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A strategy based on integer programming for optimal dosing and timing of preventive hypoglycemic treatments in type 1 diabetes management

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ABSTRACT

Background and objectives: One of the major problems related to type 1 diabetes (T1D) management is hypoglycemia, a condition characterized by low blood glucose levels and responsible for reduced quality of life and increased mortality. Fast-acting carbohydrates, also known as hypoglycemic treatments (HT), can counteract this event. In the literature, dosage and timing of HT are usually based on heuristic rules. In the present work, we propose an algorithm for mitigating hypoglycemia by suggesting preventive HT consumption, with dosages and timing determined by solving an optimization problem.

Methods: By leveraging integer programming and linear inequality constraints, the algorithm can bind the amount of suggested carbohydrates to standardized quantities (i.e., those available in "off-the-shelf" HT) and the minimal distance between consecutive suggestions (to reduce the nuisance for patients).

Results: The proposed method was tested in silico and compared with competitor algorithms using the UVa/Padova T1D simulator. At the cost of a slight increase of HT consumed per day, the proposed algorithm produces the lowest median and interquartile range of the time spent in hypoglycemia, with a statistically significant improvement over most competitor algorithms. Also, the average number of hypoglycemic events per day is reduced to 0 in median.

Conclusions: Thanks to its positive performances and reduced computational burden, the proposed algorithm could be a candidate tool for integration in a DSS aimed at improving T1D management.

1. Introduction

Type 1 diabetes is a chronic autoimmune disease causing insulin deficiency. The lack of insulin results in hyperglycemia, a condition characterized by high blood glucose (BG) levels (BG > 180 mg/dl) and responsible for complications to nerves, heart, kidneys and eyes if persistent. To avoid these complications, people with T1D need to maintain BG concentration within a glycemic safe range known as euglycemia (BG ∈ [70,180] mg/dl), by compensating for the lack of insulin exogenously. Excessive insulin administration could lead to low BG levels, i.e., hypoglycemia (BG < 70 mg/dl), which is the major obstacle to glycemic control for many patients. If untreated, hypoglycemia can lead to severe complications even in the short-term: fainting, weakness, coma, or even death [1]. For this reason, glucose levels should be monitored frequently throughout the day to check whether they exceed the safe range. This can be done by self-monitoring BG (SMBG) via fingerstick sampling, or by employing a continuous glucose monitoring (CGM) sensor [2].

These measurements are crucial to detect upcoming hypoglycemic events and eventually urging patients in taking preventive actions to restore euglycemia, such as consuming a so-called hypoglycemic treatment (HT). HTs consist of a pre-defined amount of fast-acting carbohydrates (CHO) in the form of glucose tabs, sugar packets, or gels. The quantity and timing of the HT should be chosen carefully to mitigate the hypoglycemic event while avoid large rebounds, which may lead to hyperglycemia. In other words, unnecessary CHO consumption should be minimized.

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T1D management is reportedly challenging, to the point that only one third of people with T1D are meeting their glycemic targets [3]. Furthermore, the amount of manual operations this condition imposes on the daily routine represents a major burden for patients, reducing their quality of life. In the last decade, many decision support systems (DSS) have emerged as a precious tool to assist patients in the management of T1D. As a matter of fact, DSS can integrate algorithms for insulin dosing [4–9], for the prediction of hypoglycemia [10–12] and for the suggestion of HT to prevent it [13,14,6]. These tools can support patients with proactive and personalized decisions in different scenarios of T1D management and allow them to react at a shorter time scale. Some of these algorithms have already been implemented in DSS and integrated in mobile applications [15–17], showing a beneficial impact when applied during preliminary tests.

1.1. Paper contribution

In this paper we propose an algorithm for the suggestion of preventive HT, which can be integrated in a DSS with the aim of mitigating the occurrence and severity of hypoglycemic events.

Commonly, the guidelines employed by patients for the consumption of HT consist of simple rules based on threshold surpassing. For instance, when BG drops below a certain level (e.g., 70 mg/dl), these guidelines suggest the consumption of a HT with a fixed amount of CHO (e.g., 15 g). DSS leveraging CGM information may implement more sophisticated rules. For instance, some algorithms use a predictive model of glucose dynamics to forecast future threshold surpassing and tackle hypoglycemia in advance. Some algorithms adapt the amount of CHO to consume based on glycemic slope or on the probability that the hypoglycemic event may occur. Nevertheless, the amount of CHO to consume is generally chosen heuristically.

With respect to state-of-the-art strategies, the method we propose will not choose the amount and timing of CHO heuristically. Instead, an optimization problem (OP) will be solved to find a treating strategy that i) maintains glycemic levels as close as possible to an euglycemic setpoint and ii) minimizes patient involvement, in terms of the number requested HT consumption.

In designing this new algorithm for the suggestion of the dosing and timing of HT, we addressed two important issues. The first one concerns the frequency of CHO intake suggestions. HTs usage should be as infrequent as possible, so as to minimize the nuisance for the patient. In all likelihood, the more frequently the algorithm suggests HTs, the less the patient will comply with these suggestions. The second problem concerns the quantization of the suggestions. In real life, patients cannot be expected to consume any arbitrary amount of CHO suggested by the algorithm. Viceversa, the suggestions should be compatible with the common dosages for fast-acting CHO – for instance, the ones in commercially available sugar tabs, or integer multiples of these quantities. Sparsity in time and quantization can both be applied a posteriori (e.g., by rounding the suggested CHO amount to the closest quantization value), but this choice would imply a degradation of the algorithm performances. To overcome this issue, we will integrate these requirements in the optimization procedure by formulating the problem as a constrained integer program (CIP). This idea was first explored by the authors in [18], proposing an artificial pancreas that simultaneously plans insulin and CHO administration. Here, instead, we investigate a DSS solely dedicated to HTs suggestion and with no authority on insulin delivery. This makes such a DSS compatible with any insulin delivery regimen.

This novel hypotreating strategy will then be validated in silico on the UVA/Padova T1D simulator, which is a realistic, large-scale simulator of glucose metabolism in diabetic subjects. The use of a simulator will also enable the comparison of this new algorithm with the official guidelines and state of the art algorithms for hypotreating under the same conditions.

1.2. Paper organization

The paper is organized as follows. Section 2 briefly reviews the official clinical guidelines and the available literature algorithms for HT determination. In Section 3 we will describe the design of the new algorithm, whereas Section 4 concerns its tuning and individualization. Section 5 deals with the setup of the simulated experiment (including the description of the main features of the used UVa/Padova simulator) and the assessment criteria chosen to evaluate the proposed method vs the existing literature approaches. In Section 6, we report and discuss the results. Lastly, in Section 7, we will draw some conclusions and discuss about possible future developments of the present investigation. The paper is completed with three appendices reporting technical details on the physiological model employed, the tuning of the Kalman filter and the formulation of the optimization problem.

2. State of the art

Different methods aimed at mitigating hypoglycemia through the suggestion of HT have been proposed in the literature. Such strategies may rely on heuristic or more sophisticated approaches.

The American Diabetes Association (ADA) guidelines for the treatment of hypoglycemia [19] indicate the ingestion of any form of fast-acting CHO containing 15-20 g of glucose as the preferred treatment whenever the individual is conscious and BG levels drop below 70 mg/dl. Fifteen minutes later, BG concentration should be checked again through SMBG and the treatment repeated if the hypoglycemic event is not solved yet. The re-treatment is commonly postponed to thirty minutes later when using information from CGM sensors only. Indeed, even if these devices enable a continuous monitoring of glucose levels, the absorption delay due to subcutaneous measurements imposes to wait longer for noticing the effect of a HT on BG.

In Vettoretti et al. [20], ADA guidelines are enhanced to take into account different degrees of severity and different daytimes of the hypoglycemic event. Although the logic for HT suggestions remains similar to standard ADA guidelines, the suggested quantities of CHO change. During daytime (i.e., between 6.00 AM and 10.00 PM) the algorithm suggests a HT of 15 g if CGM $\leq$ 70 mg/dl and 20 g if CGM $\leq$ 55 mg/dl. Otherwise, the algorithm always suggests 25 g during night-time (i.e., between 10.00 PM and 6.00 AM), in order minimize the number of times patients are disturbed during their sleep.

Following ADA guidelines can potentially reduce the duration and magnitude of hypoglycemic events, but avoiding them in the first place would be preferable. As CGM sensors are more and more widespread among individuals with T1D [21], hypo-treating algorithms can now leverage the information on glucose rate of change (ROC) or predicted future BG values to plan preventive actions in advance.

A method using the information on glucose ROC is represented by the work of Camerlingo et al. [13]. In that approach, preventive HT are triggered by computing the “dynamic risk” – that is, a non linear function that combines the static risk (SR) associated to BG (a concept formulated by Kovatchev et al. [22]) with the rate of change (ROC) computed from CGM measurements. Both SR and ROC can be computed directly from CGM measurements, which is therefore the only information needed by the algorithm. This strategy triggers a HT of either 15 or 20 g depending on how fast glucose levels are dropping. A value of ROC > -1 mg/dl/min is associated to a slow glucose descent and triggers a HT of 15 g. On the other hand, glucose rate of change (ROC) $\leq$ -1 mg/dl/min triggers a HT of 20 g. After suggesting a HT, the algorithm shuts off for 15 min; then, glycemia is checked again and a new HT is suggested if necessary.

The large availability of glycemic data provided by CGM sensors have enabled the development of several predictive models to forecast how BG levels will evolve. These algorithms can be used to develop rules for hypo-treating. For instance, a simple heuristic rule may consists in suggesting a HT of 15 g when predicted BG $\leq$ 70 mg/dl. Al-

though many works use exclusively CGM data to predict future glycemic levels [10–12,23], knowing what originally caused a glycemic descent could improve the prediction and potentially provide further information on how to tackle and avoid that hypoglycemic event. This is why several other works use additional inputs beside CGM measurements to predict hypoglycemia [24–28]. For instance, the information on insulin administration or CHO consumption could be crucial for early detection, as low BG levels are most commonly caused by an over-dosing of insulin to counteract the meal intake [29].

Glucose prediction models have been employed to develop various sophisticated approaches for the suggestion of CHO intake. In [14], glucose levels are predicted using an ARMAX model. Its inputs are insulin, energy expenditure and galvanic skin response. Predictions are used as a feature in a decision tree, which determines the amount of CHO to ingest. In [30,31], CHO recommendations are computed using a predictive proportional-derivative controller based on an ARMAX model. The CHO control signal is quantized a posteriori to CHO suggestions of 15 grams.

3. Materials and methods

3.1. Hypotreating algorithm

To smartly plan future HTs suggestion, the proposed method explores the possible sequences of future HTs and determines the one that minimize a suitable cost function. Such a cost function measures the efficacy of the sequence by accounting for the glucose control that the HTs are predicted to produce. Then, following the receding horizon principle, only the first HT of the computed sequence is suggested to the patient and the optimal sequence is updated once a new measurement comes in.

Generalizing the idea of [18], HTs suggestions will be denoted with the variable $c(k) \in \Gamma$ (mg/min), where $\Gamma = \{0, \gamma_1, \dots, \gamma_{N_{\text{HT}}}\}$ is the finite set containing the N_{HT} possible dosages of fast-acting CHO that the algorithm can propose.

The variable $c(k)$ is build as:

$$c(k) = \sum_{n=1}^{N_{\text{HT}}} \gamma_n c_n(k), \tag{1}$$

where $c_1(k), \dots, c_{N_{\text{HT}}}(k) \in \{0, 1\}$ are mutually exclusive binary variables, i.e. such that $\sum_{i=1}^{N_{\text{HT}}} c_i(k) \leq 1$. Each binary variable indicates if the corresponding amount of CHO is selected at instant k: $c(k) = \gamma_i$ if and only if $c_i(k) = 1$ and $c_j(k) = 0$ for all $i \neq j$. This formulation enforces quantization of the HT suggested and the integer variables introduced will allow to ensure also infrequent HTs suggestions.

The algorithm computes the sequence of HTs $[c(k), c(k+1), \dots, c(k+N-1)]$ that minimizes the cost functional

$$J = \sum_{j=0}^{N-1} \Big(q(g(k+j) - g_0(k+j))^2 + ||c(k+j)||_0 \Big), \tag{2}$$

with N being a finite prediction horizon (PH), set to $N = 18$ sampling instants (corresponding to 1 hour and 30 minutes).

The first term in (2) penalizes the distance between the predicted glucose levels, $g(k) \in \mathbb{R}$ (mg/dl), produced by the sequence and an euglycemic setpoint, $g_0 \in \mathbb{R}$ (mg/dl), set to $g_0 = 115$ mg/dl.

The second term in (2) penalizes the ℓ_0 "norm" of $c(k)$,

$$||c(k)||_0 = \begin{cases} 0 & \text{if } c(k) = 0 \\ 1 & \text{if } c(k) \neq 0 \end{cases},$$

and thus penalizes the number of (non-zero) HT suggestions in the PH. With this choice, only the number of predicted patient intervention is penalized and the amount of CHO suggested is not considered. This favors larger but rarer CHO suggestions with respect to the standard choice of penalizing the ℓ_2 norm of $c(k)$, $||c(k)||_2 = (c(k))^2$, that instead promotes smaller (but possibly more frequent) HTs.

Finally, it should be noted that

$$||c(k)||_0 = \sum_{n=1}^{N_{\text{HT}}} ||c_n(k)||_0 = \sum_{n=1}^{N_{\text{HT}}} ||c_n(k)||_2^2, \tag{3}$$

meaning that computation of the ℓ_0 "norm" of $c(k)$ can be reconducted to a quadratic problem with respect to the variables $c_1(k), \dots, c_{N_{\text{HT}}}(k)$, thanks to their binary nature.

The parameter $q \in \mathbb{R}^+$ in (2) sets the trade-off between the two penalty terms. We will often refer to q as "aggressiveness". A patient-specific tuning of the aggressiveness will be performed in Section 4.

The predicted values of g in (2) are computed via forward simulation using a linearized physiological model of glucose-insulin dynamics and starting from an estimate of the system state at the current sampling time. The state estimate is obtained by means of a Kalman Filter (KF) leveraging the same model and using the available information on CGM measurements, insulin administration and CHO intake. For sake of paper readability, details of the physiological model are reported in Appendix A, whereas the tuning of the KF is documented in Appendix B.

To enforce a minimal distance Δ_{HT} between two consecutive HT, we impose a set of linear inequality constraints on the binary variables $c_1(k), \dots, c_{N_{HT}}(k)$. Focusing on the generic i-th Boolean variable, let us introduce the single Boolean vector $C_i(k) = [c_i(k), \dots, c_i(k+N-1)]^T \in \{0,1\}^N$ and the following linear inequality constraint:

$$\tilde{\mathcal{F}} C_i(k) \leq f, \tag{4}$$

where

$$\tilde{\mathcal{F}} = \begin{bmatrix} \overbrace{1 \;\dots\; 1}^{\Delta_{HT}} & \overbrace{0 \;\dots\; \dots \;0}^{N-\Delta_{HT}} \\ 0 \;\; 1 \;\dots & 1 \;\; 0 \;\dots \;0 \\ \vdots \quad \ddots & \ddots \quad \vdots \\ \vdots \qquad \ddots & \ddots \quad 0 \\ 0 \;\dots\; \dots & 0 \;\; 1 \;\dots \;1 \end{bmatrix} \in \mathbb{R}^{N \times (N-\Delta_{HT}+1)},$$

$$f = \begin{bmatrix} 1 \\ \vdots \\ 1 \end{bmatrix} \in \mathbb{R}^{N-\Delta_{HT}+1}.$$

The first row of the inequality in (4), can be rewritten as

$$\sum_{j=1}^{\Delta_{HT}} c_i(k+j-1) \leq 1.$$

Since the elements of $C_i(k)$ are Boolean, at most one $c_i(k+j-1)$ in the interval $j \in [1,\ \Delta_{HT}]$ can be equal to 1. The second inequality poses a similar constraint on the interval $j \in [2,\ \Delta_{HT}+1]$. The only possible combination of two non-zero actions satisfying both constraints is the one that has $c_i(k) = 1$ and $c_i(k+\Delta_{HT}+1) = 1$. This consideration holds for the whole PH, so that two elements of C_n can be equal to 1 only if they are at least Δ_{HT} elements apart. This kind of constraints will be applied to all the binary variables at the same time:

$$\sum_{h=j}^{j+\Delta_{HT}-1} \Big(\sum_{i=1}^{N_{\text{HT}}} c_i(k+h) \Big) \leq 1, \quad j = 1, \dots, N-\Delta_{HT}+1,$$

thus preventing to plan two HTs (regardless of their amount) at less than Δ_{HT} instants apart. It should be noted that these constraints automatically impose also mutual exclusivity of the binary variables at each time k, thus ensuring that only HT amounts in $\Gamma = \{\gamma_1, \dots, \gamma_{N_{\text{HT}}}\}$ are suggested while the sum of different dosages (e.g., $\gamma_1 + \gamma_2$) are forbidden.

After some standard manipulations known as "condensing", which are briefly reviewed in Appendix C), the minimization of the cost functional (2), subject to the binary constraints on $c_1, \dots, c_{N_{\text{HT}}}$ and by the

sets of affine inequality constraints defined as in (4), results in the following constrained integer program (CIP):

$$C_{\text{opt}}(k) = \underset{\substack{C(k) \text{ s.t. } \mathcal{F}C(k) \leq f \\ C(k) \in \{0,1\}^{N \cdot N_{HT}}}}{\arg\min} \frac{1}{2} C^T H C + h^T C, \tag{5}$$

where

$$C(k) = \begin{bmatrix} c_1(k) \\ \vdots \\ c_1(k+N-1) \\ \hline \vdots \\ \hline c_{N_{HT}}(k) \\ \vdots \\ c_{N_{HT}}(k+N-1) \end{bmatrix} \in \mathbb{R}^{N_{HT} \cdot N}, \tag{6}$$

$$\mathcal{F} = \left[\tilde{\mathcal{F}} \mid \dots \mid \tilde{\mathcal{F}} \right] \in \mathbb{R}^{(N-\Delta_{HT}+1) \times (N_{HT} \cdot N)},$$

and H and h are suitable matrices derived by straightforwardly representing (2) in matrix notation, see Appendix C.

The CIP in (5) is solved at each sampling time and from the optimal C found, C_{opt}, the first HT suggestion is derived as follows:

$$c_{\text{sugg}}(k) = [\gamma_1, 0, \dots, 0, |\gamma_2, 0, \dots, 0, | \dots |\gamma_{N_{\text{HT}}}, 0, \dots, 0] C_{\text{opt}}.$$

If a non-zero HT is suggested at the current instant k and the user confirms the consumption, the algorithm is then shut-off for the following Δ_{HT} sampling instants in order to guarantee the sparsity in time of the suggestions.

Beside suggesting an HT when the first element of the optimal HT sequence is different from zero, the algorithm could also pre-alert the user in case a HT is envisioned in other positions of the prediction horizon. Nevertheless, since the HT strategy in the PH is continuously updated, the planned HT could be canceled and pre-alert withdrawn.

In this work, we will consider a $\Delta_{HT} = 6$ (i.e., 30 min) and four possible amounts for HT suggestions ($N_{\text{HT}} = 4$): 5, 10, 15 and 20 g. The idea is to suggest integer multiples of a sugar tablet containing 5 g of CHO. Nevertheless, the framework presented in this section is easily adaptable to any desired combination of CHO intake.

In the results reported, the CIP in (5) is solved by using Matlab and ILOG CPLEX Optimization Studio (v. 12.9) [32].

4. Aggressiveness tuning

The aggressiveness, i.e., the hyper-parameter q in (2), plays a crucial role: the higher q, the more the algorithm is prone to suggest HTs for getting closer to the reference; the lower q, the more the utilization of CHO is discouraged.

As glucose metabolism largely varies among individuals, it may be hard to find a single value of q that well suites any subject. For this reason, aggressiveness needs to be optimized for each individual.

Optimizing q by trial and error would require to test several different tunings of this parameter on a single subject and to choose the value that achieves the best glycemic regulation. Such a procedure is easy to perform in simulation, but is unviable in vivo, as testing multiple tunings would be burdensome and potentially dangerous for patients. Therefore, as proposed in [33], we will use the simulator to find an optimal tuning of the aggressiveness; then, we will use these optimal values to train a regression law which aim is to infer a personalized value of q from patients-specific physical or therapeutic parameters, e.g., their body weight.

We exploited the 100 virtual subject of the UVa/Padova T1D Simulator, split them in a training and a test set (75 and 25 subjects, respectively), and designed the following tuning pipeline:

1. simulate 3 days of simulation on the training set for several values of q;
2. find the optimal value of q for each subject as the one that minimizes some cost function;
3. train a regression law from the optimal values of q and subjects-specific parameters;
4. evaluate the performances of the algorithm on 3 days of simulation with the suboptimal tuning of q on the subjects of the test set.

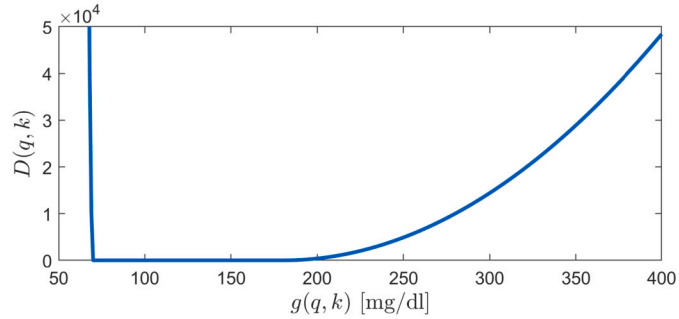

Fig. 1. Cost function applied for the minimization procedure during the optimal tuning of q.

4.1. Optimal tuning for virtual subjects

The optimal value of q is searched via grid search in the interval $[10^{-7}, 10^{-2}]$. This interval was selected based on a preliminary analysis. Forty log-spaced values are tested in this interval. The optimal value of q is chosen as the one that minimizes the following cost function:

$$\sum_{k=0}^{T_{end}} D(q,k) \tag{7}$$

where

$$D(q,k) = \begin{cases} \alpha(70 - g(q,k))^2 & \text{if } g(q,k) < 70 \\ \beta(g(q,k) - 180)^2 & \text{if } g(q,k) > 180 \\ 0 & \text{otherwise} \end{cases} \tag{8}$$

With $g(q,k) \in \mathbb{R}$ in (8) we indicate the output CGM signal obtained with a specific tuning q. The function in (8) assigns a penalty to each measurement based on the square of its distance from the euglycemic interval. The parameters α and β assign different weights to the penalties for measurements in hypoglycemia and hyperglycemia. We set $\alpha = 10^4$ and $\beta = 1$ to penalize hypoglycemia more than hyperglycemia. The resulting penalty function $D(q,k)$ is plotted in Fig. 1.

4.2. Control aggressiveness estimation

Let us consider a generic training subject p. The optimal control aggressiveness $q(p)$ has been computed for this subject as described in the previous section. Here we derive a regression model to predict the optimal tuning considering different easily accessible and subject-specific parameters as regressors: the insulin-to-carbohydrate ratio ($CR(p)$) and the correction factor ($CF(p)$), i.e., two patient-specific therapy parameters that are tuned by the clinician [34], the average basal insulin infusion ($I_b(p)$), the basal glucose level ($G_b(p)$) and the body weight ($BW(p)$) of the subject.

For this purpose, we employed a least absolute shrinkage and selection operator (LASSO) regression model to tackle the possible correlation among the features, by performing both variable selection and regularization. The resulting model has the following form:

$$\begin{aligned} \hat{q}(p) = {} & 0.014 \cdot CR(p) + 0.033 \cdot CF(p) \\ & +0.726 \cdot I_b(p) - 0.002 \cdot BW(p) \\ & +0.043 \cdot G_b(p) - 11.302, \end{aligned} \tag{9}$$

where $\hat{q}(p)$ is the tuning parameter estimated by the model. The regression model was trained using the basal glucose levels provided in the UVA/Padova Simulator for each individual virtual subject. In real-life application, this parameter could be estimated by averaging CGM measurements from night-time and fasting periods (i.e., when glucose is supposedly around basal level).

The above formula can be used for any new subject (including real subjects), providing an estimate of the optimal tuning, that can be used without requiring to run the possibly dangerous grid search procedure.

5. Benchmark algorithms, experimental setup and assessment criteria

5.1. Benchmarks algorithms

We implemented the state-of-art algorithms defined in Section 2, that will be used as benchmarks during the evaluation of the proposed method. In particular, the standard ADA guidelines [19], together with the enhanced strategy proposed in Vettoretti et al. [20] and the method proposed in Camerlingo et al. [13], hereafter labeled as ADA, Enhanced ADA, and Dynamic Risk respectively, will be used as a reference. In addition, we compared our method with a hypotreating algorithm based on BG prediction. The predictive model we used in this benchmark strategy is a population ARMAX model as the one proposed in [35]. This model leverages insulin and CHO intake as exogenous inputs, i.e., the same inputs used by our physiological model, to forecast future BG values. The algorithm suggests an HT = 15 gr whenever a value of BG ≤ 70 mg/dl is predicted. In this algorithm, the shut-off period lasts 30 minutes and the preventive action is repeated until predicted BG > 70 mg/dl. We set the order of the auto-regressive part to $n_a = 5$, the order of the moving average part to $n_c = 5$ and the order of the parts related to the two exogenous inputs to $n_{b_1} = 5$ (for insulin administration) and $n_{b_2} = 5$ (for CHO intake). Generally, these algorithms have higher prediction accuracy with shorter PH. In order to find a trade-off between a reliable prediction and enough time to take preventive actions, we decided to predict BG with a PH of 30 minutes (i.e., PH = 6 T_s).

5.2. Simulation scenario

In this work, we rely on the latest version of the UVa/Padova T1D simulator [36]. This tool is accepted by the Food and Drug Administration as an alternative to animal tests and, since 2008, it has been widely used by the scientific community.

The core of this simulator is a large-scale mathematical model of glucose metabolism in T1D subjects, which consists of 13 differential equations and more than 30 parameters. The model is equipped with a cohort of 100 virtual adult patients, that is, 100 different realizations of the parameters of the model. Each set of parameters is sampled from a joint distribution, which is inferred from unique clinical data [37]; hence, the correlation among parameters respects the one observed in real subjects.

One of the most noticeable features of this latest version of the UVa/Padova T1D simulator is time variability. It includes a model of the so-called "dawn phenomenon" and intra-day variations of insulin sensitivity that well mimic the daily patterns observed in vivo [38]. The pattern of insulin sensitivity is also subjected to random inter-day variations. CGM sensor measurement error is implemented as in [39].

The performances of the different hypo-treating strategies will be evaluated on 3 days of simulation, with each day characterized by three meals: breakfast, lunch and dinner. Meal timing and CHO content are drawn from uniform distributions to match the data reported in [40]. Table 1 reports the bounds of these distributions. Several studies reports how counting the correct CHO content of a meal is a challenging task for individuals with T1D and that carb-counting errors (CCEs) generally correlate with meal CHO amount and type [41]. In order to mimic this aspect, the CHO content that subjects announce to the hypotreating algorithms will be affected by a CCE computed as in [41].

Table 1
Minimal and maximal values of the possible CHO amount and time of consumption for the different meals.

Meal	CHO amount (g)	Time (daytime)
breakfast	[19-97]	[6.30 am - 8.00 am]
lunch	[31-124]	[11.30 am - 1.00 pm]
dinner	[28-140]	[6.00 pm - 8.30 pm]

Insulin administration is simulated as in a standard regimen for continuous subcutaneous insulin infusion (CSII) [42], i.e., using an insulin infusion pump. This regimen consists of a basal insulin infusion, administered during the whole day to meet non-prandial insulin needs, and meal-time insulin boli, which is used to cover the meal CHO content. Basal insulin requirements are patient-specific. In CSII, basal insulin is delivered via microboli. Infusion rate varies throughout the day to satisfy daily fluctuations in insulin sensitivity. In this work it was simulated as a step-wise constant signal. Insulin boli will be delivered exclusively when a meal is consumed, and the amount of insulin in the bolus will be determined using the so-called standard formula [43]:

$$i_{\text{bolus}}(k) = \frac{\hat{m}(k)}{CR} + \frac{g(k) - G_t}{CF} - IOB. \tag{10}$$

The variable $\hat{m}(k)$ indicates the CHO amount of the meal as estimated by patients (i.e., accounting for CCE). The glucose target, G_t, could be set equal to the target level in (2) (i.e., g_0) or to another value. For instance, in this work we set $G_t = G_b(p)$. The insulin-on-board, IOB, is the quantity of active insulin in the organism, and it is computed using a 6 hours insulin action curve as in [44].

To guarantee a fair comparison of different hypotreating strategies on the same subject, each virtual subject will always show the same realization of the random factors by fixing individual seeds in the generator of random numbers.

5.3. Assessment criteria

In order to carry out an unbiased evaluation of the proposed algorithm, the comparison with the benchmark methods was performed on the test subjects only, i.e. on the 25 randomly extracted virtual subjects that were not used for the regression of the optimal q. The simulation scenario lasted 3 days and included by the variability sources explained in Section 5.2.

We evaluated the glycemic control by computing four metrics commonly used for such a purpose, namely the percentage of time spent within the target glycemic range (TIR [%]), i.e., [70, 180] mg/dl, above 180 mg/dl, and below 70 mg/dl (TAR [%], and TBR [%] respectively), together with the number of hypoglycemic events [45,46] and the number of subjects experiencing hypoglycemia. In addition, to quantify the burden in terms of therapeutic actions introduced by the proposed algorithm compared to the benchmark, we computed the average number and grams of hypo-treatments suggested per day.

To assess statistical differences in glycemic metrics and amount/number of HTs between the proposed algorithm and the benchmark methods, we performed a paired t-test for metrics having Gaussian distribution, and a Wilcoxon signed rank test for metrics that have not. Gaussianity was determined via Lilliefors test, with a significance level of 5%. Statistical differences between the number of subjects experiencing hypoglycemia are tested using a Fisher exact test. In all these tests, we corrected the significance level of 5% for multiple comparisons via Bonferroni method and used a significance level of 1,25%.

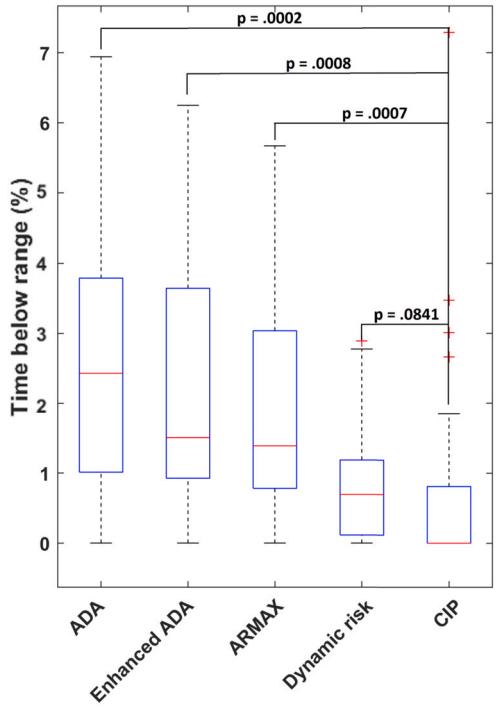

Fig. 2. Boxplot of the TBR [%] distribution resulting from the in silico assessment for standard ADA, enhanced ADA, ARMAX, dynamic risk, and CIP algorithm respectively, together with the corresponding p-values from the statistical testing.

6. Results

Table 2 reports the median and interquartile range of TBR, TIR, and TAR metrics on the test patients, while Fig. 2 shows the distribution of TBR for the five hypo-treating methods, with the corresponding p-value on the test patients. As can be noted from both Table 2 and Fig. 2, the proposed algorithm (hereafter named CIP for convenience) outperforms the benchmarks when considering the TBR, achieving a median of 0%, together with the lowest 75th percentile. Indeed, the highest median is reached by the standard ADA guidelines (2.43%), followed by the enhanced ADA (1.50%), the ARMAX model (1.39%), and lastly the dynamic risk algorithm (0.69%). In addition, the improvement in terms of TBR achieved by the proposed methodology resulted statistically significant compared to standard ADA, enhanced ADA, and ARMAX.

The positive results concerning the TBR are also confirmed by the number of hypoglycemic events that occurred on average during one day for each hypo-treating strategy, as shown in Fig. 3. The use of CIP has considerably reduced the onset of hypoglycemia, leading to a median of 0 events per day, as opposed to the other methods, which show a median of 0.7 events for standard ADA, enhanced ADA, and ARMAX, and 0.3 for dynamic risk method. The reduction in the number of hypoglycemic events is statistically significant with respect to ADA, Enhanced ADA and ARMAX (p-value < 0.001).

On the other hand, the TIR and TAR distributions reported in Table 2 do not show appreciable nor statistically significant differences between the CIP algorithm and the benchmarks. The only exception is the TIR achieved by the ADA guidelines, that was significantly inferior, although by a negligible amount, with respect the proposed method (p-value $= 0.008$).

Of the 25 subjects in the test set, 23 experienced hypoglycemia when treated with ADA guidelines, enhanced ADA guidelines and with the algorithm based on ARMAX prediction. This number decreases to 20 with the algorithm based on dynamic risk and to just 11 subjects when using CIP. A Fisher exact test confirmed a non-random association between

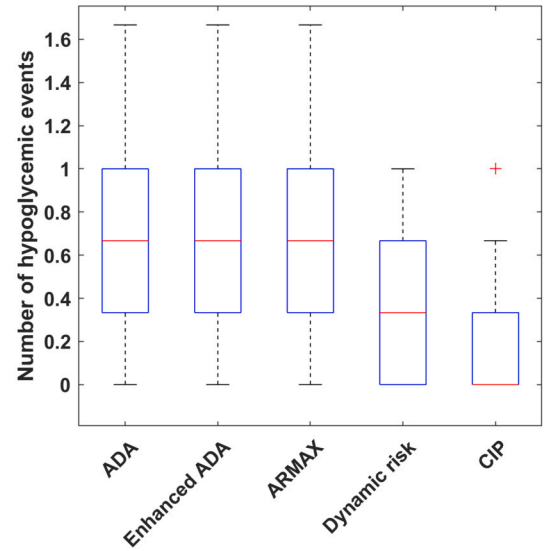

Fig. 3. Boxplot of the average number of hypoglycemic events for each subject, resulting from the in silico assessment for standard ADA, enhanced ADA, ARMAX, dynamic risk, and CIP respectively.

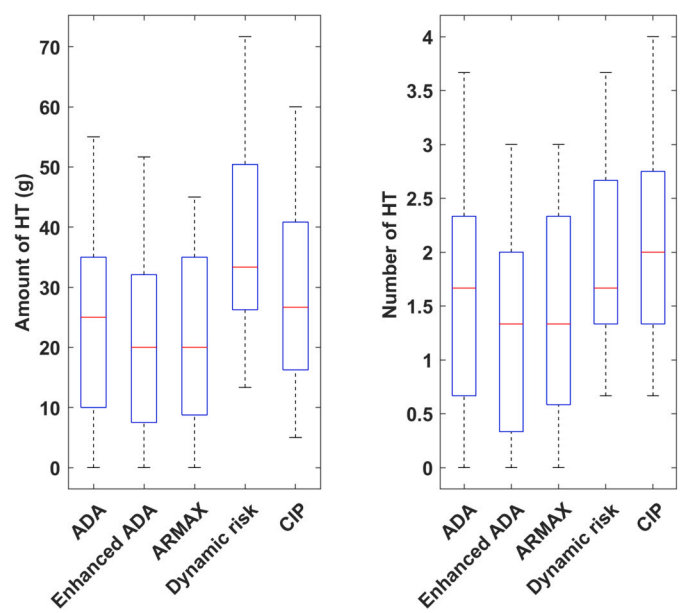

Fig. 4. Boxplot of the average grams and number of suggested HTs for each subject, resulting from the in silico assessment for standard ADA, enhanced ADA, ARMAX, dynamic risk, and CIP respectively.

the number of subjects experiencing hypoglycemia with the first three methods vs our algorithm (p-value < 0.001)

Moreover, we evaluated the burden introduced by the CIP-based algorithm with respect to the benchmarks, in terms of amount (Fig. 4, left panel) and number (Fig. 4, right panel) of HT suggested on average during one day. We also analyzed the frequency of the selected HT amounts for those methods involving the use of different possible quantities (enhanced ADA, dynamic risk, and CIP), reported in Fig. 5. We noticed that our method reduced the HT grams compared to dynamic risk algorithm, without introducing a major increase of the amount as regard to the standard ADA, enhanced ADA, and ARMAX model. Moreover, while the majority of dynamic risk and enhanced ADA suggested HT is equal to 20 and 15 grams respectively, the proposed algorithm proves to evenly use all the available quantities. The number of HT suggested moderately increases, from about 1.5 per day with the benchmarks to

Table 2
Comparison of the results obtained with our novel approach and the benchmark hypotreating strategies, reported as mean ± standard deviation for metrics found to be Gaussian (Lilliefors test) or as median [25th – 75th percentile] otherwise.

	ADA guidelines	Enhanced ADA	ARMAX prediction	Dynamic risk	CIP
TBR [%] median (25th – 75th percentile)	2.43 (1.01, 3.79)	1.50 (0.93, 3.65)	1.39 (0.78, 3.04)	0.69 (0.12, 1.19)	0.00 (0.00, 0.81)
TIR [%] mean (± std deviation)	70.49 (± 9.62)	71.11 (± 9.86)	71.68 (± 9.75)	71.36 (± 7.93)	72.45 (± 10.27)
TAR [%] median (25th – 75th percentile)	27.54 (21.60, 33.14)	27.56 (21.03, 33.32)	27.77 (20.89, 23.21)	28.23 (23.22, 32.34)	28.70 (21.14, 31.38)

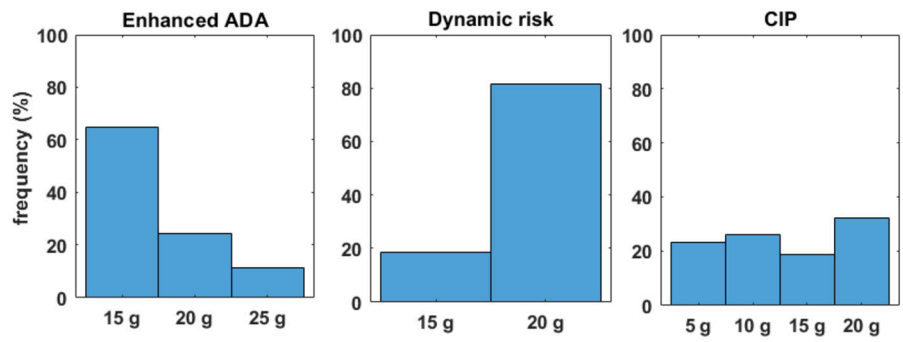

Fig. 5. Frequency of the resulting suggested HTs for enhanced ADA, dynamic risk and CIP, respectively.

2 per day with CIP. This increase resulted statistically significant with respect to the enhanced ADA (p-value < 0.001) and ARMAX (p-value < 0.01) strategies.

Fig. 6 reports glucose profiles (upper panel), carbohydrates intake (central panel) and insulin administration (lower panel) during a simulation day for a representative virtual subject from the test set. While insulin boluses may change between different hypotreating strategies due to the correction term (i.e., the second term) in (10), basal insulin infusion and meals are assumed to be the same regardless of the treatment. The day considered is characterized by three meals. After the post-prandial glucose peak due to the second meal (announced around noon), glycemia starts decreasing rapidly - possibly as a result of an over-estimated bolus. The hypoglycemia risk is exacerbated by the increase in basal insulin level. However, the CIP-based algorithm (pink line) is capable of completely avoiding the hypoglycemic event thanks to a smart and preventive planning of CHO intake. By optimizing the amount of CHO to ingest, the CIP algorithm is also capable of minimizing rebound hyperglycemia, achieving the lowest post-prandial peak and TAR after the third meal (announced around 19pm). The algorithm based on dynamic risk (green line) is also capable of avoiding hypoglycemia completely. However, it appears to be responding over-aggressively to hypoglycemia, as demonstrated by the rebound hyperglycemia following the second meal and by the unnecessary HT following the third meal. The algorithm based on the ARMAX model (yellow line) seems to be performing better than the remaining two. By triggering a HT intake shortly before the hypoglycemic event, it was able to reduce the time spent in hypoglycemia. On the other hand, the ADA (blue line) and enhanced ADA (red line) algorithms have no predictive logic and only reacted to the hypoglycemic event once it started. As a result, they achieved the higher TBR and deeper glycemic nadir.

7. Discussion and future work

In this work, we designed the optimization problem to penalize the number of HTs suggestions and to maintain glucose values close to a glycemic reference g_0. Nevertheless, different cost functions could be considered for this problem. For instance, the algorithm could penalize the amount of suggested CHO instead, or penalize glucose values outside of a target region using a zone penalty, [47].

In [18] we proposed a control algorithm for an AP system that could coordinate insulin infusion and the intake of small quantities of CHO. CHO intake suggestions were controlled using integer programming, as in the present work. The simultaneous control of CHO intake and insulin infusion was meant to tighten glycemic regulation with respect to AP systems controlling only insulin. The algorithm we propose here to determine the timing and dosage of HT does not require any authority on insulin administration. Hence, it can be easily adapt to most insulin regimen and be integrated to the therapy favored by the patient.

In the considered simulated scenario, we assumed the subjects were adopting continuous subcutaneous infusion for insulin administration. Nonetheless, the method we developed can also work with other insulin regimens, such as smart insulin pens. There are, however, some limitations. Firstly, the information on insulin administration should be automatically provided to the algorithm. Requiring information on insulin administration and meal CHO content represents a major drawback of this algorithm compared to other methods requiring glucose measurements only (such as ADA guidelines or the method based on dynamic risk). Secondly, the algorithm should be tested (and possibly re-tuned) to guarantee its safety when used in combination with long-acting insulin analogues, like the ones used in multiple daily insulin regimen.

Although the UVa/Padova simulator has been validated and is accepted by the scientific community, it is important to note that the achieved results need to be confirmed in dedicated clinical trials. This analysis in silico represents a first – yet necessary – step towards the validation of this algorithm. We acknowledge the model used in the algorithm and the one used in the simulator share a similar structure. However, we believe that the inter-subject variability, the time-varying phenomena (like the daily insulin sensitivity variation and the dawn phenomenon), and the linearization procedure are all factors contributing to provide a significant mismatch between the model used in the algorithm and the plant described in the simulator.

This analysis in silico also provided a preliminary analysis concerning the computational cost of this algorithm. Using a desktop PC, the CIP solution was found in 0.03 ± 0.023 seconds (mean ± std deviation). Since the sampling period of the algorithm is 5 minutes, this computational cost seems compatible with a possible integration of the algorithm in a real decision support system – even though the implementation in a smartphone could imply a loss of performance. As a

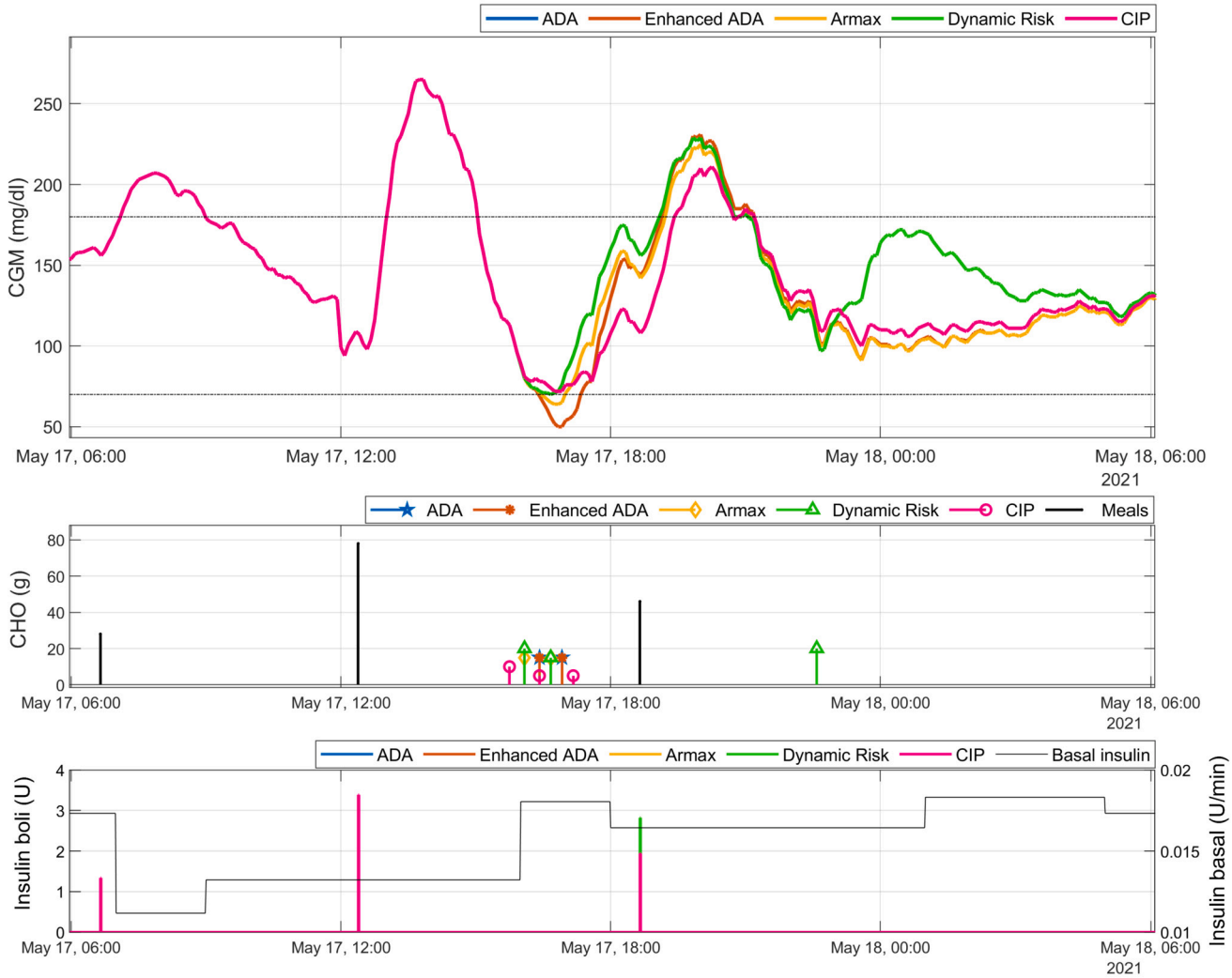

Fig. 6. Glucose control achieved with the 5 different hypotreating methods on a representative virtual subject in the test set. The upper panel reports the CGM measurements, the middle panel reports the carbohydrates intake (both HTs and meals), and the lower panel reports insulin administration (boluses in the left axis, basal infusion on the right axis).

safety measure, the algorithm is interrupted if a solution to the CIP is not found within 4 min. The suggestion proposed by the dynamic risk algorithm is proposed instead. This case was never experienced during the tests in silico. The algorithm could be easily adapted for longer PH and different combinations of CHO amounts. While the computational cost is more affected by the overall structure of the integer program (e.g., the sparsity of the matrices describing the problem), it should be noted that increasing the amount of binary variables can rise exponentially the cost of solving the problem in the worst-case scenario.

8. Conclusions

In this work, we proposed a novel algorithm for the prevention of hypoglycemic events through smart planning of HTs suggestions. The algorithm requires as inputs the CGM signal together with information on insulin administration and CHO content of consumed meals. By design, the algorithm tries to minimize the effort required by patients, by suggesting HTs which are sparse in time, that is, not more than one every 30 minutes, and quantized to predefined values, i.e., 5, 10, 15 and 20 grams of CHO. We evaluated the proposed algorithm using the UVA/Padova T1D simulator, by performing a comparison with several state-of-art methods for hypo-treating. Results in silico showed a significant improvement compared to the state-of-art techniques for hypo-treating, by significantly reducing the TBR, together with the number of hypoglycemic events, while maintaining a similar burden in terms of number and amount of suggested HTs.

Since its computational burden and functioning are compatible with real time and real life usage, the proposed algorithm can be a candidate tool for integration within a DSS aiming at limiting occurrence and severity of hypoglycemic events in the daily management of T1D.

CRediT authorship contribution statement

J. Pavan: Data curation, Conceptualization, Formal analysis, Methodology, Validation, Visualization, Writing – original draft, Writing – review & editing. **G. Noaro:** Conceptualization, Data curation, Formal analysis, Methodology, Validation, Visualization, Writing – original draft, Writing – review & editing. **A. Facchinetti:** Conceptualization, Funding acquisition, Project administration, Supervision, Writing – original draft, Writing – review & editing. **D. Salvagnin:** Methodology, Supervision, Writing – review & editing. **G. Sparacino:** Funding acquisition, Project administration, Supervision, Writing – review & editing. **S. Del Favero:** Conceptualization, Funding acquisition, Methodology, Project administration, Supervision, Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: The research presented in this work was supported by Dexcom Inc., San Diego, CA. The authors hold a patent application on the technology presented in this work.

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Appendix A. Glucose-insulin model

The proposed algorithm for the treatment of hypoglycemia relies on the prediction of future glycemic levels. To this purpose, we employed a linearized and discretized version of the physiological model of glucose-insulin dynamics within the UVa/Padova T1D simulator. The same linear model was employed for all 100 virtual subjects.

In state space form, the model can be represented as:

$$\begin{cases} \bar{x}(k+1) = A\bar{x}(k) + B_i\bar{i}(k) + B_m\hat{m}(k) + B_c c(k) \\ \bar{g}(k) = C\bar{x}(k) \end{cases} \tag{A.1}$$

The state vector, $\bar{x}(k) \in \mathbb{R}^{13}$, is the deviation of the state of the system $x(k)$ from the operating point around which the model was linearized, x_{eq}. The output variable, $\bar{g}(k) \in \mathbb{R}$ (mg/dl), is the deviation of glucose levels $g(k)$ from a patient-specific, fictitious equilibrium point G_b, called basal glucose.

The variable $\bar{i}(k) \in \mathbb{R}$ (pmol/kg/min) is the normalized insulin administration, defined as

$$\bar{i}(k) = \frac{i(k) - i_b(k)}{BW}; \tag{A.2}$$

where $i(k) \in \mathbb{R}$ (pmol/min) is the total insulin administration, $i_b(k) \in \mathbb{R}$ (pmol/min) is patient's basal insulin administration and BW (Kg) is patient's body weight. The difference $i(k) - i_b(k)$ accounts for all insulin administration exceeding basal needs, e.g., prandial or corrective boluses.

The variable $\hat{m}(k) \in \mathbb{R}$ (mg/min) represent the announced meal intake, i.e., the CHO content of the meal as estimated by patients. This variable could be affected by counting errors.

The variable $c(k)$ represents HTs suggestions. By expressing $c(k)$ as the linear combination of mutually exclusive binary variables, it is constrained to only assume values in Γ. At difference with $\bar{i}(k)$ and $\hat{m}(k)$, $c(k)$ can be manipulated by the algorithm to mitigate hypoglycemic events.

The system in (A.1) is both stabilizable and detectable.

Appendix B. Tuning the Kalman filter

The prediction of future glycemic levels in (2) is obtained via forward simulation from an estimate of the current system state, $\hat{x}(k) \in \mathbb{R}^{13}$, and by no meal consumption and basal insulin infusion along the PH (see Appendix C). The state estimate is obtained, at each sampling instant, by relying on a Kalman Filter. Following [48], the measurement noise covariance matrix is set to $\Sigma_v = 9.8496\ \text{mg}^2/\text{dl}^2$. The process noise covariance matrix $\Sigma_w \in \mathbb{R}^{13\times 13}$ is a diagonal matrix whose diagonal elements $w_1, \dots, w_{13}$ are reported in Table B.3.

Table B.3
Diagonal values of the matrix Σ_w employed in the Kalman Filter.

Elements	Value [%]	Measurement unit
w_1, w_2, w_3	0.1	mg^2
w_4, w_5	10	mg^2/kg^2
w_6, w_7, w_8	0.1	pmol^2/l^2
$w_9, w_{10}, w_{11}, w_{12}$	0.1	$\text{pmol}^2/\text{kg}^2$
w_{13}	10	mg^2/dl^2

Appendix C. Condensing

Let k be the current instant. By leveraging the state evolution law described in (A.1), any future glycemic value $\bar{g}(k+j)$, with $j = 1, \dots, N-1$, can be iteratively predicted from the current state estimate $\hat{x}(k)$ as:

$$\bar{g}(k+j) = CA\hat{x}(k+j) + \\ + \sum_{n=0}^{j-1} CA^{j-n-1}(B_i\bar{i}(k+n) + B_m\hat{m}(k+n) + B_c c(k+n)), \tag{C.1}$$

that in matrix notation reads

$$\mathcal{G}(k) = \mathcal{A}\hat{x}(k) + \mathcal{B}_i\mathcal{I}(k) + \mathcal{B}_m\mathcal{M}(k) + \mathcal{B}_c\mathcal{C}(k) \tag{C.2}$$

where

$$\mathcal{G}(k) = \begin{bmatrix} \bar{g}(k) \\ \vdots \\ \bar{g}(k+N-1) \end{bmatrix}, \quad \mathcal{A} = \begin{bmatrix} CA \\ \vdots \\ CA^N \end{bmatrix},$$

$$\mathcal{B}_i = \begin{bmatrix} CB_i & 0 & \dots & 0 \\ CAB_i & CB_i & \ddots & 0 \\ \vdots & \ddots & \ddots & 0 \\ CA^N B_i & CA^{N-1}B_i & \dots & CB \end{bmatrix},$$

$$\mathcal{B}_m = \begin{bmatrix} CB_m & 0 & \dots & 0 \\ CAB_m & CB_m & \ddots & 0 \\ \vdots & \ddots & \ddots & 0 \\ CA^N B_m & CA^{N-1}B_m & \dots & CB_m \end{bmatrix},$$

$$\mathcal{B}_c = \left[\gamma_1\bar{\mathcal{B}}_c, \quad \dots, \quad \gamma_{N_{HT}}\bar{\mathcal{B}}_c\right],$$

$$\bar{\mathcal{B}}_c = \begin{bmatrix} C\bar{B}_c & 0 & \dots & 0 \\ CA\bar{B}_c & C\bar{B}_c & \ddots & 0 \\ \vdots & \ddots & \ddots & 0 \\ CA^N\bar{B}_c & CA^{N-1}\bar{B}_c & \dots & C\bar{B}_c \end{bmatrix},$$

$$\mathcal{I}(k) = \begin{bmatrix} \bar{i}(k) \\ 0 \\ \vdots \\ 0 \end{bmatrix}, \quad \mathcal{M}(k) = \begin{bmatrix} \hat{m}(k) \\ 0 \\ \vdots \\ 0 \end{bmatrix},$$

and $\mathcal{C}(k)$ defined as in (6). As insulin boluses and meal intake are rare events during the day, the vectors $\mathcal{I}(k)$ and $\mathcal{M}(k)$ are supposed to be 0 in the PH - with the only exception of insulin boluses administered and meals announced at the current instant k ($\bar{i}(k)$ and $\hat{m}(k)$, respectively).

The cost function in (2) can then be reformulated in matricial notation as:

$$J = (\mathcal{G} - \mathcal{G}_0)^T\mathcal{Q}(\mathcal{G} - \mathcal{G}_0) + \mathcal{C}^T\mathcal{C} \tag{C.3}$$

where

$$\mathcal{Q} = \begin{bmatrix} q & 0 & \dots & 0 \\ 0 & q & & \vdots \\ \vdots & & \ddots & 0 \\ 0 & \dots & 0 & q \end{bmatrix}, \quad \mathcal{G}_0 = \begin{bmatrix} g_0(k) \\ \vdots \\ g_0(k+N-1) \end{bmatrix}.$$

By substituting (C.2) in (C.3), we obtain:

$$\begin{aligned} J =&(\mathcal{A}\hat{x}(k) + \mathcal{B}_i\mathcal{I}(k) + \mathcal{B}_m\mathcal{M}(k)+ \\ &+ \mathcal{B}_c\mathcal{C}(k))^T\mathcal{Q}(\mathcal{A}\hat{x}(k) + \mathcal{B}_i\mathcal{I}(k)+ \\ &+ \mathcal{B}_m\mathcal{M}(k) + \mathcal{B}_c\mathcal{C}(k)) + \mathcal{C}(k)^T\mathcal{C}(k). \end{aligned} \tag{C.4}$$

This can be expressed in a classical integer quadratic program form as:

$$J = \frac{1}{2}\mathcal{C}(k)^T H\mathcal{C}(k) + h^T\mathcal{C}(k), \tag{C.5}$$

with

$$H = \mathcal{B}_c^T\mathcal{Q}\mathcal{B}_c + I$$

$$h = (\mathcal{A}\hat{x}(k) + \mathcal{B}_i\mathcal{I}(k) + \mathcal{B}_m\mathcal{M}(k) - \mathcal{G}_0)^T\mathcal{Q}\mathcal{B}_c$$

and I being an identity matrix of appropriate size.

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