Jovanovič, F.J. Doyle III, Multi-Zone-MPC: clinical inspired control algorithm for the artificial pancreas, IFAC Proc. Vol. 44 (1) (2011) 7120–7125.

[15] R. Gondhalekar, E. Dassau, F.J. Doyle III, Velocity-weighting & velocity-penalty MPC of an artificial pancreas: improved safety & performance, Automatica 91 (2018) 105–117.

[16] D. Shi, E. Dassau, F.J. Doyle, Adaptive zone model predictive control of artificial pancreas based on glucose-and velocity-dependent control penalties, IEEE Trans. Biomed. Eng. 66 (4) (2018) 1045–1054.

[17] I. Hajizadeh, S. Samadi, M. Sevil, M. Rashid, A. Cinar, Performance assessment and modification of an adaptive model predictive control for automated insulin delivery by a multivariable artificial pancreas, Ind. Eng. Chem. Res. 58 (26) (2019) 11506–11520.

[18] C.K. Boughton, R. Hovorka, New closed-loop insulin systems, Diabetologia 64 (2021) 1007–1015.

[19] D. Dermawan, M.A.K. Purbayanto, An overview of advancements in closed-loop artificial pancreas system, Heliyon (2022) e11648.

[20] M. Nwokolo, R. Hovorka, The artificial pancreas and type 1 diabetes, J. Clin. Endocrinol.Metab. (2023) dgad068.

[21] M. Masierek, K. Nabrdalik, O. Janota, H. Kwiendacz, M. Macherski, J. Gumprecht, The review of insulin pens-past, present, and look to the future, Front. Endocrinol. 13 (2022).

[22] E. Estremera, A. Cabrera, A. Beneyto, J. Vehi, A simulator with realistic and challenging scenarios for virtual T1D patients undergoing CSII and MDI therapy, J. Biomed. Inform. 132 (2022) 104141.

[23] L. Ljung, System Identification. Theory for the User, 2nd edition, 1999,

[24] J.B. Rawlings, D.Q. Mayne, Tabla de raciones de hidratos de carbono, Fundación Diabetes (2013). https://www.fundaciondiabetes.org/sabercomer/tabla_de_raciones_de_hidratos_de_carbono.

[25] B.P. Kovatchev, M. Breton, C. Dalla Man, C. Cobelli, In silico preclinical trials: a proof of concept in closed-loop control of type 1 diabetes, 2009,

[26] N. Resalat, J. El Youssef, N. Tyler, J. Castle, P.G. Jacobs, A statistical virtual patient population for the glucoregulatory system in type 1 diabetes with integrated exercise model, PLoS ONE 14 (7) (2019) e0217301.

[27] M.E. Wilinska, L.J. Chassin, C.L. Acerini, J.M. Allen, D.B. Dunger, R. Hovorka, Simulation environment to evaluate closed-loop insulin delivery systems in type 1 diabetes, J. Diabetes Sci. Technol. 4 (1) (2010) 132–144.

[28] M.R. Smaoui, R. Rabasa-Lhoret, A. Haidar, Development platform for artificial pancreas algorithms, PLoS ONE 15 (12) (2020) e0243139.

[29] J. Löfberg, YALMIP: a toolbox for modeling and optimization in MATLAB, in: Proceedings of the CACSD Conference, 2004. Taipei, Taiwan

[30] Gurobi Optimization, LLC, Gurobi Optimizer Reference Manual, 2022, https://www.gurobi.com.

[31] D.C. Klonoff, J. Wang, D. Rodbard, M.A. Kohn, C. Li, D. Liepmann, D. Kerr, D. Ahn, A.L. Peters, G.E. Umpierrez, et al., A glycemia risk index (GRI) of hypoglycemia and hyperglycemia for continuous glucose monitoring validated by clinician ratings, J. Diabetes Sci. Technol. (2022).

[32] R.A. Lal, L. Ekhlaspour, K. Hood, B. Buckingham, Realizing a closed-loop (artificial pancreas) system for the treatment of type 1 diabetes, Endocr. Rev. 40 (6) (2019) 1521–1546.

[33] K. Zhou, D. Isaacs, Closed-loop artificial pancreas therapy for type 1 diabetes, Curr. Cardiol. Rep. (2022) 1–9.