Automatic Adaptation of Basal Insulin using Sensor-augmented Pump Therapy

Pau Herrero, Ph.D.[1], Jorge Bondia, PhD[2], Marga Giménez, PhD[3], Nick Oliver, FRCP[4] and Pantelis Georgiou, Ph.D.[1]

Author Affiliations: [1]Centre for Bio-Inspired Technology, Institute of Biomedical Engineering, Imperial College London, London, UK; [2]Institut Universitari d'Automàtica i Informàtica Industrial, Universitat Politècnica de València, València, Spain. [3]Division of Diabetes, Endocrinology and Metabolism, Department of Medicine, Faculty of Medicine Imperial College, London, UK.; [4]Diabetes Unit, Endocrinology Department, ICMDiM. Hospital Clínic, Barcelona, Spain;

Pau Herrero and Pantelis Georgiou: Centre for Bio-inspired Technology, Department of Electrical and Electronic Engineering, Imperial College London, South Kensington Campus, London SW7 2AZ, U.K., +44 (0)2075940840, {pherrero, pantelis}@imperial.ac.uk

Marga Giménez: Diabetes Unit, Endocrinology Department, ICMDiM. Hospital Clínic, Barcelona, Spain, gimenez@clinic.cat

Jorge Bondia: Institut Universitari d'Automàtica i Informàtica Industrial, Universitat Politècnica de València, València, Spain. jbondia@isa.upv.es

Nick Oliver: Charing Cross Hospital, Imperial College Healthcare NHS Trust, Fulham Palace Road, London W6 8RF, nick.oliver@imperial.ac.uk

Abbreviations: T1DM (Type 1 Diabetes Mellitus); CSII (Continuous Subcutaneous Insulin Infusion); R2R (Run-to-Run) CBR; (Case-Base Reasoning); TDD (Total Daily Dose).

Key Words: type 1 diabetes; basal insulin; adaptive control; artificial intelligence; run-to-run; case-based reasoning.

Corresponding Author: Pau Herrero, Ph.D.; Centre for Bio-Inspired Technology,

Department of Electrical and Electronic Engineering, Imperial College London, South Kensington Campus, London SW7 2AZ, U.K. pherrero@imperial.ac.uk

Figures and table count: 9 figures, 10 tables.

Funding Source: This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement 689810.

Conflict-of-Interest Disclosure: None

Abstract

Background

People with insulin-dependent diabetes rely on an intensified insulin regimen. Despite several guidelines, they are usually impractical and fall short in achieving optimal glycemic outcomes. In this work, a novel technique for automatic adaptation of the basal insulin profile of people with diabetes on sensor-augmented pump therapy is presented.

Methods

The presented technique is based on a Run-to-Run control law that overcomes some of the limitations of previously proposed methods. To prove its validity, an *in silico* validation was performed. Finally, the artificial intelligence technique of Case-Based Reasoning is proposed as a potential solution to deal with variability in basal insulin requirements.

Results

Over a period of 4 months, the proposed Run-to-Run control law successfully adapts the basal insulin profile of a virtual population (10 adults, 10 adolescents and 10 children). In particular, average percentage time in target [70,180]mg/dl was significantly improved over the evaluated period (first week vs. last week): 70.9±11.8 vs. 91.1±4.4(adults); 46.5±11.9 vs. 80.1±10.9(adolescents); 49.4±12.9 vs. 73.7±4.1(children). Average percentage time in hypoglycemia (<70mg/dl) was also significantly reduced: 9.7±6.6 vs. 0.9±1.2(adults);

10.5±8.3 vs. 0.83±1.0(adolescents); 10.9±6.1 vs. 3.2±3.5(children). When compared against an existing technique over the whole evaluated period, the presented approach achieved superior results on percentage of time in hypoglycemia: 3.9±2.6 vs. 2.6±2.2(adults); 2.9±1.9 vs. 2.0±1.5(adolescents); 4.6±2.8 vs. 3.5±2.0(children), without increasing the percentage time in hyperglycemia.

Conclusion

The presented study has shown the potential of a novel technique to effectively adjust the basal insulin profile of a type 1 diabetes population on sensor-augmented insulin pump therapy.

1. Introduction

Type 1 diabetes mellitus (T1DM) is an autoimmune condition characterized by elevated blood glucose levels due to the lack of endogenous insulin production **[1]**. People with T1DM require exogenous insulin delivery to regulate glucose. Current therapies for T1DM management include the administration of multiple daily injections (MDI) or continuous subcutaneous insulin infusion (CSII) with pumps.

A basal-bolus insulin regimen involves taking a longer acting form of insulin to keep blood glucose levels stable through periods of fasting and separate injections of shorter acting insulin to prevent rises in blood glucose levels resulting from meals. Such a regimen attempts to roughly emulate how the body of a person without diabetes delivers insulin. People with T1DM using insulin pumps are able to pre-program different infusion rates along the day, hence they are able to achieve finer control **[2]**. **Figure 1** shows an example of the insulin profile of a typical CSII basal-bolus regimen.

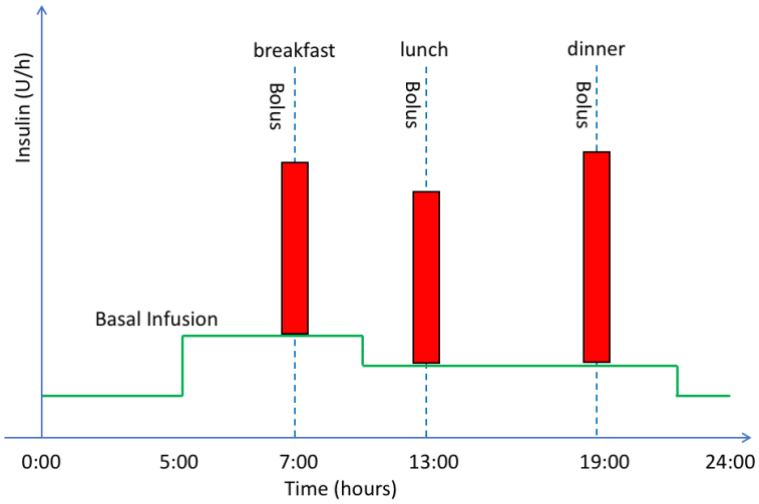


Figure 1. Plasma insulin profile of a typical basal-bolus regimen using CSII. Red vertical bars correspond to meal bolus and solid green horizontal lines represent the basal insulin profile.

Several guidelines exist for adjusting insulin doses in a basal-bolus regime **[3][4][5]**; these often require a cumbersome process of trial and error supported by an expert clinician.

Total basal insulin can be estimated based on the total daily dose (TDD) (e.g. basal = 0.5TDD) but requirements are rarely constant during the day and tend to be higher in the early morning (e.g. dawn phenomenon). In addition, insulin requirements may significantly change due to perturbations such as, physical exercise, psychological stress, hormonal cycles and recurrent illness **[1],** which makes adjusting insulin therapy a challenging task. In CSII therapy, different guidelines have been proposed to adjust the basal insulin profiles along the day, which usually consist of assigning different basal rate over different time windows **[3]**.

Since it is difficult to adjust basal insulin during the post-prandial period, people with T1DM are asked to skip one meal per day and with the help of a continuous glucose monitor (CGM) or regular capillary self-monitoring, are able to adjust the corresponding basal profiles. However, this process is inconvenient and impractical in many cases.

Meal bolus insulin is usually computed by means of the so-called bolus calculator, a simple mathematical formula that accounts for the amount of ingested carbohydrates, the pre-meal

glucose levels and the remaining active insulin from previous boluses (i.e. insulin-on-board) **[6]**. Such formula is described by

$$B = \frac{CHO}{ICR} + \frac{(G - G_T)}{ISF} - IOB, \qquad (1)$$

where B (U) is the total calculated bolus, CHO (g) is the estimated amount of ingested carbohydrates, ICR (g/U) is the insulin-to-carbohydrate-ratio, G (mg/dl) is the measured glucose at meal time, G_T (mg/dl) is the glucose target, ISF (mg/dl/U) is the insulin sensitivity factor, and IOB (U) is the insulin-on-board, which represents an estimation of the remaining active insulin in the body and which can be calculated using a linear decay expressed as

$$IOB = B_p \left(1 - \frac{T_{int}}{T_{act}}\right), \qquad (2)$$

where B_p the previously administered insulin bolus, T_{int} is the elapsed time since the last administered insulin bolus and T_{act} is the insulin action time, which is subject dependent.

Note that Equation (2) is just a particular way to estimate IOB using a linear decay. Other methods to estimate IOB have been proposed by different authors (e.g. curvilinear decay) [7, 8, 9], with some of them taking into account time-varying characteristics such as intra-day variability [10]. Parameters ICR and ISF are also scenario-dependent and guidelines exist to calculate them **[11].**

Seeing the complexity of insulin dosing, there is a need for more automated and efficient strategies to adapt such regimens, removing self-management burden and improving outcomes. Different authors have previously proposed methods to automatically adjust the bolus-basal insulin therapy. The concept of adaptive bolus calculator was first proposed by Owen et al. by means of the utilization of Run-to-Run (R2R) control **[12**], and later, clinically tested by Palerm et al. **[13]**. Although showing some promising preliminary clinical results, this approach has the limitation of being very sensitive to meal composition and does not account for hyperglycemia. In **[14]**, Tuo et al. proposed a similar technique based on a high order R2R control scheme. Similarly to the approach by Owen et al., the employed control

law by Tuo et al. does not account for hypoglycemia. Finally, Herrero and colleagues proposed a new R2R control law combined with Case-Based Reasoning that overcomes some of the previous limitations **[15][16][17]**.

Regarding the adaptation of the basal insulin profile, Palerm et al. **[18]** proposed a R2R algorithm which is used to adjust four basal rates along the day using capillary measurements taken at the extremes of the selected time intervals. One limitation of this method is that it does not account for hypoglycemic and hyperglycemic events within the time intervals.

Toffanin and colleagues recently introduces a R2R algorithm for adaptation a 24-hour basal insulin injection. Such technique is based on the well-stablished glycemic metrics of percentage time in euglycemia and hypoglycemia computed from continuous glucose sensor data **[19]**.

In the context of an artificial pancreas (i.e. hybrid closed-loop control), different solutions have been proposed to adjust the basal insulin and the meal bolus. A method to adapt basal therapy based on the value and rate of change of blood glucose was proposed by Wang et al. **[20]**. Herrero et al. proposed a R2R technique to automatically adjust the insulin-to-carbohydrate ratio of the bolus calculator within a hybrid artificial pancreas that uses information from the closed-loop controller **[21]**. Dassau et al. clinically evaluated an adaptive artificial pancreas where basal insulin delivery settings were adapted weekly, and carbohydrate ratios were adapted every 4 weeks **[22]**. Finally, a R2R approach which adapts the basal insulin delivery during the night and the carbohydrate-to-insulin ratio during the day, based on glycemic metrics calculated from subcutaneous continuous glucose sensor data has been proposed by Toffanin et al. **[23]** which has been later clinically evaluated **[24].**

In this work, we present a novel technique to automatically adjust the 24-hour basal insulin regimen of a person with diabetes on sensor-augmented insulin pump therapy. The introduced technique uses an enhanced version of the R2R algorithm by Palerm et al. **[18]** by

taking advantage of continuous glucose monitoring (CGM) technology. It also improves on the work proposed by Toffanin et al. **[19]** by allowing different basal insulin rates along the day, as required by insulin pump users.

It is important to remark that previously proposed techniques for automatically adapting the basal-insulin therapy do not consider temporary events such as physical exercise, illness, and hormone cycle. For this purpose, and following the same approach as the work proposed by Herrero et al. for adapting meal-insulin boluses **[15][16][17]**, the artificial intelligence technique of Case-Based Reasoning **[25]** is proposed as a potential solution to account for variability on basal insulin requirements due to such temporary events.

2. Methods

2.1 Run-To-Run control

Run-To-Run (R2R) is a control methodology designed to exploit repetitiveness in the process that is being controlled **[26]**. Its purpose is to enhance performance, using a mechanism of trial and error. The simplest formulation of R2R may be,

$$u_{k+1} = u_k + K \cdot error, \qquad (3)$$

where *u* is the control action, *K* is a tuning gain and *error* is the tracking error defined as the difference between a measurement from the process and a set-point.

Insulin dosing has a repetitive nature. Therefore, R2R control can be used to exploit such characteristic. As previously discussed, R2R control has been extensively used for adapting the meal-bolus insulin regimen [**13] [14] [16**] and single-dose injection basal-insulin **[19] and** overnight basal-insulin [**22][23]**, but in less extend for adapting the 24-hour basal regimen in pump therapy **[18]**.

2.2 Proposed R2R algorithm

The proposed R2R algorithm for adapting the 24-hour basal-insulin regimen of a person with T1DM is based on the hypothesis that four time intervals are enough to account for the changes in basal insulin requirements due to circadian variations. In addition, it assumes that the time of the day-time when a person is closest to the fasting conditions is just before the meals and during the night time (e.g. 6 hours after dinner). Therefore, the meal-time glucose measurements, and a night-time measurement, are considered to adjust the basal-insulin rates between such times ($t_{breakfast}$, t_{lunch}, t_{dinner}, $t_{dinner}+6h$). Note that such time intervals might slightly change from day-to-day. **Figure 2** shows a graphical representation of the four time intervals defining the basal profile ($Basal_1$, $Basal_2$, $Basal_3$, $Basal_4$).

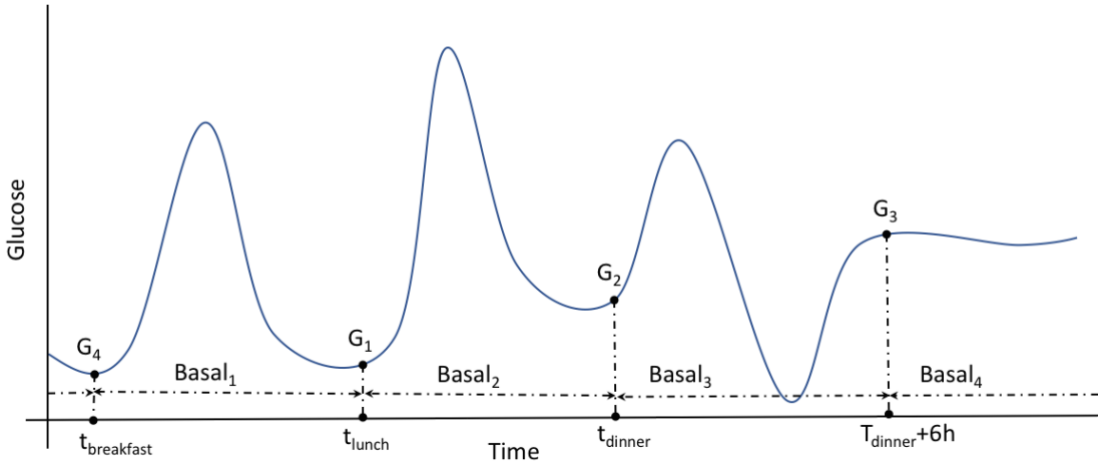


Figure 2. Graphical representation of the four time intervals defining the basal profile ($Basal_1$, $Basal_2$, $Basal_3$, $Basal_4$). Time points $t_{breakfast}$, t_{lunch}, t_{dinner} correspond to the meal intake times and G_1, G_2, and G4 to their corresponding glucose levels.

The proposed R2R algorithm is based on the control law introduced by Palerm et al **[18]**, which is described as

$$Basal_i(k+1) = Basal_i(k) + k_1 \cdot \left(\frac{(G_{start}+G_{end})}{2} - G_T\right) + k_2 \cdot (G_{start} - G_{end}), \quad (4)$$

where sub-index *i* indicates the time interval (*i*=[*1,2,3,4*]), index *k* indicates the iteration (i.e. run), k_1 and k_2 are tuning gains, G_{start} is the glucose value at the beginning of the interval, G_{end} is the glucose value at the end of the interval, and G_T is the glucose target.

This control law was designed to be used with capillary measurements and has the limitation of not taking into account if hypoglycemic and hyperglycemia events occur between measurements. In this work, a new control law that takes advantage of CGM technology by accounting for hypoglycemia and hyperglycemia within the considered time intervals is proposed. Current CGM technology has been approved by the FDA as a non-adjunctive technology, which makes it much more user friendly by significantly reducing the number of required capillary measurements (i.e. calibration). In addition to considering variability due to the circadian cycle, the proposed control law allows taking into account the type of day (e.g. sickness day). The control law is described as

$$Basal_i^j(k) \tag{5}$$
$$= \begin{cases} Basal_i^j(k-1) + k_1 \cdot \left(\frac{(G_{start} + G_{min} + G_{end})}{3} - G_T\right) + k_2 \cdot dG, & if\, G_{min} < 70 \\ Basal_i^k(k-1) + k_1 \cdot \left(\frac{(G_{start} + G_{min} + G_{end})}{3} - G_T\right) + k_2 \cdot dG + k_3 \cdot \left(G_{avg} - G_T\right), & otherwise \end{cases}$$

where sub-index *i* indicates the time interval, the super-index *j* represents the type of day (e.g. sickness day), *k* indicates the iteration (i.e. run) , k_1, k_2 and k_3 are tuning gains, G_{start} is the glucose value at the beginning of the interval, G_{min} is the postprandial minimum glucose value calculated over a postprandial glucose window from 2-hour post meal to the next meal or 6 hours if the meal does not occur before, G_{end} is the glucose value at the end of the interval, G_T is the glucose target and *dG* is the slope of a linear regression of the glucose values G_{start}, G_{min} and G_{end} and their corresponding time instants, and G_{avg} is the glucose average over a postprandial glucose window from 3-hour post meal to the next meal or 6 hours if the meal does not occur before. For the overnight time interval ($Basal_4$), G_{avg} is computed over the whole period.

The reason for excluding the initial meal-time glucose measurement, and the following 2 hours, in the computation of G_{min} is because these glucose measurements are not consequence of the basal rate being adapted, but the result of the previous basal-insulin rate. Finally, the first 3 hours are excluded in the calculation of G_{avg} within $Basal_1$, $Basal_2$ and $Basal_3$ intervals to eliminate the postprandial excursion due to the meal intake. **Figure 3** shows a graphical representation of the variables involved in the proposed R2R control law.

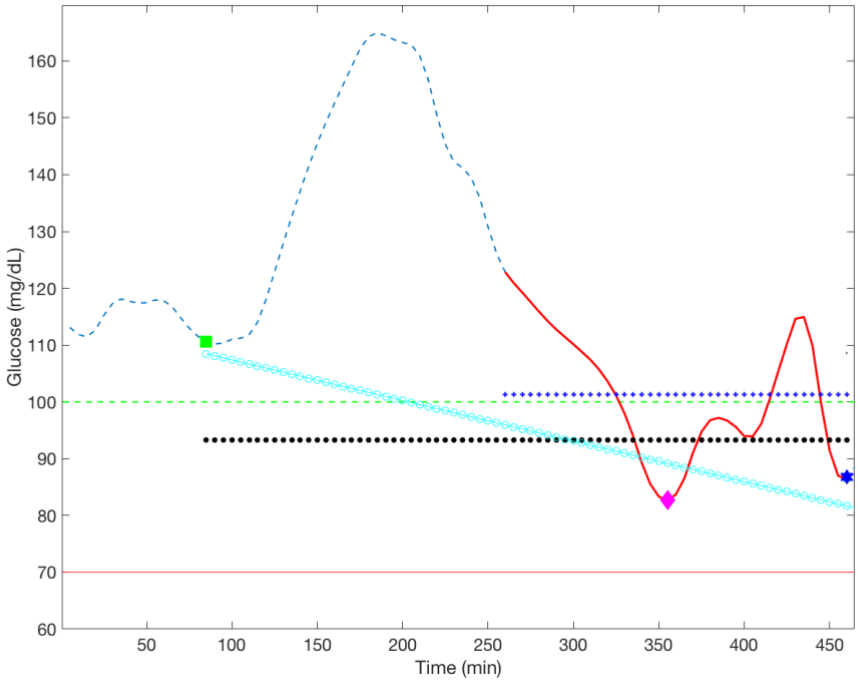


Figure 3. Graphical representation of the proposed R2R control law over a post-prandial excursion. Dashed blue line represent the CGM measurement; green square, pink diamond and blue star markers correspond to G_{start}, G_{min} and G_{end} respectively. Solid red line corresponds to the postprandial window [$G_{start}+3h$, $G_{start}+6h$]; horizontal black circled line is the average of G_{start}, G_{min} and G_{end}; horizontal crossed blue line is G_{avg} and inclined circled cyan line is the linear regression of G_{start}, G_{min} and G_{end}.

It is worth noting that the proposed R2R controller shares some similarities with the one proposed by Toffanin and colleagues **[19]**, since both define two different laws based on the CGM performance and both put particular emphasis on hypoglycemia minimization. However, unlike Toffanin's work, the proposed controller allows to adapt different basal-insulin rates along the day, as required by insulin pump users.

In order to make the proposed control law more robust in front of uncertainty and sensor errors, the applied basal rate is obtained by computing the average of three consecutive adaptations corresponding to same basal rate segment (*i*) of the same day type (*j*). This is expressed by

$$avgBasal_i^j = \frac{Basal_i^j(k) + Basal_i^j(k-1) + Basal_i^j(k-2)}{3}, \qquad (6)$$

where *k* represents the run within the same basal rate segment (*i*) of the same day type (*j*).

Safety constraint are put in place to avoid excessive adaptations. A relative constraint to limit the adaptation by ±30% and a global constraint to limit the maximum and minimum rates to three times and a third of the original rate, respectively, are implemented.

2.3 Stability Analysis

Stability of the control law expressed by Equation (5) is investigated next. Remark that, for each time interval $i \in \{1, \dots, 4\}$, G_{min}, G_{end}, G_{avg} and dG in (5) are indeed functions of the starting glucose value for that interval, G_{start}, and the applied basal value, $Basal_i$. Thus, the system (5) can be expressed as

$$Basal_i^{k+1} = \begin{cases} Basal_i^k + k_1 \cdot \left(h\left(Basal_i^k, G_{start}\right) - G_T\right) + k_2 \cdot dG\left(Basal_i^k, G_{start}\right), \\ if\, G_{min}(Basal_i^k, G_{start}) < 70 \\ Basal_i^k + k_1 \cdot \left(h\left(Basal_i^k, G_{start}\right) - G_T\right) + k_2 \cdot dG\left(Basal_i^k, G_{start}\right) \\ + k_3 \cdot \left(G_{avg}(Basal_i^k, G_{start}) - G_T\right), \;\; otherwise \end{cases} \qquad (7)$$

where

$$h\left(Basal_i^k, G_{start}\right) := \frac{(G_{start}+G_{min}(Basal_i^k,G_{start})+G_{end}(Basal_i^k,G_{start}))}{3}. \quad (8)$$

Analogously to **[19]**, a simulation study was conducted to identify functions in (7) for a set of starting glucose and basal values, fixing all other parameters in the simulation, for a postprandial ($i \in \{1,2,3\}$) and a night period ($i = 4$). As a result, a set of quadratic functions for each period was obtained:

$$h\left(Basal_i^k, G_{start}\right) = \alpha_h(G_{start})\left(Basal_i^k\right)^2 + \beta_h(G_{start})Basal_i^k + \gamma_h(G_{start}) \quad (9a)$$

$$dG\left(Basal_i^k, G_{start}\right) = \alpha_{dG}(G_{start})\left(Basal_i^k\right)^2 + \beta_{dG}(G_{start})Basal_i^k + \gamma_{dG}(G_{start}) \quad (9b)$$

$$G_{min}\left(Basal_i^k, G_{start}\right) = \alpha_{Gmin}(G_{start})\left(Basal_i^k\right)^2 + \beta_{Gmin}(G_{start})Basal_i^k + \gamma_{Gmin}(G_{start}) \quad (9c)$$

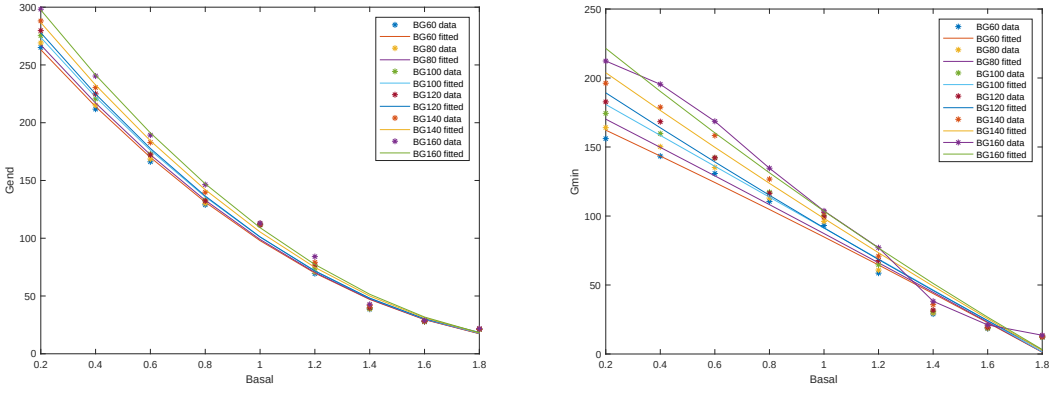
$$G_{avg}\left(Basal_i^k, G_{start}\right) = \alpha_{Gavg}(G_{start})\left(Basal_i^k\right)^2 + \beta_{Gavg}(G_{start})Basal_i^k + \gamma_{Gavg}(G_{start}) \quad (9d)$$

$$G_{end}\left(Basal_i^k, G_{start}\right) = \alpha_{end}(G_{start})\left(Basal_i^k\right)^2 + \beta_{Gend}(G_{start})Basal_i^k + \gamma_{Gend}(G_{start}) \quad (9e)$$

The following monotonicity properties hold:

- h, G_{min}, G_{avg} and G_{end} are monotonically increasing with respect to G_{start}.
- dG is monotonically decreasing with respect to G_{start}.
- h, G_{min}, G_{avg}, G_{end} and dG are monotonically decreasing with respect to $Basal_i^k$.

Figure 4 shows, as illustration, the fitted functions for a starting glucose ranging in 60 to 160 mg/dL in the case of the postprandial period.



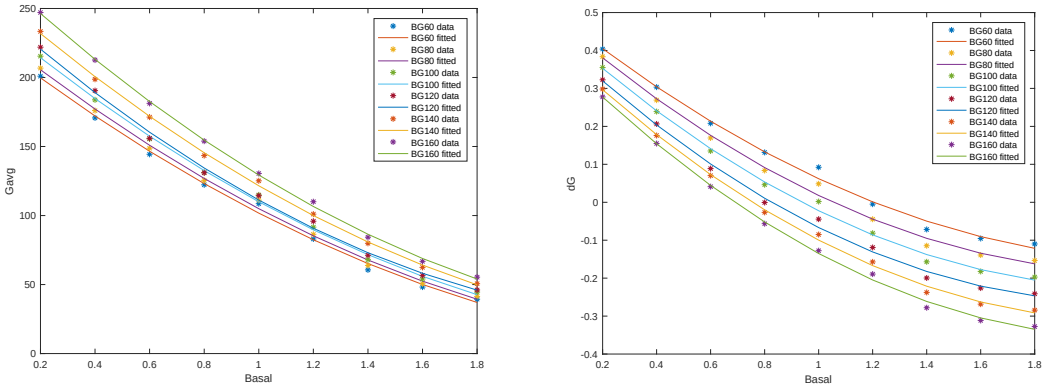


Figure 4. Fitted quadratic functions for G_{end}, G_{min}, G_{avg} and dG for a postprandial period and a sweep in starting glucose values in the range 60 to 160 mg/dL.

Since (7) is a first-order system, its stability can be derived from the phase plot, which depicts $Basal_i^{k+1}$ versus $Basal_i^k$ (curve corresponding to the right-hand side of (7)). **Figure 5** shows the phase plot for a postprandial and night period, and a sweep in G_{start}. Denoting as $Basal^*$ the crossing of the curve, for a given G_{start}, with the line $Basal_i^{k+1} = Basal_i^k$ (unit slope line), $\left|Basal_i^{k+1} - Basal^*\right| < \left|Basal_i^k - Basal^*\right|$ must hold for $Basal^*$ to be an equilibrium point, i.e., the curve must lie inside the ±45 degrees sector with origin $Basal^*$, as it is in our case. For any G_{start}, if $Basal_i^k > Basal^*$, then the basal will be decreasing towards $Basal^*$ until convergence. If $Basal_i^k < Basal^*$, then the basal will be increased towards $Basal^*$ until convergence. At each time step, G_{start} will be the value of G_{end} for the previously evaluated time interval (e.g, G_{start} at lunch is G_{end} at breakfast), meaning that a curve switching in the phase plot will happen. However, these are monotonically decreasing with respect to G_{start} and G_{end} is monotonically decreasing with respect to basal, which means that the switching will happen in a monotonic way according to the direction of basal changes in the previous time interval.

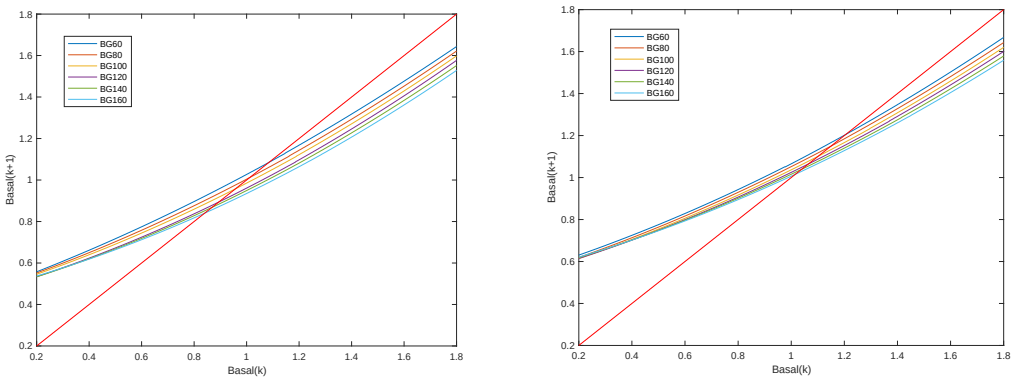


Figure 5. Phase plots of (6) for a postprandial period (left) and night period (right), and a sweep in starting glucose values in the range 60 to 160 mg/dL.

2.4 Case-Based Reasoning

The proposed R2R algorithm is able to deal with intra-day variability in insulin requirements due circadian variations by separating the 24-h basal insulin profile into four time intervals. It is also able to deal with some degree of inter-day variability due to temporary events such as physical exercise, recurrent illness, psychological stress, and menstrual cycle. However, when the number of temporary events increases (e.g. different intensities of exercise or stress) the problem might become untreatable. Similarly to the work proposed by Herrero et al. for recommending meal insulin boluses **[15]**, the utilization of Case-Based Reasoning is proposed as a potential solution to overcome this limitation.

Case-Based Reasoning (CBR) is an artificial intelligence problem solving framework that solves a newly encountered problem, based on the information obtained from previously solved problems and stored as cases in a case-base **[25]**. A clinician who diagnoses a patient's disease by recalling another patient that exhibited similar symptoms is using case-based reasoning.

CBR is usually described in four steps: *Retrieve* the most similar cases to the problem to be solved from the case-base; *Reuse* the solutions of retrieved cases; *Revise* the outcome of the

applied solution to the new problem; and *Retain* the new problem if its solution is considered useful for solving future problems. **Figure 6** show the four steps of the CBR cycle (*Retrieve, Reuse, Revise, Retain*).

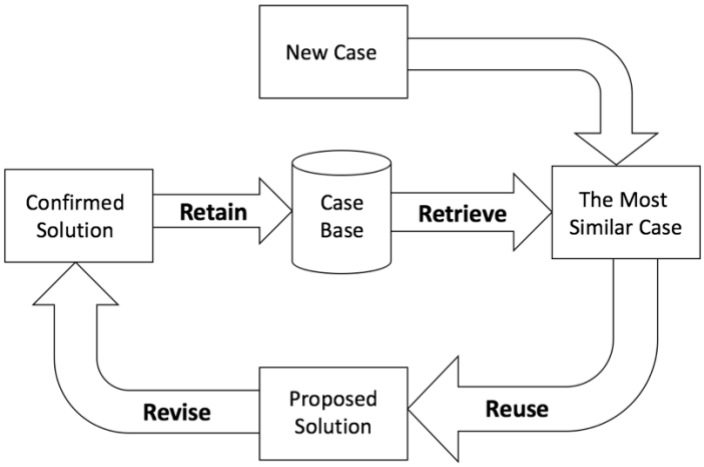


Figure 6. CBR cycle (*Retrieve, Reuse, Revise, Retain*).

In this work, CBR is used to recall previous scenarios where basal insulin requirements were similar to the current scenario (e.g. dinner after moderate aerobic exercise) and then reuse such information to calculate the current basal insulin. Due to the significant inter-subject variability in type 1 diabetes, cases are stored in a subject-specific case-base.

Changes in insulin requirements along the day due to circadian variations are defined as a context within the case-base. Cases of the different contexts are not compared against each other since they are considered to be too different. **Table 1** shows a context and parameters, together with their potential values, considered in this work. Note that these parameters are just a subset of the parameter affecting insulin requirements. Other parameters that are known to affect insulin sensitivity, or affect blood glucose levels, and which could be considered in a real-life application of the proposed algorithm are: alcohol consumption, hours and quality of sleep, traveling across time zones and meal absorption.

Table 1. Context and parameters with their corresponding values.

Parameter (P) / Context (C)	Values
Time of day (C)	post-breakfast, post-lunch, post-dinner, night
Aerobic exercise (P)	none, moderate, intense
Psychological stress (P)	none, mild, severe
Menstrual cycle (P)	menstrual, follicular, ovulation, luteal
Illness (P)	none, mild, severe

Cases are retrieved from the case-base (*Retrieve* step) by means of a k-nearest neighbors (KNN) algorithm, i.e. computing the distance (e.g. Euclidian) between the current case and all the cases in the case-base and by selecting the case(s) with the shorter distance **[27]**. In particular the Euclidian distance is employed, which is described by

$$Distance_k = \sqrt{\sum_{j=1}^{n} w_j \left(V_j^C - V_j^k\right)^2}, \qquad (10)$$

where *k* indicates the distance between the current case and the case *k* in the case-base, *n* is the number of parameters defining a case, V_j^C is the value of parameter *j* for the current case, V_j^k is the value of parameter *j* for a case *k* in the case-base and w_j is the weight associated to parameter *j*. In order to calculate such distance, the distance between parameters, i.e. $\left(V_j^C - V_j^k\right)$, is defined as 0 if the values are equal, 1 if the value are adjacent (e.g. none vs. moderate), or 2 if the values are non-adjacent (e.g. none vs. intense). In this work, parameters are weighted equally (i.e. $w_1 \ldots w_n = 1$), but these can be tunable in a real-life application.

If the retrieved case *k* is different from the current case (i.e. $Distance_k \neq 0$), its solution (basal rate) needs to be adjusted by a percentage before applying it to the current scenario (*Reuse* step). Such percentage (P_T) is defined as follow

$$P_T = 100 \prod_{j=1}^{n} \frac{P_j^C}{P_j^R}, \qquad (11)$$

where P_j^c and P_j^R represent the percentages corresponding to parameter j for the current case and the retrieved case, respectively. **Table 2** shows the applied percentages for each one of the values of the selected parameters. Note that in a clinical scenario, these values need to be individualized by the clinician to fit the needs of a particular person with T1DM.

Table 2. Applied percentages on the basal-insulin rate for each one of the values of the selected parameters.

Parameter	Value (Percentage)
Aerobic exercise	none (100%), moderate (50%), intense (20%)
Psychological stress	none (100%), mild (140%), severe (170%)
Menstrual cycle	none (100%), follicular (150%), luteal (170%)
Illness	none (100%), mild (130%), severe (180%)

If the retrieved case is different from the current case (i.e. $Distance_k \neq 0$), then, a new case is created with the new adapted solution, and it is stored in the case-base (*Retain* step). Once the solution of a case has been applied, a retrospective revision of the resulting glycemic outcome is carried out (*Revision* step) by means of the proposed R2R control law (Equation 5). Note that the solution of a case in the case-base is only updated after being revised three times (Equation (6)).

Unlike the traditional CBR approach **[25]** where the solutions of the cases in the case-base are static, in this work, the solutions (i.e. basal rate) can be adapted if they are found to be sub-optimal. This strategy partially solves the so-called problem of *cold start* in CBR (i.e. insufficient initial cases in the case-base) by initializing the case-base with a small set of safe

cases (most likely sub-optimal) and letting the system converge towards an optimal solution while adapting solutions of existing cases and adding new cases to the case-base.

When compared to a lookup table-based approach, where all the cases resulting from all combinations of parameters are independently adapted with the R2R control law, the proposed CBR algorithm is expected to converge swifter to an optimal basal-insulin therapy thanks to reusing information from similar cases.

Finally, a very important issue which must be accounted for in a CBR application is the case-base maintenance. Case-base maintenance is used to control the size of the case-base and removes cases that have lost their validity (e.g. too old).

It is important to remark that, due to the limited number of cases available in the employed simulator, the evaluation of the proposed CBR algorithm has not been possible. It is important to remark that the feasibility of CBR in a clinical setting has already been proven **[17]** in the context of meal-bolus adaptation.

2.5 In Silico evaluation under intra-day and inter-day variability

The UVa-Padova T1DM simulator (v3.2) **[28]** was used to evaluate the proposed R2R technique against the R2R control law proposed by Palerm and colleagues **[18]**.

Intra-day variability and uncertainty on meal type, meal time, carbohydrate estimation, meal absorption, insulin absorption and insulin sensitivity, were introduced in the simulator as described by Herrero and colleagues **[21]**. In addition, inter-day variability was represented by three types of days, which were generated multiplying by 1.1 (day 1), 0.5 (day 2) and 1 (day 3) the insulin sensitivity parameters (V_{mx} and K_{p3}) in the simulator model **[29]**. Note that the selected insulin sensitivity changes are not necessarily physiological and their sole purpose is to test the algorithm. In addition, two days had an of exercise 60min at 50% V02max at 5pm (day 1 and day 2) and one did not (day 3). For this purpose, the model of

exercise proposed by Shiavon et al **[30]** was included in the simulator. In total, 12 different scenarios composed by 4 contexts per day (post-breakfast, post-lunch, post-dinner, night) and 3 types of days were generated. Hence, the two R2R control laws were applied on each one of the 12 different scenarios.

The 10-adult, 10-adolescent and 10-child subjects available in the simulator were used for evaluating purposes. The initial basal insulin infusion rate for the virtual subjects was the one provided by the default insulin therapy of the simulator. The selected CGM to perform the simulations was the Dexcom G4 platinum. A virtual pump with no error was selected to deliver the insulin. A 17-week scenario was employed, with the first week having no adaptation. The selected daily pattern of carbohydrate dose intake was 7am (40g), 1pm (80g) and 7pm (60g).

The following glycemic metrics, which are widely accepted by the diabetes technology community to evaluate glucose controllers **[31]**, were selected for comparison purposes: mean blood glucose (BG) in mg/dl; percentage time in glucose target range [70,180] mg/dl (% in Target); percentage time below target (i.e. hypoglycemia) (% < Target); percentage time above target (i.e. hyperglycemia) (% > Target); risk index (R); low blood glucose index (LBGI); and high blood glucose index (HBGI).

2.6 Controllers tuning

Table 3 and **Table 4** shows the tuning parameters employed for the *in silico* evaluation of the control law proposed by Palerm et al. in **[18]** and the proposed control law, respectively. Note that the tuning of the R2R by Palerm et al. is significantly different from the tuning proposed in the original work (i.e. an order of magnitude). This might be explained by the difference between the employed simulators, being the UVa-Padova T1DM simulator a validated software tool accepted by the FDA as a substitute to animal trials.

Table 3. Tuning parameters for the control law proposed by Palerm et al. **[15].**

	Adults	Adolescents	Children
k_1	0.001	0.001	0.0005
k_2	0.001	0.001	0.0005

Table 4. Tuning parameters for the proposed control law.

	Adults	Adolescents	Children
k_1	0.001	0.001	0.0005
k_2	0.7	0.7	0.35
k_3	0.0001	0.0001	0.00005

3. Results

Table 5, Table 6 and Table 7 show the average results corresponding to the 10 adults, 10 adolescents and 10 children at week #1 (no adaptation) and at week #17 after 16 weeks of basal adaptations. Note that all the calculated glycemic metrics for the three cohorts significantly improve over the 17 weeks.

Table 5. Average glycemic outcomes corresponding to week #1 (no adaptation) and week #17 for the 10 adult subjects.

Week	BG	%inT	%<T	%>T	RI	LBGI	HBGI	TDD
#1	138.8±12.9	70.9±11.8	9.7±6.6	19.3±8.6	7.2±3.7	2.7±2.2	4.5±2.3	42.1±9.9
#17	128.5±5.3	91.1±4.4	0.9±1.2	7.9±4.5	2.4±0.8	0.4±0.3	2.0±0.7	43.8±9.2
p-value	p<0.05	p<0.01	p<0.01	p<0.01	p<0.01	p<0.01	p<0.01	P<0.05

Table 6. Average glycemic outcomes corresponding to week #1 (no adaptation) and week #17 for the 10 adolescent subjects.

Week	BG	%inT	%<T	%>T	RI	LBGI	HBGI	TDD
#1	175.0±24.9	46.5±11.9	10.5±8.3	42.9±9.8	15.8±6.8	4.5±4.3	11.3±4.6	31.9±8.1
#17	140.4±12.4	80.1±10.9	0.83±1.0	19.0±10.9	4.4±2.1	0.4±0.2	3.9±2.0	35.4±8.5
p-value	p<0.01	p<0.01	p<0.01	p<0.01	p<0.01	p<0.05	p<0.01	p<0.01

Table 7. Average glycemic outcomes corresponding to week #1 (no adaptation) and week #17 for the 10 child subjects.

Week	BG	%inT	%<T	%>T	RI	LBGI	HBGI	TDD
#1	169.6±16.9	49.4±12.9	10.9±6.1	39.7±9.3	14.9±6.0	4.6±3.6	10.3±3.6	16.7±3.6
#17	144.6±10.3	73.7±4.1	3.2±3.5	23.1±6.3	6.1±1.0	1.2±1.2	5.0±1.4	18.2±3.8
p-value	p<0.01	p<0.01	p<0.01	p<0.01	p<0.01	p<0.01	p<0.01	p<0.01

Table 8, Table 9 and Table 10 show the comparison of the glycemic outcomes achieved with the R2R control law by Palerm and colleagues **[18]** and by the one the proposed in the current work computed over the whole simulation period (17 weeks). Note that the proposed approach achieves a superior performance over the three cohorts regarding the percentage time in hypoglycemia, without increasing the percentage time in hyperglycemia.

Table 8 – Comparison between average glycemic control achieved with the R2R control law by Palerm et. al against the control law proposed in the current work. Results correspond to the 10 adult subjects in the simulator.

	BG	%inT	%<T	%>T	RI	LBGI	HBGI	TDD
Palerm et. al	129.0±6.5	84.6±5.1	3.9±2.6	11.5±4.8	3.8±1.2	1.2±0.7	2.6±0.9	40.9±8.9
Proposed	131.6±6.0	85.9±5.3	2.6±2.2	11.5±4.7	3.4±1.2	0.8±0.7	2.6±0.8	40.7±8.9
p	p<0.01	p<0.01	p<0.01	p = 0.9	p<0.01	p<0.01	p = 0.3	p = 0.06

Table 9 – Comparison between glycemic control achieved with the R2R control law by Palerm et. al against the control law proposed in the current work. Results correspond to the 10 adolescent subjects in the simulator.

	BG	%inT	%<T	%>T	RI	LBGI	HBGI	TDD
Palerm et. al	149.3±15.5	70.8±10.1	2.9±1.9	26.49.9	7.1±2.8	1.1±0.7	5.9±2.8	32.2±7.8
Proposed	150.5±15.1	72.1±9.9	2.0±1.5	25.9±10.0	6.6±2.6	0.8±0.6	5.7±2.6	32.4±7.8
p	p < 0.05	p<0.01	p<0.01	p = 0.1	p<0.01	p<0.01	p<0.05	p<0.05

Table 10 – Comparison between glycemic control achieved with the R2R control law by Palerm et. al against the control law proposed in the current work. Results correspond to the 10 child subjects in the simulator.

	BG	%inT	%<T	%>T	RI	LBGI	HBGI	TDD
Palerm et. al	151.3±12.2	67.5±6.2	4.6±2.8	27.9±7.3	8.1±2.1	1.6±0.9	6.5±2.0	16.8±3.4
Proposed	153.5±10.7	68.6±6.3	3.5±2.0	27.9±6.9	7.7±1.9	1.2±0.7	6.4±1.8	16.8±3.5
p	p<0.05	p<0.01	p<0.01	p = 0.8	p<0.01	p<0.01	p=0.3	p=0.9

Figure 7 shows a comparison between Palerm et al. R2R and the new R2R of the weekly evolution for three of the evaluated glycemic metrics (%inT, %<T and %>T) for the adult cohort. Note that, despite oscillations due to the inter-day variability, the algorithm converges after approximately 10 weeks. **Figure 8** shows the glucose profile of adult #1 over the 17-week simulation together with the corresponding glycemic metrics (%inT, %<T and %>T). **Figure 9** displays the evolution of the 12 basal rates over time corresponding to **Figure 8**. Note that basal levels for different days differ up to 100%.

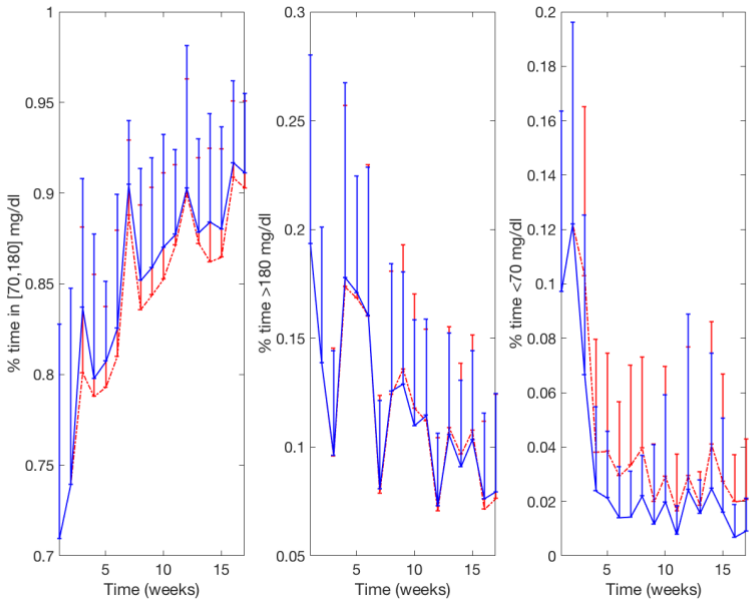


Figure 7. Weekly evolution of the average percentage time in target (%inT), percentage time below target (%<T) and percentage time above target (%>T) corresponding to the adult cohort corresponding the original R2R controller (dashed red line) and the new R2R controller (solid blue line). Error bars represent the standard deviation.

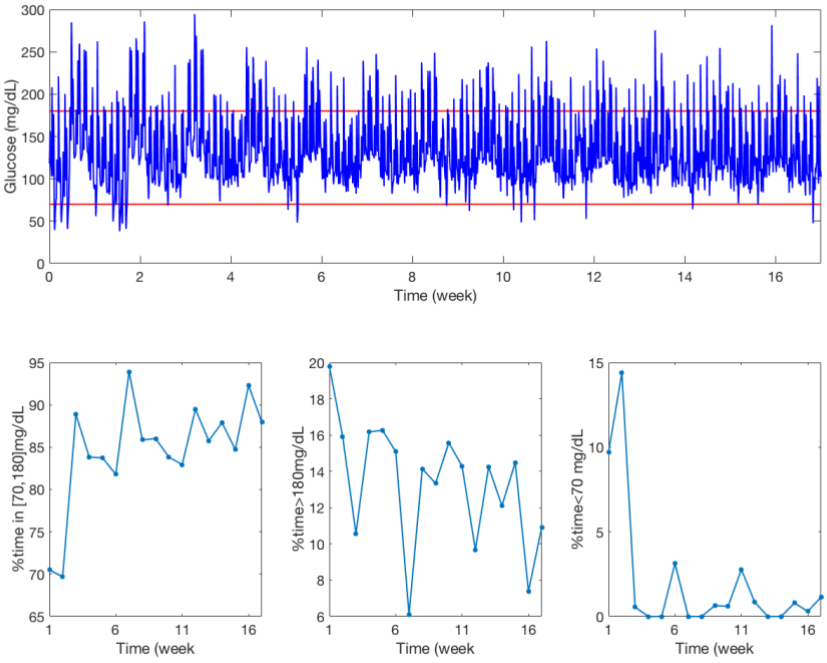


Figure 8. Glucose profile for adult #1 over the 17-week simulation (upper graph) together with the corresponding glycemic metrics (lower graphs).

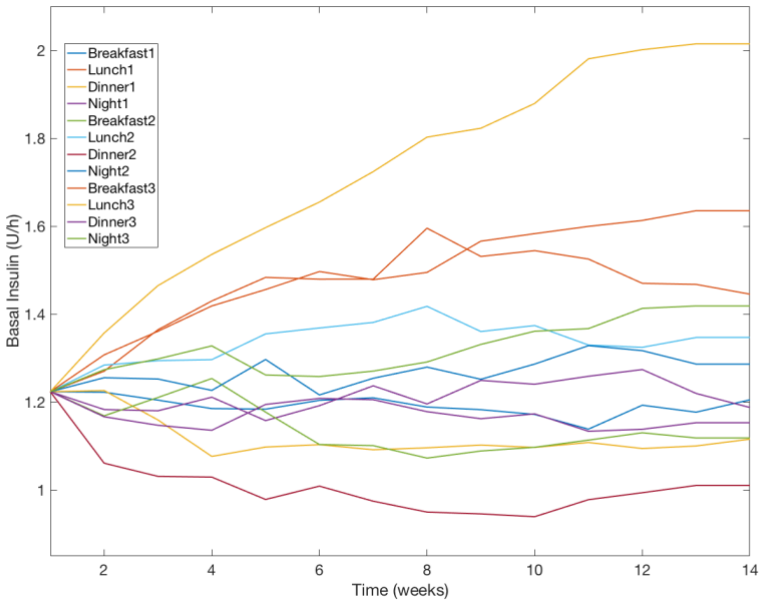


Figure 9. Temporal evolution of the 12 basal rates corresponding Figure 8. Breakfast, Lunch, Dinner and Night indicate the context and the accompanying number represents the day type.

4. Discussion

In a virtual T1DM population (10 adults, 10 adolescents, 10 children), over a 17-week scenario with intra-day and inter-day variability, the presented basal insulin adaptation technique based on R2R control significantly improves all the evaluated glycemic metrics. When compared against an existing technique by Palerm et al **[18]**, the proposed algorithm outperforms the former in the three studied cohorts by reducing the time in hypoglycemia, increasing the time in target while not increasing the time in hyperglycemia. A marginal increase in mean glucose (i.e. <2mg/dL) is observed.

When analyzing the weekly evolution of the evaluated glycemic metrics, it can be observed that glycemic metrics take about 10 weeks to converge to a relatively steady state. This convergence rate could be increased by using a less conservative strategy when saturating/filtering the adaptations, but at the expenses of losing robustness.

Although the robustness of the proposed algorithm has been tested to some degree by introducing significant intra-subject and inter-subject variability in the in-silico study, which might be not too far from a real-life scenario, a systematic robustness analysis is still desirable. This can be considered a limitation of the current work and a complete robustness evaluation is included as future work. Such analysis should evaluate the ability of the algorithm to adjust basal insulin rates in case of systematic variations in bolus calculator parameters. In addition, it would be interesting to evaluate possible compensations between bolus calculator parameters and basal insulin infusion, as could appear in real life.

An additional challenge that could be added to further test the robustness of the algorithm would be the misclassification of the type of day.

One important aspect that has not been considered in this work, and which it is essential in a real-life scenario, is the needs to take into account hypo-treatments and/or insulin correction boluses, since they can have a significant input on the glycemic outcomes. One solution to

this problem is to discard these scenarios from the adaptations when such information is available. This was the approached followed by Reddy and colleagues in the evaluation of an adaptive meal-bolus calculator **[17]**.

It is important to remark that the effectiveness of the Case-based Reasoning (CBR) algorithm could not be evaluated due to the limitations of the employed simulator. In order to prove the efficacy of the CBR algorithm, a clinical trial is required. Note that the clinical feasibility of CBR in the context of meal bolus calculations has been proved by Reddy et al **[14]**.

Once the technology has been validated in a pivotal study and gone through the corresponding regulatory approvals, this could be implemented on a sensor-augmented insulin pump with Internet connectivity (e.g. Cellnovo System, Pencoed, UK), which would allow remote adaptation and supervision by expert clinicians. Future work also includes the evaluation of the presented technique in combination with a meal bolus adaptation technique such as the one proposed by Herrero and colleagues **[16].**

5. Conclusion

Based on the presented in silico study, the proposed basal insulin adaptation technique has the potential to effectively adjust the 24-hour basal insulin profile of a type 1 diabetes population on sensor-augmented insulin pump therapy. Further clinical studies are required to evaluate its effectiveness in a real scenario.

6. References

[1] Daneman D, Type 1 diabetes. The Lancet. 2006; 367(9513):847-858.

[2] Pickup JC. Management of diabetes mellitus: is the pump mightier than the pen? Nat Rev Endocrinol. 2012 Feb 28; 8(7):425-33.

[3] Jovanovic L. Optimizing insulin therapy in patients with diabetes, CME Activity jointly sponsored by Washington Hospital Center and MedStar Research Institute. 2002. Insulin therapy and algorithms for treating type 1 diabetes mellitus; 13–19.

[4] Davidson PC, Hebblewhite HR, Steed RD, and Bode BW: Analysis of guidelines for basal bolus insulin dosing: basal insulin, correction factor, and carbohydrate-to-insulin ratio. Endocr Pract 2008; 14:1095-1101.

[5] Walsh J, Roberts R, Bailey T. Guidelines for optimal bolus calculator settings in adults, J. Diabetes Sci. Technol. 2011; 5 (1):129–135.

[6] Schmidt S, Nørgaard K. Bolus calculators. J Diabetes Sci Technol. 2014 Sep;8(5):1035-41.

[7] Wilinska ME, Chassin LJ, Schaller HC, Schaupp L, Pieber TR, Hovorka R. Insulin kinetics in type-1 diabetes: continuous and bolus delivery of rapid acting insulin. IEEE Transactions on Biomedical Engineering. 2005. 52(1):3-12.

[8] Zisser H, Robinson L, Bevier W, Dassau E, Ellingsen C, Doyle FJ, Jovanovic L. Bolus calculator: a review of four "smart" insulin pumps. 2008. Diabetes technology and therapeutics. 10(6):441-444.

[9] León-Vargas F, Garelli F, De Battista H and Vehí J. Postprandial blood glucose control using a hybrid adaptive PD controller with insulin-on-board limitation. Biomedical Signal Processing and Control. 2013. 8(6):724-732.

[10] Toffanin C, Zisser H, Doyle FJ 3rd, Dassau E. Dynamic insulin on board: incorporation of circadian insulin sensitivity variation. Journal of diabetes science and technology. 2013. 7(4): 928-940.

[11] Walsh J, Roberts R, Bailey T. Guidelines for insulin dosing in continuous subcutaneous insulin infusion using new formulas from a retrospective study of individuals with optimal glucose levels. J Diabetes Sci Technol. 2010; 4:1174-1181.

[12] Owens C, Zisser H, Jovanovic L, Srinivasan B, Bonvin D, Doyle FJ 3rd. Run-to-run control of blood glucose concentrations for people with Type 1 diabetes mellitus. IEEE Trans Biomed Eng. 2006 Jun;53(6):996-1005.

[13] Palerm C, Zisser H, Bevier WC, Jovanovic L, and Doyle III FJ. Prandial insulin dosing using run-to-run control application of clinical data and medical expertise to define a suitable performance metric. Diabetes Care. 2007. 30(5):1131-1136.

[14] Tuo J, Sun H, Shen D, Wang H, Wang Y. Optimization of insulin pump therapy based on high order run-to-run control scheme. Computer Methods and Programs in Biomedicine. 2015; 120:123-134.

[15] Herrero P, Pesl P, Reddy M, Oliver N, Georgiou P. Toumazou C. Advanced insulin bolus advisor based on run-to-run control and case-based reasoning. IEEE J Biomed Health Inform. 2015;19(3):1087-1096.

[16] Herrero P, Pesl P, Bondia J, Reddy M, Oliver N, Georgiou P, and Toumazou C. Method for automatic adjustment of an insulin bolus calculator: in silico robustness evaluation under intra-day variability. Comput Methods Programs Biomed. 2015;119(1):1-8.

[17] Reddy M, Pesl P, Xenou M, Toumazou C, Johnston D, Georgiou P, Herrero P, Oliver N. Clinical safety and feasibility of the Advanced Bolus Calculator for Type 1 Diabetes (ABC4D): a 6-week non-randomised pilot study. Diabetes Technology and Therapeutics. 2016; 18(8):487-493.

[18] Palerm CC, Zisser H, Jovanovič L, Doyle FJ. A Run-to-Run Control Strategy to Adjust Basal Insulin Infusion Rates in Type 1 Diabetes. *Journal of process control*. 2008;18(3-4):258-265.

[19] Toffanin C., Messori M., Cobelli C., Magni L. Automatic adaptation of basal therapy for Type 1 diabetic patients: A Run-to-Run approach. Biomedical Signal Processing and Control. 2017. 31: 539-549.

[20] Wang Y, Percival MW, Dassau E, Zisser HC, Jovanovič L, Doyle FJ. A Novel Adaptive Basal Therapy Based on the Value and Rate of Change of Blood Glucose. Journal of diabetes science and technology (Online). 2009;3(5):1099-1108.

[21] Herrero P, Bondia J, Adewuyi O, Pesl P, El-Sharkawy M, Reddy M, Toumazou C, Oliver N, Georgiou P. Enhancing automatic closed-loop glucose control in type 1 diabetes with an adaptive meal bolus calculator - in silico evaluation under intra-day variability. Comput Methods Programs Biomed. 2017 Jul; 146:125-131.

[22] Dassau E, Pinsker JE, Kudva YC, Brown SA, Gondhalekar R, Dalla Man C, et al. 12-Week 24/7 Ambulatory Artificial Pancreas with Weekly Adaptation of Insulin Delivery Settings: Effect on Hemoglobin A1c and Hypoglycemia. Diabetes Care Oct 2017, [In Press].

[23] Toffanin C, Visentin R, Messori M, Di Palma F, Magni L, Cobelli C. Towards a Run-to-Run Adaptive Artificial Pancreas: In Silico Results. IEEE Trans Biomed Eng. 2017 [Epub ahead of print]

[24] Messori M, Kropff J, Del Favero S, Place J, Visentin R, Calore R, et al., and for the AP@home consortium. Individually Adaptive Artificial Pancreas in Subjects with Type 1 Diabetes: A One-Month Proof-of-Concept Trial in Free-Living Conditions Diabetes Technology & Therapeutics. 2017; 19(10):560 -57.

[25] Aamodt A, and Plaza E. Case-based reasoning: Foundational issues, methodological variations, and system approaches. AI Commun. 1994; 7(1):39-59.

[26] Wang Y, Gaoc F, and Doyle III FJ. Survey on iterative learning control, repetitive control, and run-to-run control. Journal of Process Control. 2009. 19(10):1589–1600.

[27] Altman NS. An Introduction to Kernel and Nearest-Neighbor Nonparametric. Regression. The American Statistician. 1992; 46(3): 175:185.

[28] B.P. Kovatchev, M. Breton, C. Dalla-Man, and C. Cobelli, In silico preclinical trials: a proof of concept in closed-loop control of Type 1 diabetes. J. Diabetes Sci. Technol. 2009; 3(1):44–55.

[29] Dalla-Man C, Rizza RA, and Cobelli C, Meal simulation model of the glucose-insulin system, IEEE Trans. Biomed. Eng. 2007; 54(10):1740–1749.

[30] Schiavon M, Dalla-Man C, Kudva YC, Basu A, and Cobelli C. In Silico Optimization of Basal Insulin Infusion Rate during Exercise: Implication for Artificial Pancreas. J Diabetes Sci Technol. 2013 Nov; 7(6): 1461–1469.

[31] Maahs DM et al. Outcome Measures for Artificial Pancreas Clinical Trials: A Consensus Report. Diabetes Care. 2016 Jul;39(7):1175-9.