# Advanced Insulin Bolus Advisor Based on Run-To-Run Control and Case-Based Reasoning

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***Abstract*—This paper presents an advanced insulin bolus advisor for people with diabetes on multiple daily injections or insulin pump therapy. The proposed system, which runs on a smartphone, keeps the simplicity of a standard bolus calculator while enhancing its performance by providing more adaptability and flexibility. This is achieved by means of applying a retrospective optimization of the insulin bolus therapy using a novel combination of run-to-run (R2R) that uses intermittent continuous glucose monitoring data, and case-based reasoning (CBR). The validity of the proposed approach has been proven by *in-silico* studies using the FDA-accepted UVa-Padova type 1 diabetes simulator. Tests under more realistic *in-silico* scenarios are achieved by updating the simulator to emulate intrasubject insulin sensitivity variations and uncertainty in the capillarity measurements and carbohydrate intake. The CBR(R2R) algorithm performed well in simulations by significantly reducing the mean blood glucose, increasing the time in euglycemia and completely eliminating hypoglycaemia. Finally, compared to an R2R stand-alone version of the algorithm, the CBR(R2R) algorithm performed better in both adults and adolescent populations, proving the benefit of the utilization of CBR. In particular, the mean blood glucose improved from $166 \pm 39$ to $150 \pm 16$ in the adult populations ($p = 0.03$) and from $167 \pm 25$ to $162 \pm 23$ in the adolescent population ($p = 0.06$). In addition, CBR(R2R) was able to completely eliminate hypoglycaemia, while the R2R alone was not able to do it in the adolescent population.**

***Index Terms*—Artificial intelligence, decision support systems, diabetes, iterative learning control, knowledge-based systems, run-to-run control.**

## I. Introduction

TYPE 1 diabetes mellitus (T1DM) is a chronic metabolic disease characterized by an autoimmune destruction of the insulin-secreting $\beta$-cells of the endocrine pancreas. The resulting absolute insulin deficiency results in hyperglycemia [i.e., high blood glucose (BG)]. At present, the majority of people with T1DM control their BG levels through multiple daily injections (before meals and basally) in order to mimic the natural insulin secretion of the pancreatic $\beta$-cells and by drawing blood from the fingertips and testing the glucose level with an electronic glucose meter (self-monitoring of BG) [1], [2]. An alternative therapy to multiple daily injections is provided by continuous subcutaneous insulin infusion (insulin pump therapy), which allows variable basal rates of insulin and avoids multiple uncomfortable injections.

Large intervention trials [3] have shown that tight glycaemic control prevents long term micro- and macrovascular complications, at the expense of an increased frequency of hypoglycaemia, highlighting the importance of optimizing insulin doses throughout the day, reducing diabetes complications which place a heavy burden on health services [2]. Bolus insulin doses with meals are calculated by estimating carbohydrate intake, dividing by a fixed carbohydrate: insulin ratio and adding a correction dose derived from the individuals insulin sensitivity factor. To automate this process, several algorithms have been developed [5]–[9]. However, with exception of insulin bolus calculators incorporated in most of the commercially available insulin pumps and in some glucose meters [9], none of these algorithms have been adopted commercially. This lack of commercialization is partly down to economic risk, security issues, and inertia to change [10], but the main reason for the lack of available systems is the relatively small therapeutic benefit achieved by these systems compared with the significant burden required by the users. For this reason, additional effort toward more intelligent autonomous systems is required.

The clinical benefit of run-to-run (R2R) control for automatically adjusting the insulin-to-carbohydrate ratio (ICR) parameter of a bolus calculator has been studied with some initial promising results [11]. However, its applicability is limited by the assumption of strict repetitiveness in the daily routine of people with T1DM.

This paper presents an innovative decision support algorithm for meal insulin dosing that provides enhanced adaptability and flexibility to current bolus calculators by using R2R control [12] and case-based reasoning (CBR) [13]. It is important to note that, unlike existing closed-loop control algorithms for glucose control [14]–[16], which deliver an insulin dose every 5 min based on a real-time optimization, our proposed algorithm is a decision support system providing bolus insulin dose recommendations based on retrospective optimization, which requires approval by the user. The validity of the presented algorithm is demonstrated through an *in-silico* study using the UVa-Padova T1DM simulator [17], which has been modified to incorporate intrasubject variability, noise in the capillary blood measurements, and uncertainty in the carbohydrate intake. This algorithm has

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now been integrated into a user-friendly smartphone platform for use by subjects with diabetes in a clinical trial.

## II. Methods

### A. Insulin Bolus Calculators

Insulin bolus calculators are simple decision support systems incorporated in most of the commercially available insulin pumps [9], and more recently available within capillary BG monitors [18]. These calculators consist of a relatively simple formula [see (1)] that uses subject-specific metabolic parameters to calculate an insulin dose. The standard bolus calculator is described as

$$B = \frac{\mathrm{CHO}}{\mathrm{ICR}} + \frac{G - G^T}{\mathrm{ISF}} - \mathrm{IOB} \tag{1}$$

where $B$ is the recommended dose of insulin (IU) to be taken; CHO is the total amount of carbohydrate in the meal (gram), ICR is the insulin-to-carbohydrate ratio (g/IU), which describes how many grams correspond to one unit fast acting insulin; $G$ is the current capillary BG level (mg/dL); $G^T$ is the target BG level (mg/dL); ISF is the insulin sensitivity factor (mg/l/IU), which is a personal relation describing how large a drop in BG one unit of insulin gives rise to; and IOB is the insulin-on-board, which describes the amount of insulin still in the body from previous injections. Different formulas are being used by different manufacturers to estimate IOB (e.g., linear or curvilinear), being the linear estimation the simplest one and described as

$$\mathrm{IOB} = B_{k-1}\left(1 - \frac{t - T_B}{T_{\mathrm{IOB}}}\right) \tag{2}$$

where $B_{k-1}$ is the previously administered bolus, $t$ is the time that IOB wants to be estimated, $T_B$ is the time the bolus was administered, and $T_{\mathrm{IOB}}$ is a predefined interval during which the administered insulin is supposed to be active (e.g., 6 h).

It is important to note that parameters ISF and ICR are usually not constant and may vary depending on parameters such as circadian rhythms, physical activity levels, hormone cycles, psychological stress, alcohol consumption, and recurrent illness. Although some of the most recent commercially available bolus calculators [18] allow considering some of these effects (e.g., exercise and stress), this feature is rarely used due to the significant burden that represents. Although the clinical benefit of using bolus calculators has been demonstrated [19], [20], their performance remains suboptimal and to achieve a significant improvement in glycemic control, a more dynamic, personalized, intelligent system is required. For this purpose, the utilization of iterative learning control and CBR is proposed.

### B. R2R Control

R2R is a control method designed to exploit repetitiveness in the process that is being controlled [12]. Its purpose is to enhance performance, using a mechanism of trial and error. Owens *et al.* [8] used this idea to exploit the repetitive nature of the insulin therapy regimen of the diabetic patient. This algorithm uses an update law that corrects the ICR of (1) for the next day based on a performance metric used to evaluate the postprandial glucose excursion.

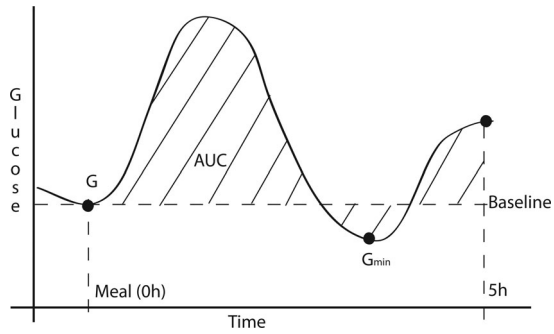


Fig. 1. Graphical representation of the postprandial glucose area under the curve (AUC) (i.e., striped area). Horizontal dashed line represents the baseline to calculate the AUC. Vertical dashed line represents the meal ingestion time (0 h) and the 5 h postprandial period. $G$ is the BG value at the time of meal ingestion (0 h) and $G_{\mathrm{min}}$ is the minimum glucose values during the postprandial excursion (5 h).

A pilot clinical study showed the efficacy of the R2R algorithm in T1DM subjects [11]. However, the R2R algorithm presents some limitations that may restrict its scope of applicability. First of all, the algorithm requires two capillarity BG samples to evaluate the postprandial excursion. On top of the burden that this represents to the subject, the postprandial excursion of a mixed meal depends on the composition, and these two measurement points may not be valid to evaluate certain meals. Then, R2R assumes that the insulin therapy regimen of the person with T1DM is repetitive, which is somewhat unrealistic in many cases. It is important to note that the original R2R algorithm [11] only distinguishes between three situations (breakfast, lunch, and dinner). Therefore, the utilization of the R2R algorithm may be limited to subjects willing to carry out at least nine capillarity measurements per day and with a very repetitive daily routine.

### C. R2R Using Continuous Glucose Monitoring (CGM) Data

In this study, we propose a new version of the R2R algorithm that uses CGM data [21] to eliminate the need of the two postprandial measurements. Instead, the postprandial area under the curve calculated using CGM data is employed. The new update law to adjust the bolus calculator parameters ICR is as follows:

$$\mathrm{ICR}_{k+1} = \mathrm{ICR}_k + K(\mathrm{AUC}^r - \mathrm{AUC}_k) \tag{3}$$

where $K$ is a tunable gain that represents the aggressiveness of adaptation of the R2R control algorithm; subindex $k+1$ indicates the updated ICR and subindex $k$ the previous ICR; $\mathrm{AUC}_k$ is the postprandial glucose area under the curve (e.g., at 5 h) and $\mathrm{AUC}^r$ is the reference glucose area under the curve (i.e., target), which should be determined by an expert based on retrospective CGM data or a meal tolerance test data. As depicted in Fig. 1, the AUC is calculated considering the preprandial capillarity glucose measurement ($G$) as the baseline.

It is important to note that this update law is based on the hypothesis that AUC is reasonably linear with respect to the

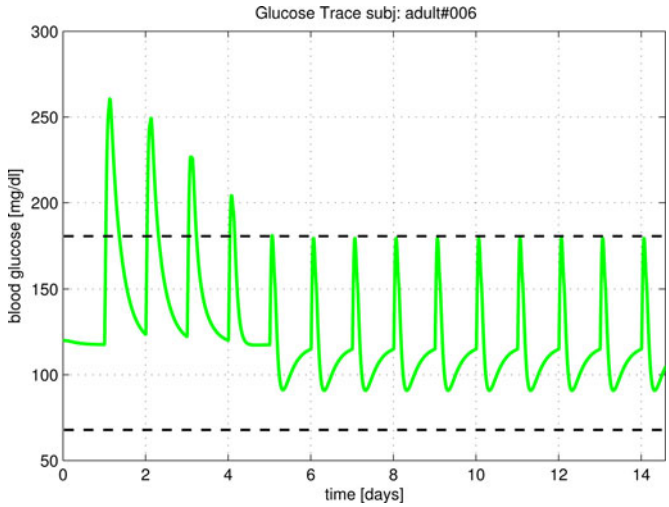


Fig. 2. Glucose concentration resulting from applying the proposed R2R algorithm over 14 days (single meal) on subject adult 6 of the T1DM simulator with an initial nonoptimal ICR. Upper and lower dashed lines indicate hyper-/hypoglycemia limits (i.e., target zone).

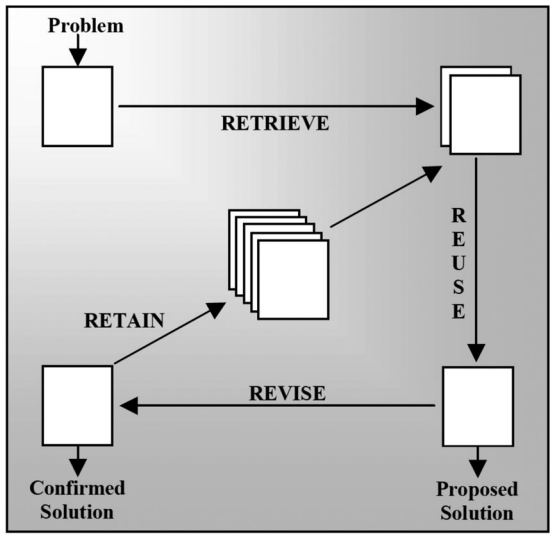


Fig. 3. CBR cycle proposed by Aamodt and Plaza [14].

amount of ingested carbohydrates. This hypothesis has been proven to be satisfied for small to moderate carbohydrate loads (e.g., CHO $< 80$ g) [22], and it is also satisfied in the T1DM simulator [18], even if the meal compositions are different.

Thus, for a known glucose area under the curve $\mathrm{AUC}_1$ corresponding to an amount of carbohydrates $\mathrm{CHO}_1$, it is possible to estimate the area under the curve $\mathrm{AUC}_2$ corresponding to a carbohydrate load $\mathrm{CHO}_2$ using the following linear relation:

$$\mathrm{AUC}_2 = \frac{\mathrm{AUC}_1 \cdot \mathrm{CHO}_2}{\mathrm{CHO}_1}. \tag{4}$$

Fig. 2 shows an *in-silico* example of utilization of the proposed R2R algorithm, where the ICR of a virtual subject from the T1DM simulator is initialized to a nonoptimal value, and it converges toward an optimal value and remains stable in the glucose target zone (i.e., [70, 180] mg/dl).

Although our novel R2R algorithm already provides more flexibility in front of different meal composition than the original R2R, this may not be enough to deal with intrasubject insulin sensitivity variations due to perturbations such as exercise, physiological stress, hormone cycles, or alcohol consumption. For this reason, we propose the utilization multiples incidences of the R2R algorithm for each one of the situations that a subject with T1DM can face (e.g., early high glycemic breakfast with moderate postexercise). It is worth noting that, even if a R2R instance for current situation does not exist, a similar instance could be employed. Dealing with all these possible instances can be very challenging due to the high combinatorial complexity. For this reason, we proposed the utilization of CBR.

### *D. Case-Based Reasoning*

CBR [23] is an artificial intelligence technique, which has been extensively applied in medicine [24]. CBR tries to solve newly encountered problems by applying the solutions learned from solving similar problems encountered in the past. This is equivalent to the way a human might solve a problem, recalling a problem encountered in the past and, depending on whether the solution was successful or unsuccessful, either applying or avoiding that solution for the current situation. In CBR, past situations are stored in cases, which contain knowledge related to the various aspects of the situation. A case consists of three major parts: the problem description, the solution to the problem, and the outcome [23]. According to Aamodt and Plaza [13], general CBR consists of four steps, as summarized below and, illustrated in Fig. 3.

1) *Retrieve* the most similar case(s) from a case base.
2) *Reuse* the information and knowledge in that case(s) to solve the problem.
3) *Revise* the proposed solution based on the obtained outcome.
4) *Retain* the parts of this experience likely to be useful for future problem solving.

The use of CBR for diabetes has been centred on the prognosis and risk of developing diabetes [25]. The first project to use CBR for recommending an insulin dose in diabetes management was the Telematic Management of Insulin-Dependent Diabetes Mellitus project [26], where a CBR engine was integrated with a rule-based reasoning engine and a probabilistic model of the effects of insulin on BG levels. More recently, the 4 Diabetes Support System (4DSS) project [27] used CBR as the primary reasoning modality in a decision support tool for patients on insulin pump therapy, and introduced other factors into the calculations, such as life events that can influence BG levels. However, both systems were focused on providing decision support to the physicians using retrospective data and not real-time decision support for people with diabetes. In this study, we propose to use CBR technology to provide to an insulin bolus calculator the required flexibility and adaptability in diabetes management.

## III. CBR(R2R) Algorithm

The proposed CBR algorithm is as follows. A case is defined by the triplet

$$\mathbf{C}: = \{\mathbf{P}, \mathbf{S}, \mathbf{O}\} \tag{5}$$

where $\mathbf{P}$ is a set of parameters describing the problem (i.e., meal insulin dose calculation), $\mathbf{S}$ is the solution to the problem (i.e., insulin dose), and $\mathbf{O}$ is the outcome of applying the solution $\mathbf{S}$ to the problem described by $\mathbf{P}$ (i.e., postprandial excursion evaluation).

Cases are stores in a case base defined as

$$\mathbf{CB} := \{\mathbf{C_1}, \ldots, \mathbf{C_k}, \ldots, \mathbf{C_n}\} \tag{6}$$

where $\mathbf{C_k}$ is the case $k$ in the case base. It is important to note that the case base is individualized for each subject.

### A. Case Parameters

Among the parameters describing the problem of calculating the insulin dose to cover the ingestion of a meal, we find parameters such as time of ingestion, glucose concentration, meal information, physical activity, insulin-on-board, psychological stress, illness, alcohol consumption, and hormone cycles. Although all these parameters may have an influence when calculating an insulin dose, the utilization of a T1DM simulator for testing the validity of the proposed algorithm limited the number of parameters that could be considered. The parameters that could be taken into account are described by

$$\mathbf{P} := \{T, G, \mathrm{CHO}, E, \mathrm{IOB}\} \tag{7}$$

where $T$ is the time of the day; $G$ is the capillary BG concentration from a capillary measurement at the time of meal intake; CHO is the estimated amount of ingested carbohydrate, and $E$ is an external perturbation, such as physical activity; IOB is an estimation of the insulin on board.

*1) Case Solution:* The solution $\mathbf{S}$ of a case are the parameters of the bolus calculator and is represented as

$$\mathbf{S} := \{\mathrm{ICR}, \mathrm{ISF}\} \tag{8}$$

where ICR is the ICR and ISF is the insulin sensitivity factor reported in (1).

### B. Case Outcome

The outcome $\mathbf{O}$ of the solution $\mathbf{S}$ is defined as

$$\mathbf{O} := \{\mathrm{AUC}, G_{\min}\} \tag{9}$$

where AUC is the area under the curve of the 5-h postprandial glucose excursion, and $G_{\min}$ is the minimum postprandial glucose value, both calculated using a CGM (see Fig. 1).

### C. Retrieving Step

As stated in Section II-D, the first step of the CBR cycle consists of retrieving the most similar case from the case base ($\mathbf{CB}$). Many different techniques have been proposed for retrieving cases from a case library [28]. The retrieving mechanism chosen in the current application is based on a weighted average distance function defined as

$$D = \frac{K_{P_1} d_{P_1} + \cdots + K_{P_j} d_{P_j} + \cdots + K_{P_n} d_{P_n}}{K_{P_1} + \cdots + K_{P_j} + \cdots + K_{P_n}} \tag{10}$$

where

$$d_{P_j} = \frac{abs(P_{j_k} - P_j)}{[P_j]} \tag{11}$$

where $P_j$ is a parameter from the current problem, $P_{j_k}$ is the corresponding parameter of the retrieved case $k$ from the case memory, $K_{P_j}$ is a weight associated to the parameter $P_j$, which needs to be *a priori* specified by an expert, and allows to assign the importance of a parameter on the retrieving procedure, and $[P_j]$ is the range of feasible values for $P_j$. Note that some of these ranges may be subject specific and need to be defined *a priori* based on retrospective data. Then, the case from the case library corresponding to the minimum distance $D$ is the retrieved case.

Although five parameters have been selected to describe a case (7), not all of them are required in the retrieving phase. The only parameters to be considered when comparing them are the ones that are not used in the bolus calculator formula (1), which correspond to the parameters that have an influence on the insulin sensitivity and consequently on the solution of the case (ICR and ISF). These parameters are: time of meal ingestion ($T$) and physical activity ($E$). Although these parameters have a continuous range of variability (e.g., 0–24 h), for the sake of simplicity and practicality, they were discretised as follows:

1) T:= {breakfast, lunch, dinner}.
2) E:= {none, moderate, intense}.

The decision to categorically divide the parameters into three parts is motivated by the desire to avoid generating too many cases because then the system would be very difficult to maintain. However, the number of divisions and their categorical labeling is something that can be easily customized and personalized, since for certain subjects we may have more divisions (e.g., subjects enjoying different types of sports). Although the same parameter value (e.g., moderate exercise) can have a completely different effect on different subjects, the fact that the case base is individualized makes that the only point that is important is that the parameter is consistently reported.

Finally, the distance ($d_{P_j}$) is defined to be equal to 0, 1, or 2 depending on if the values of the compared parameters are the same (e.g., breakfast and breakfast), adjacent (e.g., breakfast and lunch), or nonadjacent (e.g., breakfast and dinner); and the range is 2 for both parameters. The weights for the selected parameters are referred to as $K_T$ and $K_E$ and reported in Table III.

### D. Reusing Step

Reusing the retrieved solution to solve the current problem is done by applying the bolus calculator formula stated by (1). However, in order to robustify the algorithm, the hyperglycaemia correction bolus corresponding to the second term of (1) is only applied when the preprandial capillary glucose levels ($G$) are above or below predefined hyperglycaemia ($G^H$) and hypoglycaemia thresholds ($G^L$).

### *E. Revising Step*

The revising step consists of updating the solution $\{\mathrm{ICR}, \mathrm{ISF}\}$ of the retrieved case when the obtained outcome $\{\mathrm{AUC}, G_{\min}\}$ is not considered satisfactory. Such update rule is summarized as follows.

If the following condition is satisfied

$$G_{\min} \leq G^L \tag{12}$$

then, ICR is updated as

$$\mathrm{ICR}_{k+1} = \mathrm{ICR}_k \cdot \frac{G^L}{G_{\min}} \tag{13}$$

where the subindices $k$ and $k+1$ indicate the current and updated ICR values, respectively. Otherwise, if the following condition is satisfied

$$(G^L < G \leq G^H) \ \wedge \ \mathrm{AUC}_k \notin \left[\frac{\mathrm{AUC}^r}{\mathrm{Tol}}, \ \mathrm{AUC}^r \cdot \mathrm{Tol}\right] \tag{14}$$

where $G$ is the premeal capillary BG measurement and Tol is a tolerance parameter to avoid unnecessary revisions due to error measurements and uncertainty in the inputs, then, ICR is revised using the update rule described by (3).

If none of the previous conditions holds true, no adaptation of ICR is carried out. It is important to note that the reason why no adaptation of ICR is done when the condition $(G^L < G \leq G^H)$ does not hold is because a correction bolus is delivered together with the meal bolus (see Section III-D). Hence, the nonoptimal outcome cannot be only associated to a nonoptimal ICR, but also to a nonoptimal ISF.

In order to provide robustness to the algorithm in front of measurement noise and manual input uncertainty (e.g., CHO estimation), (14) is required to be satisfied two consecutive times for the same case in order to be able to update ICR using (3). For this purpose, a counter associated to each case is employed which is increased by one each time (14) is satisfied and set to zero if not.

Finally, parameters ISF (mg/l/IU) is updated based on the correlation with ICR (g/IU) reported in [30]. This correlation is described by

$$\mathrm{ISF} = 4.44 \cdot \mathrm{ICR}. \tag{15}$$

### *F. Retaining Step*

When no similar case to the problem being solved is found in the case base, a new case is created with a predefined solution. This new case is then incorporated into the case base for further optimization and utilization.

### *G. Safety Constraints*

To prevent insulin overdosing, two constraints were incorporated to avoid an excessive update of the solution $\mathrm{ICR}ICR_{k+1}$ calculated by (3). The first constraint limits its increment (or decrement) as follows:

$$\mathrm{ICR}_{k+1} = \min(\mathrm{ICR}_{k+1}, \ \mathrm{ICR}_k + S \cdot C \cdot \mathrm{ICR}_0) \tag{16}$$

where $C$ is a tuning constant (see Table III), subindex 0 refers to initialization value, min is the minimum function, and $S$ is the sign function defined as $S = \mathrm{sgn}(\mathrm{ICR}_{k+1} - \mathrm{ICR}_k)$. Then, another constraint limits the minimum and maximum values of ICR can take as follows:

$$\mathrm{ICR}_k = \min(\max(\mathrm{ICR}^m, \ \mathrm{ICR}_k), \ \mathrm{ICR}^M) \tag{17}$$

where the superindexes $m$ and $M$ refer to the minimum and maximum predefined values, and $\min$ and $\max$ are minimum and maximum functions (see Table III).

TABLE I
VARIABILITY ON MEAL INGESTION TIME AND CARBOHYDRATE LOAD

| | Breakfast | Lunch | Dinner |
|---|---|---|---|
| Time | [6 am, 8 am] | [12, 2 pm] | [8 pm,10 pm] |
| CHO (grams) | [30–50] | [40–70] | [30–60] |

## IV. *In-Silico* TESTING

The commercial version of the UVa-Padova T1DM simulator [17] was used to test the presented CBR(R2R) algorithm. Ten adult subjects and ten adolescent subjects were used for this purpose. The ten paediatric subjects available in the simulator, which have rarely been used in previous studies [30], [31], were not taken into consideration due to their extreme glucose dynamics. The chosen basal insulin infusion rate for the *in-silico* subjects was the one provided by the default insulin therapy of the simulator. The selected CGM and insulin pump models to perform the simulations were the Abbot Freestyle Navigator and Deltec Cozmo.

### *A. In-Silico Protocol*

A scenario of one-month duration with realistic variability in meal times (i.e., breakfast, lunch, and dinner) and carbohydrate intakes was automatically generated. Table I shows the upper and lower bounds of such variability.

Since the T1DM simulator does not incorporate intrasubject variability of insulin sensitivity [32] and the effect of physical activity, such changes were artificially introduced by multiplying the insulin delivery (i.e., bolus and basal) by correction gains (18) and (19). Insulin sensitivity was considered to vary along the day following the standard patterns used clinically to adjust basal insulin rates [33]. Furthermore, insulin sensitivity was considered to randomly change along the day in order to simulate changes in lifestyle such as physical exercise and stress

$$B^d = B \cdot K_D, \tag{18}$$

$$BA^d = BA \cdot K_D \cdot K_A \tag{19}$$

where $B$ and $BA$ are calculated bolus and default basal insulin, superindex $d$ indicates delivered; $K_D$ is a gain to simulate intraday variability, which takes the values shown in Table II, and $K_A$ is a gain to simulate interday variability, which randomly takes a value from the interval $[1; 0.8, 1.2]$ every day.

TABLE II
VALUES AND TIME INTERVALS FOR GAIN $K_D$

| | 12 am–4 am | 4 am–10 am | 10 am–6 pm | 6 pm–12 am |
|---|---|---|---|---|
| $K_D$ | 0.7 | 1 | 1.5 | 2.5 |

TABLE III
PARAMETERS VALUES USED FOR THE *In Silico* TESTING OF THE CBR(R2R) ALGORITHM

| $Tol$ | $K$ | $C$ | $\mathrm{ICR^m}$ | $\mathrm{ICR^M}$ | $T_{\mathrm{IOB}}$ |
|---|---|---|---|---|---|
| 1.3 | 0.002 | 0.3 | $0.2 \cdot \mathrm{ICR}_0$ | $4 \cdot \mathrm{ICR}_0$ | 6 h |
| $G^T$ | $G^L$ | $G^H$ | $K_T$ | $K_E$ | |
| $120 \frac{mg}{dL}$ | $80 \frac{mg}{dL}$ | $180 \frac{mg}{dL}$ | 1 | 1 | |

### B. Measurement Errors and Uncertainty

Real-time continuous glucose measurements obtained from the T1DM simulator were used to determine $G_{\min}$ and AUC values. Capillary glucose measurements ($G$) were generated by adding a $5\%$ error (uniform distribution) to the plasma glucose value generated by the T1DM simulator. The selected $5\%$ error was based on the American Diabetes Association recommendation of $CV < 5\%$ bias [34]. Finally, because subjects with T1DM introduce significant errors when counting carbohydrates, a $20\%$ error (uniform distribution) was considered in the estimation of carbohydrates.

### C. Tuning and Initialization

Reference area under the curve parameter ($\mathrm{AUC}_r$) was individually determined using a meal tolerance test functionality provided by the T1DM simulator, which allows obtaining an optimal postprandial glucose excursion. In a real clinical setting, this parameter could be determined by a clinical expert based on retrospective CGM data or a meal tolerance test data. The gain $K$ was tuned to converge toward the solution in a reasonable time frame (e.g., 1 week); the selection of the values for the remaining parameters, which were the same for all subjects, was based on the combination of multiple simulations and clinical knowledge. Note that, in a clinical setting, the gain $K$ could be calculated using linear regression to best match the clinically determined dose adjustment as proposed in [11]. Parameter Tol was chosen to cope with the error due to the CGM sensor, and parameters $G^T$, $\mathrm{ICR}^m$, $\mathrm{ICR}^M$, $G^L$, $G^H$, $K_T$, and $K_E$ were selected based on clinical expertize. Finally, parameter $T_{\mathrm{IOB}}$ was selected based on the values reported by different pump manufacturers (i.e., 2 h $\leq T_{\mathrm{IOB}} \leq$ 7 h). Although this parameter may have a significant intrasubject and intersubject variability, a conservative value of 6 h was selected for all subjects.

Table III shows the values for these parameters. The parameter $\mathrm{ICR}_0$ was initialized to a nonoptimal value obtained multiplying by 2 the default subject-specific ICR value provided by the T1DM simulator, which allows us to achieve optimal glycemic control.

### D. Safety and Efficacy Measures

The following safety and efficacy measures [36] (presented as Mean $\pm$ Standard Deviation) were used: The primary outcome was mean BG (mg/dL); secondary outcomes were percentage of time and incidence below range (any $\mathrm{BG} < 70$ mg/dL), percentage of time within the 70–180 mg/dL target range, percentage of time above range in hyperglycemia ($\mathrm{BG} > 180$ mg/dL), and BG risk index and risk zones of the control variability grid analysis (CVGA) [37]. CVGA is a method for visualization of the extreme glucose excursions caused by a control algorithm in a group of subjects, with each subject presented by one data point for any given observation period. CVGA is divided into nine zones (A, B, lower-B, upper-B, lower-C, upper-C, lower-D, upper-D, E), being zones A+B (including lower and upper) considered as optimal control and zones D+E considered as suboptimal control.

## V. RESULTS

### A. Convergence Analysis

In their work [9], Owen *et al.* proposed a convergence analysis for their R2R algorithm. However, the same analysis cannot be directly applied to the presented CBR(R2R) algorithm due to the different nature of the algorithms, i.e., addition of a CBR algorithm. Nevertheless, it is important to note that CBR(R2R) is equivalent to multiple incidences of an R2R algorithm. Therefore, by assuming that the information provided to the CBR(R2R) algorithm is within realistic limits of uncertainty, which allow to correctly retrieve the correct case from the case base, the convergence analysis of CBR(R2R) is reduced to the analysis of a single incidence of R2R. Therefore, if the proposed R2R algorithm is proven to converge, the CBR(R2R) algorithm is, by extension, also convergent. To carry out a convergence analysis of the R2R algorithm, a scenario containing one meal with carbohydrate load variability of [40, 60] gram (uniform distribution) was employed. The initial BG was randomly selected within the range [70,140] mg/dl (uniform distribution). The analysis was performed by isolating the parameters CHO, capillary BG and CGM measurements while adding different levels of uncertainty to these parameters. Unlike the convergence analysis proposed in [8], we considered uncertainties within their realistic bounds and the combination of such uncertainties. The initial $\mathrm{ICR}_0$ for the R2R algorithm was randomly selected within a range of $[0.25 \cdot \mathrm{ICR},\ 4 \cdot \mathrm{ICR}]$ (uniform distribution), where ICR is the optimal ICR provided by the T1DM simulator. Table IV shows the performance of the R2R algorithm for each case study after 20 iterations together with the results for a bolus calculator without adaptation. For this purpose, the ten adult subjects of the T1DM simulator were employed. It can be seen that the algorithm is capable to converge to the target range, i.e., [70, 180] mg/dl, even when significant levels of uncertainty are added. Finally, no significant variability was observed on the number of iterations needed to converge to the glucose target range for the selected levels of uncertainty.

TABLE IV
CONVERGENCE ANALYSIS

| | % time in target | Iterations to reach 90% time in target |
|---|---|---|
| Bolus Calculator | 63.8±26.3 | - |
| R2R | | |
| No Uncertainty | 100.0±0.0 | 5.3±5.4 |
| CHO 10% | 99.0±3.3 | 5.2±5.1 |
| CHO 20% | 98.3±5.3 | 4.1±4.7 |
| CHO 30% | 97.6±5.3 | 3.3±3.1 |
| Capillary BG 5% | 100.0±0.0 | 3.5±3.2 |
| Capillary BG 10% | 98.2±5.6 | 4.3±4.3 |
| Capillary BG 15% | 98.1±4.2 | 4.5±4.2 |
| CGM (Freestyle Navigator) | 98.9±3.3 | 3.6±3.3 |
| CHO 20% + BG 5% + CGM | 98.5±3.2 | 3.4±2.7 |

### *B. CBR(R2R) In-Silico Validation*

The CBR(R2R) algorithm was evaluated using the one-month scenario presented in Section IV-A and four simulation runs. First of all, an initial simulation run (Run 1) was carried out using the bolus calculator formula (1) with nonoptimal parameters (ICR and ISF) and without any adaptation. Run 2 consisted of applying the CBR(R2R) algorithm with a case base containing a unique case with the same solution as the bolus calculator. Runs 3 and 4 were like Run 2, but starting from the case base generated in the corresponding previous runs. In order to evaluate the benefit of enhancing the R2R algorithm with CBR, the R2R algorithm in a stand-alone mode was executed in the same scenario. For this purpose, the R2R algorithm in a stand-alone mode was configured with three instances of the algorithm corresponding to breakfast, lunch, and dinner.

Tables V and VI show the simulation results corresponding to four runs of the R2R algorithm in a stand-alone mode and the CBR(R2R) algorithm, respectively. Results are presented as mean $\pm$ 1 standard deviation. Improvement on mean BG levels, percentage of time in hyper-/hypoglycaemic range, risk index, as well as percentage in risk zones A + B and D + E of the CVGA, were analyzed using a paired *t*-test with a significance established at $p < 0.05$.

In Table V (i.e., CBR stand-alone mode), a part from the percentage in time below target, all the metrics corresponding to the adult population got worse. Although some improvements were observed in the adolescent population, these ones were not statistically significant. On the other hand, almost all safety and efficacy measures showed statistically significant improvements in both populations when the CBR(R2R) algorithm was employed (see Table VI ).

When comparing the two versions of the algorithm [i.e., R2R versus CBR(R2R)], the mean BG (i.e., primary outcome) improved from $166 \pm 39$ to $150 \pm 16$ in the adult populations and from $167 \pm 25$ to $162 \pm 23$ in the adolescent population. In addition, CBR(R2R) was able to completely eliminate hypoglycaemia, while the R2R alone was not able to do it in the adolescent population. Fig. 4 shows an example for subject adult#010 comparing the R2R and the CBR(R2R) algorithm during Run 4 of the simulation.

## VI. DISCUSSION

We presented a novel decision support algorithm for insulin dosing that enhances current standard bolus calculators through the utilization of an R2R, CBR, and intermittent usage of CGM data.

Good *in-silico* results using an FDA-accepted type 1 diabetes simulator were obtained with the presented CBR(R2R) algorithm. First of all, a convergence analysis for the novel R2R algorithm was successfully carried out. To evaluate the incremental benefit of using R2R and CBR, the full version of the algorithm [i.e., CBR(R2R)] was compared against the R2R control algorithm in a stand-alone mode. This comparison demonstrated a clear benefit of using CBR in combination with R2R with respect to using R2R alone. The R2R stand-alone version not only underperformed the CBR(R2R) version, but in some cases (i.e., adult population) performed worse than the standard bolus calculator. The reason for the poor performance of the R2R stand-alone version can be explained by its inability to cope with the significant insulin variability introduced in the simulations. It is important to note that R2R is based on the assumption of daily repetitiveness in the process, which is not the case for the employed scenario. The obtained results demonstrate that the propose CBR(R2R) algorithm is able to tackle with intrasubject variability and external perturbations, and robustness in front of uncertain inputs, i.e., carbohydrate intake and noisy CGM measurements.

It is important to remark that, although very useful for designing and testing purposes, simulators have their limitations. In general, simulation environments tend to overestimate the benefits of an intervention, since they do not incorporate all of the uncertainty and perturbations that occur in the real world. For this reason, clinical studies are required in order to fully validate the proposed algorithm. Therefore, modifications in the current version algorithm may be required when tested in a real scenario.

Although the proposed algorithm showed robustness against sensor noise in simulation, CGM technology still presents some problems of accuracy and reliability that may affect the performance of the proposed algorithm in a real-life setting. One way to reduce this problem would be the utilization of two sensors [37]. However, this solution may be too cumbersome for the subject. Another way to improve sensor accuracy would be to ask for a postprandial recalibration (e.g., 2 h), which seems a reasonable measure since it is the recommendation given for the standard therapy. Finally, in order to deal with sensor failures (e.g., sensor drifts and communication problems), a fault detection algorithm could be incorporated to the system [31].

It is important to note that the utilization of a CGM device does not need to be continuous, since the decision support system can still provide advice during the days when no CGM data are available by using the available cases in the case base, even if they are not optimal. Obviously, the R2R control update law can only be executed when these data are available. Therefore, using the CGM sensor periodically, although it may take longer to converge an optimal solution, may be beneficial in some cases because of usability issues.

TABLE V
EVALUATION OF THE R2R IN THE STAND-ALONE MODE

| **10 adults** | mean BG [mg/dl] | % time below 70 | % time above 180 | % time in target | risk index | % A+B | % D+E |
|---|---|---|---|---|---|---|---|
| Run1 | 156±12 | 0.3±0.5 | 24.6±11.5 | 75.2±11.7 | 5.4±2.2 | 44.5±10.7 | 1.9±3.3 |
| Run2 | 158±21 | 0.1±0.2 | 25.6±16.5 | 74.3±16.5 | 5.9±3.9 | 45.0±15.3 | 2.6±4.8 |
| Run3 | 163±33 | 0.0±0.1 | 27.0±20.9 | 73.0±20.9 | 6.9±6.2 | 45.1±18.3 | 4.0±7.6 |
| Run4 | 166±39 | 0.0±0.0 | 28.2±22.7 | 71.8±22.7 | 7.7±7.6 | 44.5±18.6 | 4.7±9.2 |
| *p* value | 0.34 | 0.17 | 0.51 | 0.52 | 0.28 | 1 | 0.19 |
| **10 adolescents** | | | | | | | |
| Run1 | 170±20 | 0.0±0.0 | 36.5±17.8 | 63.5±17.8 | 7.8±3.5 | 38.1±16.2 | 3.1±2.6 |
| Run2 | 166±23 | 0.1±0.3 | 34.8±19.1 | 65.1±19.0 | 7.3±3.8 | 40.6±18.8 | 2.6±2.8 |
| Run3 | 167±25 | 0.1±0.1 | 35.2±19.8 | 64.7±19.7 | 7.5±4.0 | 40.3±19.7 | 3.0±3.5 |
| Run4 | 167±25 | 0.1±0.1 | 35.3±20.2 | 64.6±20.2 | 7.4±4.0 | 39.7±20.4 | 2.7±3.5 |
| p value | 0.53 | 0.19 | 0.69 | 0.7 | 0.52 | 0.59 | 0.16 |

*Significant with $p < 0.05$

TABLE VI
EVALUATION OF THE CBR(R2R) ALGORITHM

| **10 adults** | mean BG [mg/dl] | % time below 70 | % time above 180 | % time in target | risk index | % A+B | % D+E |
|---|---|---|---|---|---|---|---|
| Run1 | 156±12 | 0.3±0.5 | 24.6±11.5 | 75.2±11.7 | 5.4±2.2 | 44.5±10.7 | 1.9±3.3 |
| Run2 | 154±15 | 0.1±0.2 | 23.2±12.3 | 76.7±12.3 | 5.1±2.5 | 47.2±13.4 | 1.6±3.1 |
| Run3 | 151±16 | 0.0±0.1 | 20.1±13.4 | 79.9±13.3 | 4.7±2.5 | 51.1±14.5 | 1.5±3.0 |
| Run4 | 150±16 | 0.0±0.0 | 18.1±13.4 | 81.9±13.4 | 4.3 ±2.5 | 52.7±15.1 | 1.2±3.0 |
| *p* value | 0.031* | 0.17 | 0.0032* | 0.0029* | 0.012* | 0.019* | 0.29 |
| **10 adolescents** | | | | | | | |
| Run1 | 170±20 | 0.0±0.0 | 36.5±17.8 | 63.5±17.8 | 7.8±3.5 | 38.1±16.2 | 3.1±2.6 |
| Run2 | 166±22 | 0.0±0.0 | 33.5±18.7 | 66.5±18.7 | 7.2±3.6 | 41.9±17.7 | 2.7±2.6 |
| Run3 | 163±22 | 0.1±0.2 | 31.6±19.3 | 68.3±19.2 | 6.6±3.6 | 42.7±18.3 | 2.1±2.1 |
| Run4 | 162±23 | 0.0±0.0 | 31.2±19.2 | 68.8±19.2 | 6.4±3.6 | 43.3±19.5 | 1.4±1.8 |
| *p* value | 0.0056* | - | 0.017* | 0.017* | 0.0021* | 0.014* | 0.011* |

*Significant with $p < 0.05$

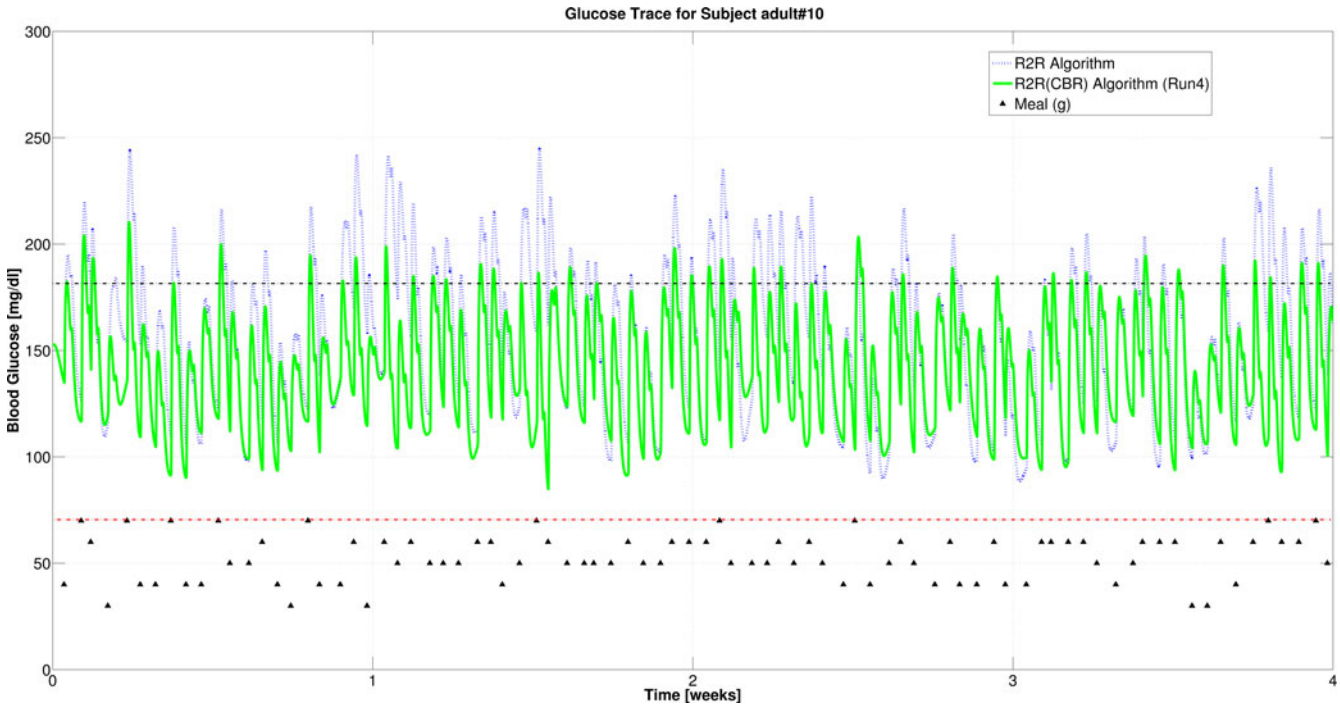


Fig. 4. Example of glucose traces (adult#010) corresponding to Run 4 for R2R algorithm (dashed line) and for CBR(R2R) algorithm (solid line). Upper and lower horizontal dashed lines indicate hyper-/hypoglycaemia limits, respectively (i.e., target zone). Triangular markers indicate meals and their corresponding carbohydrate load.

One could argue that the utilization of CBR is unnecessary to solve the stated problem (i.e., only two parameters to compare) and that a look-up table containing the multiples incidences of the R2R algorithm could be used instead. However, it has to be considered that in a real setting, the number of parameters is going to be higher and that many problems are not going to be in the case base. Therefore, CBR offers an elegant solution to deal with this problem.

Finally, the presented system has been integrated into a smartphone platform with a user-friendly interface and is now being clinically applied for the treatment of diabetes.

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