Towards a Run-to-Run Adaptive Artificial Pancreas: In Silico Results

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***Abstract*—Objective: Contemporary and future outpatient long-term artificial pancreas (AP) studies need to cope with the well-known large intra- and inter-day glucose variability occurring in type 1 diabetic (T1D) subjects. Here we propose an adaptive Model Predictive Control (MPC) strategy to account for it and test it in silico.**

Methods: A Run-to-Run (R2R) approach adapts the subcutaneous basal insulin delivery during the night and the carbohydrate-to-insulin ratio (CR) during the day, based on some performance indices calculated from subcutaneous continuous glucose sensor data. In particular, R2R aims, first, to reduce the % of time in hypoglycemia and, secondarily, to improve the % of time in euglycemia and average glucose. In silico simulations are performed by using FDA-accepted University of Virginia/Padova T1D simulator enriched by incorporating three novel features: intra- and inter-day variability of insulin sensitivity, different distributions of CR at breakfast, lunch and dinner, and dawn phenomenon.

Results: After about two months, using the R2R approach with a scenario characterized by a random $\pm 30\%$ variation of the nominal insulin sensitivity the time in range and the time in tight range are increased by 11.39% and 44.87%, respectively, and the time spent above 180 mg/dl is reduced by 48.74%.

Conclusions: An adaptive MPC algorithm based on R2R shows in silico great potential to capture intra- and inter-day glucose variability by improving both overnight and postprandial glucose control without increasing hypoglycemia.

Significance: Making an AP adaptive is key for long-term real life outpatient studies. These good in silico results are very encouraging and worth testing in vivo.

***Index Terms*—Automatic adaptation, model, type 1 simulator, subcutaneous glucose sensor, subcutaneous insulin delivery**

I. Introduction

In the past decade the diabetes community has seen unprecedented advances in artificial pancreas (AP) technology, which moved from short-term inpatient studies to short trials at home employing wireless, portable, wearable AP systems. A comprehensive review of the early developments in the AP field and of the first inpatient closed-loop control studies can be found in [1], and several recent reviews highlight additional progresses in this field [2], [3], [4]. In [5] an AP system based on a Modular Model Predictive Control architecture (MMPC)has been proposed with the core module being is the Model Predictive Control (MPC) described in [6], [7]. For in-vivo testing the MMPC has been implemented on the Diabetes Assistant (DiAs) [8], a wearable platform, which has been previously tested and validated vs. Sensor Augmented Pump therapy (SAP) in feasibility, safety and efficacy. Several studies were conducted in adults in gradually less structured and less monitored settings: inpatient first [9], [10], 2-day in hotel settings [11], [12], and, recently, 2-month evening & night at home [13]. The formerly conducted studies had a limited duration and were restricted to evening and night, thus allowing to neglect the impact of intra- and inter-day glucose response variability of each subject, e.g. to insulin and meals. The latter is a well-known phenomenon and became a major issue with the introduction of longer (week/month) home trials. This large subject-specific variability calls for an adaptive controller.

In [14], [15] the control adaptation is obtained by updating of the model parameters every sample (5 or 10 minutes). Differently, in this paper an adaptive MPC algorithm based on the Run-to-Run (R2R) approach is proposed. The R2R is a well-known learning-type control algorithm [16] that learns information about the control quality from the current run and changes the control variable to apply in the next run. The R2R strategy has already been used for glucose control in patients with Type 1 diabetes (T1D) on the basis of a few daily self-monitoring blood glucose (SMBG) measurements [17], [18], [19], [20], [21] or using continuous glucose monitoring (CGM) [22], [23], [24], [25], [26], [27] to adapt day-by-day basal insulin delivery or the insulin meal bolus.

R2R in the AP context (i.e. with continuous time (5-10 minutes) closed-loop control suggestions) was introduced in [28], where the aggressiveness of the controller was adapted by using the maximum and minimum glucose values provided by CGM. In this work, we propose a much more realistic R2R approach for tuning the MPC algorithm which adapts the basal insulin delivery during the night and the time-varying carbohydrate-to-insulin ratio (CR) during the day. The R2R adaptation is based on well-accepted performance metrics, e.g the % time spent below & above the euglycemic range and average glucose, with priority given to avoid hypo phenomena. In silico simulations are performed by using the 2013 version of the FDA-accepted University of Virginia/Padova Simulator [29] enriched by three novel features: i) incorporation of intra- and inter-day variability of insulin sensitivity (SI), described in [30]; ii) different distributions of carbohydrate-to-insulin ratio (CR) at breakfast, lunch and dinner; and iii) dawn phenomenon.

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II. Multiple-Day T1DM Simulator

The three new features introduced into the FDA-accepted University of Virginia/Padova T1D simulator [29] to create a realistic month scenario to test the MPC R2R adaptive strategy are described below.

A. Intra- and Inter-day Variability of Insulin Sensitivity

A recent study was conducted on T1DM subjects, who underwent a mixed meal with triple tracer approach at breakfast (B), lunch (L) and dinner (D), with all meals having same amount and composition [31]. This allowed to reliably estimate SI at B, L, D: in fact, the particular protocol design allowed to eliminate the confounding effects of meal composition, and thus we were able to relate the intra-day glucose variability to the sole SI variability. The results of the experiment revealed the existence of diurnal patterns of SI, with, on average, SI lower at B than L and D. This knowledge has been incorporated into the simulator [30], in which SI is described by model parameters V_{mx} and k_{p3}, representing insulin action on glucose utilization by tissues and on glucose production by the liver, respectively. In particular, each in silico subject has been associated to a certain intra-day variability pattern, namely the nominal pattern. Distribution of V_{mx} and k_{p3} at B, L, and D are shown in Fig.1a,b. The inter-day variability is then generated by randomly modulating the nominal pattern (see *Scenario 1* in Section III-C). In addition, a slower increasing/decreasing trend of SI has been added (see *Scenario 2* in Section III-C).

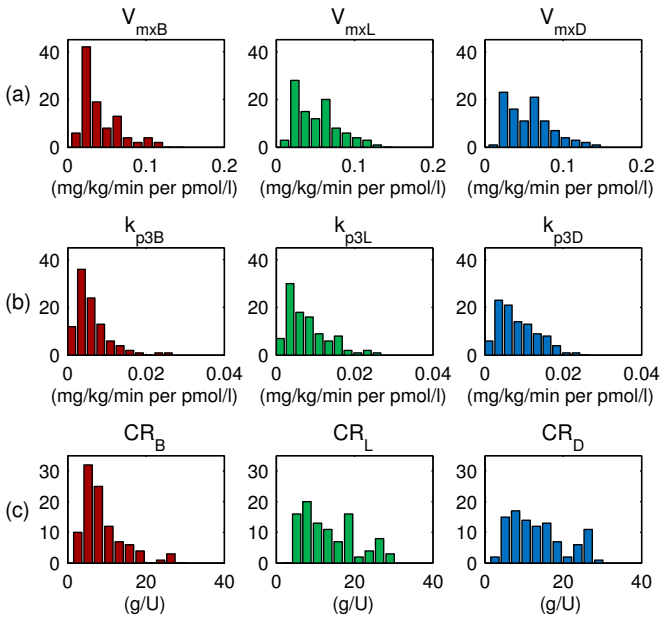

Fig. 1. (a): distributions of V_{mx} at Breakfast (left), Lunch (middle), and Dinner (right). (b): distributions of k_{p3} at Breakfast (left), Lunch (middle), and Dinner (right). (c): distributions of CR at Breakfast (left), Lunch (middle), and Dinner (right).

B. Distributions of Carbohydrate-to-Insulin Ratio at Breakfast, Lunch and Dinner

On the basis of the time-varying SI, each in silico subject has been equipped with multiple CR, which vary at B, L, and D. Multiple CR are determined similarly to what described in [29]. Each in silico subject, with its specific SI nominal pattern, receives 40, 80, and 60 g of carbohydrates (CHO), respectively for the determination of CR values at B, L, and D, starting from its basal level. The optimal insulin bolus is determined so that (1) glucose concentration, measured 3 hours after the meal, is between 85% and 110% of the basal; (2) the minimum glucose concentration is above 90 mg/dl; and (3) the maximum glucose concentration is between 40 and 80 mg/dl above the basal level. CR is then calculated as the ratio between the amount of ingested CHO and the optimal insulin bolus:

$$CR_j = \frac{CHO_j}{bolus_j}, \text{ with } j = B, L, D$$

Distribution of CR at B, L, and D are shown in Fig.1c. Correction Factor (CF) was determined with the so-called 1700 rule [32] that is,

$$CF = \frac{1700}{TDI}$$

where TDI is the total daily insulin, determined for each virtual patient as the sum of optimal insulin boluses at B, L, and D, and of the basal infusion rate.

C. Dawn Phenomenon

A model of nocturnal glucose variability has been developed to describe the ”dawn” phenomenon, which consists in a rise in blood glucose concentrations in early morning due to both an increased Endogenous Glucose Production (EGP) and an increased insulin requirements [33], [34]. In particular, Mallad et al [33] quantified an almost 30 mg/dl increase in glucose concentration from 3:00 am to 7:00 am and observed an increase of EGP of about 1.5 mg/kg/min in the same interval. Thus, we modelled the EGP variation as a linear increase of basal EGP (EGPb) from 3:00 am to 7:00 am. Similarly, the increased insulin requirement is described as a decrease in insulin-dependent glucose utilization (Uid). Inter-subject and inter-day variability of both time interval and magnitude of EGPb increase and Uid decrease are obtained as random modulation of the averages reported in [33].

III. Run-to-Run strategy for adaptive MPC tuning

The MPC algorithm considered in this paper is the linear model predictive control described in [7] used to calculate insulin delivery during the day. The principal parameters used for control tuning and individualization are the basal insulin delivery, the CR, the CF and the body weight (BW). In particular, the MPC computes an insulin variation with respect to the basal profile, uses CR and CF (taking into account also the insulin on board) to compute the insulin reference in the cost function, and BW and CR to tune the control aggressiveness (q). The goal of this paper is to propose an adaptive MPC in order to: (i) optimize the tuning of the controller parameters; (ii) adapt them to the slow inter-day variability. A good candidate approach is the so-called R2R strategy, which adjusts the parameters to be used in the next day (run) on the basis of the performance measured during the

previous day (run). In particular, at the end of each day the MPC parameters are modified using the basal and CR values updated through R2R strategy. The choice of the performance metrics is a critical point. The success of R2R strategy needs to be assessed by appropriate performance metrics. CGM sensors (key component of an AP) allow to calculate clinically relevant metrics, including, e.g., the percentage of time spent in euglycemic range, the percentage of time spent below and above the range, and the average glucose. In particular, since a major concern in T1D therapy is to avoid hypoglycemia, the updating law is primarily designed to lead to 0 the percentage of time spent below 70 mg/dl. Once this primary goal is achieved, a secondary updating law is designed to reduce the percentage of time spent above 180 mg/dl and to lead the average Blood Glucose (BG) to the desired target.

A. Algorithm: theory

This approach has been applied to update either the basal insulin delivery or the meal insulin bolus. Since the bolus is strictly related to the amount of carbohydrates in the meal, the update is realized through the CR parameter. In order to keep independent the effects of these two variables, the basal delivery adaptation is computed during the night, i.e. when no meal perturbations are present, whereas the CR update is performed during the day by keeping the basal delivery constant. Moreover, the evaluation intervals are continually adapted in order to be disjointed, even in presence of varying mealtimes across the days. The basal therapy is updated within the night interval, where it is assumed to be constant. The run period is set equal to 24h, which corresponds to the circadian rhythm of subjects variations. For each run, the variation of the basal insulin rate is proportional to the applied basal delivery and to the performance indices computed during the previous run. In order to give priority in avoiding hypoglycemia, a switching condition depending on the percentage of time spent below 70 mg/dl is introduced. In particular, at run k, the updating law is defined as follows:

$$b(k+1) = \begin{cases} b(k) - \bar{b}k_1^b T_b^b(k) & \text{if } T_b^b(k) > 0 \\ b(k) + \bar{b}(k_2^b T_a^b(k) & \\ \qquad +k_3^b \dfrac{G_m^b(k) - G_T^b}{G_T^b}\Big) & \text{if } T_b^b(k) = 0 \end{cases}$$

where b is the basal insulin delivery, the constants k_1^b, k_2^b, k_3^b are the R2R gains, G_T^b is the glycemic target, $\bar{b}$ is the initial basal therapy, and T_b^b, T_a^b, G_m^b are the R2R performance indices associated with the night interval. In particular, T_b^b is the percentage of time spent below 70 mg/dl, T_a^b is the percentage of time spent above 180 mg/dl, and G_m^b is the average glucose concentration in the evaluation interval, which is equal to the night interval delayed by 3 hours. It is worth emphasizing that, if a meal occurs within this interval, its end is set equal to the meal time. A similar updating law is used to optimize the CR values, which are assumed to be constant along n daily intervals $[t_j^B; t_{j+1}^B]$, $j = 1, ..., n$, with $t_{n+1}^B = t_1^B$. In particular, at run k, the updating law for the j^{th} interval is defined as follows:

$$B_j(k+1) = \begin{cases} B_j(k) - \bar{B}_j k_1^B T_b^{B_j}(k) & \text{if } T_b^{B_j}(k) > 0 \\ B_j(k) + \bar{B}_j(k_2^B T_a^{B_j}(k) + & \\ \qquad k_3^B \dfrac{G_m^{B_j}(k) - G_T^B}{G_T^B}\Big) & \text{if } T_b^{B_j}(k) = 0 \end{cases}$$

where $B_j(k) = 1/CR_j(k)$ is the inverse of the CR at run k during the interval j, the constants k_1^B, k_2^B, k_3^B are the R2R gains, G_T^B is the glycemic target, constant for all the intervals, $\bar{B}_j$ is the initial value in the interval j, and $T_b^{B_j}$, $T_a^{B_j}$, $G_m^{B_j}$ are the R2R performance indices associated with the j interval. In particular, $T_b^{B_j}$ is the percentage of time spent below 70 mg/dl, $T_a^{B_j}$ is the percentage of time spent above 180 mg/dl, and $G_m^{B_j}$ is the average glucose concentration collected in the j^{th} evaluation interval. The maximum length of each j^{th} evaluation interval is 7h; it starts from the meal time in the j^{th} interval and is truncated if another meal occurs.

The stability of the proposed strategy can be demonstrated by applying the method described in [27], where a R2R approach for adapting a piecewise basal therapy in an open-loop context is proposed. A key assumption is the use of disjoint intervals. Indeed, if the intervals of basal and bolus insulin delivery are not disjoint, the problem moves from several scalar to a multivariable framework, with a significant increase of complexity both in terms of algorithm tuning and stability analysis.

The initial value $\bar{b}$, $\bar{B}$ are usually set equal to the values adopted for the conventional basal-bolus therapy, while the gains k_1^b, k_2^b, k_3^b,k_1^B, k_2^B, k_3^B are equal for all the intervals and all the patients.

The tuning of the gains must consider, in addition to stability issues, performance and safety issues. In particular, there is a trade-off between a R2R algorithm that learns quickly (the value of the parameters mainly depends from the last days) or slowly (the value of the parameters depends from a longer past period). The main drawback of a faster R2R is that it is more affected by occasional situations and prone to several safety problems related to important inter-day life style variability. The drawback of a slower R2R is that a longer time is required to improve the performance. In any case, daily changes of the patient's life style (e.g. stress, exercise, different meals) must be compensated by the MPC controller and not by the R2R strategy that should only learn slow changes in patient behaviour (i.e. weeks/month). In silico robustness scenarios have been of great help in fine tuning the gains.

B. Real life algorithm

The introduced algorithm has strong theoretical properties, but needs some adjustments in order to cope with the uncertainties of a real life scenario and possible malfunctioning of an AP system. In particular, the following aspects are considered:

- Memory limitation: the AP system stores only a limited amount of data, not allowing covering the entire 24-hour period.

- Malfunctioning: likely events are pump occlusions and connectivity losses.
- User over rules: to ensure safety, the AP allows the user to change all settings, including the controller suggestions (boluses), the algorithm (from closed- to open-loop) or by setting a temporary basal rate.
- Hypothesis violation: the algorithm assumes no overlapping between the intervals and non occurrence of simultaneous events, e.g. only one meal per interval. Such a situation is likely not happening in a real life scenario.

In order to handle the memory limitation, the update for each parameter is computed as soon as the needed data have become available, with the purpose to reduce the amount of data to store. The update is performed only if the user has not changed its clinical parameters and if no malfunctioning has occurred. Indeed, these events would introduce changes in the performance indices that are not directly caused by the control algorithm tuning. Moreover, the data for a specific interval can be limited by the occurrence of events like a previous meal that still influences the glucose concentration or a closed-loop interruption due to system failure; in this case the update is computed only if the amount of available data is above a certain threshold. Multi-consecutive meals are considered if they occur in the same interval; in this case the CR update is performed as usual by using as evaluation interval the union of the evaluation intervals.

C. Simulation scenario

The R2R algorithm is tested on the 100 in silico adults of the simulator described in Section II. The night interval considered for basal insulin update is [0:00 am; 8:00 am] for all the patients. The n $(n = 3)$ time intervals that define the piecewise constant CR are defined by $t_1^B =$ 8:00 am, $t_2^B =$ 1:00 pm, $t_3^B =$ 8:00 pm for all the patients.

The gains are fixed to $k_1^b = 0.15$, $k_2^b = 0.175$, $k_3^b = 0.005$, and $G_T^b = 115$ mg/dl, for the basal and to $k_1^B = 0.3$, $k_2^B = 0.05$, $k_3^B = 0.01$, and $G_T^B = 115$ mg/dl, for CR update.

Two in silico scenarios are considered: the first, *Scenario 1*, is a 56-day scenario allowing to test the ability of R2R to optimize the tuning of controller parameters, and is characterized by a random $\pm 30\%$ variation of the nominal insulin sensitivity from the beginning and throughout the trial. The second, *Scenario 2*, lasts 28 days and aims to test the adaptation of R2R to a slow increasing/decreasing trend of insulin sensitivity; this is realized by combining the insulin sensitivity variability model with a linear modulation of the nominal insulin sensitivity from $\pm 10\%$ at the beginning to the $\pm 30\%$ at the end of the trial. For both scenarios, the CR of each interval is initialized with the nominal value randomly modified of $\pm 20\%$. Three meals per day are considered at 8:00 am, 1:00 pm, and 8:00 pm containing 40 g, 80 g, and 60 g of CHO, respectively; these settings are chosen in order to mimic the habits occurring in real life, like those observed in [13]. Moreover, if the BG falls below 65 mg/dl, the protocol prescribes a rescue carbohydrate dose of 16 g, defined as hypo-treatment (ht). Two ht are separated by at least 30 minutes. The CGM sensor is affected by the error noise described in [7]. The simulations are performed by using the closed-loop MPC strategy (CL) described in [7] and the adaptive MPC enhanced by R2R strategy (CL$_{R2R}$).

D. Metrics and statistical analysis

Performance metrics follow the consensus statement endpoints for AP trial described in [35] and include average (A) BG and standard deviation (SD), percentage of time spent in euglycemic range [70-180] mg/dl (T_r), percentage of time spent in tight range [70-140] mg/dl (T_{tr}), percentage of time spent above 180 mg/dl (T_a), percentage of time spent above 250 mg/dl (T_{a250}), percentage of time spent below 70 mg/dl (T_b), percentage of time spent below 60 mg/dl (T_{b60}), percentage of time spent below 50 mg/dl (T_h), average number of ht per patient ($\#\overline{ht}$), percentage of basal, bolus and the total daily insulin (TDI) delivered to the patient. These metrics are computed during day & night (D&N), during night (N, 0:00 pm - 8:00 am), and as an average of all the post-prandial (PP) periods (4h) of the specified week.

Median $[25^{th}, 75^{th}]$ percentiles for non-Gaussian distributed data and mean ($\pm$ standard deviation) otherwise are reported for the various indices. Confidence intervals on the mean or median are reported as well. The gaussianity and homoscedasticity of the data distributions are assessed by the Lilliefors test and two-sample F-test, respectively. In order to evaluate the significant differences, the more appropriated statistical test is selected based on the characteristics of the data distributions. If at least one distribution is non-Gaussian, the Wilcoxon rank sum test is used; if both distributions are Gaussian and homoscedastic, a two-sample t-test is performed; otherwise, if the homoscedasticity is not satisfied, the two-sample t-test with Satterthwaites approximation is used.

The performance of CL and CL$_{R2R}$ is also evaluated by using the Control Variability Grid Analysis (CVGA) introduced in [36] and subsequently improved in [6]. A single point represents the couple of 2.5 and 97.5 percentiles of BG values reached by the virtual patient during the considered week.

IV. Results

Scenario 1: The results are shown in Figs.2-4. The simulated BG on Week 1, Week 4, and Week 8 are represented in Fig.2 as median $[25^{th}, 75^{th}]$ percentiles: the postprandial overshoots detected after breakfast and dinner (Fig.2a) are considerably reduced after a month of R2R (Week 4, Fig.2b). A further reduction is achieved after two months (Week 8, Fig.2c), also with a reduced BG variability.

Performance metrics are shown in Fig.3, where median $[25^{th}, 75^{th}]$ percentiles of average BG (a), percent time in range (b), percent time in tight range (c) and percent time spent above 180 mg/dl (d) are shown: while performance indices in CL simulations remain substantially unchanged, all the CL$_{R2R}$ indices improve day-by-day exhibiting a substantially monotone trend.

CVGA plots (Fig.4) confirm the CL$_{R2R}$ improvement by better populating the center of the A and B zones.

Numerical comparison of CL vs CL$_{R2R}$ on the whole trial duration is reported in Table I for *Scenario 1*, where the

	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8
A (mg/dl)	0.86%	2.51%	3.75%	4.81%	4.47%	5.38%	6.36%	6.29%
T_r (%)	1.69%	6.15%	7.72%	8.31%	9.67%	9.52%	10.73%	11.39%
T_{tr} (%)	5.6%	15.31%	25.82%	28.37%	33.89%	43.05%	43.06%	44.87%
T_a (%)	7.94%	18.66%	28.30%	33.95%	42.67%	47.49%	46.81%	48.74%

TABLE I

COMPARISON OF THE PERCENTAGES OF IMPROVEMENTS REACHED THROUGH THE USE OF THE R2R ALGORITHM WITH *Scenario 1*.

improvement shown by CL_{R2R} is evident. All the performance details on Week 1, Week 4 and Week 8, i.e. during the first, the fourth and the last week of the trial, are reported in Table II. It is worth noting that indices related to hypoglycemia, i.e. T_b, T_{b60}, T_h, $\#ht$, are always non-Gaussian with median, 25^{th} and 75^{th} percentiles equal to 0 in both CL and CL_{R2R}. These results do not mean the total absence of hypoglicemic events. In fact, the CVGA reported in Fig.4 of Week 1, Week 4 and Week 8 show that for some patients the minimum BG is less than 50 mg/dl. In all the runs CL_{R2R} is able to reduce the points in D zone. Over the weeks there are no significant changes of the basal and bolus percentages, while there is a significant increase of TDI delivered by CL_{R2R} vs. CL.

Table I shows the improvements of CL_{R2R} measured as percentage vs. CL along the 8 weeks of *Scenario 1*. After one week: the time spent above 180 mg/dl is reduced by 7.94%, the average BG is reduced by 0.86%, the time in tight range is increased by 1.69%, and the time in range by 5.6%. After a month (Week 4), the decrease of the time spent above 180 mg/dl is 33.95% and the average BG is decreased by 4.81%, whereas the time in range is increased by 8.31% and the time in tight range by 28.37%. After two months (Week 8), the performance remains stable. The CR and basal changes carry on during the R2R process and are reported in Table III.

Scenario 2: The results shown in Figs. 5-7 and Tables III, IV, are similar to those described above. After 4 weeks, the improvement of CL_{R2R} vs. CL is evident: both median and variability ($[25^{th}, 75^{th}]$ percentiles) are decreased (Fig.5b). The distribution of outcome metrics also highlights the improvement of the CL_{R2R} vs. CL (which slightly worsens the performance), revealing the ability of R2R approach to follow the slow trend of inter-day variability. The comments on hypoglycemic metrics and delivered insulin discussed above still hold. All the performance details on Week 1 and Week 4 are reported in Table IV showing that, at the end of the trial (Week 4), the performance obtained with both CL_{R2R} and CL are very similar to their counterparts at Week 4 of *Scenario 1*. CVGA results further underline the importance of the R2R approach to control blood glucose in a time-variant fashion, i.e. the sole CL is not fully adequate to follow slow inter-day variations, with a consequent decrease of performance with respect to the beginning of the trial; however this does not affect the safety of the control, since the performance are virtually superimposable to those obtained at Week 4 of *Scenario 1*. The CRs and basal changes carry on during the R2R process and are reported in Table III.

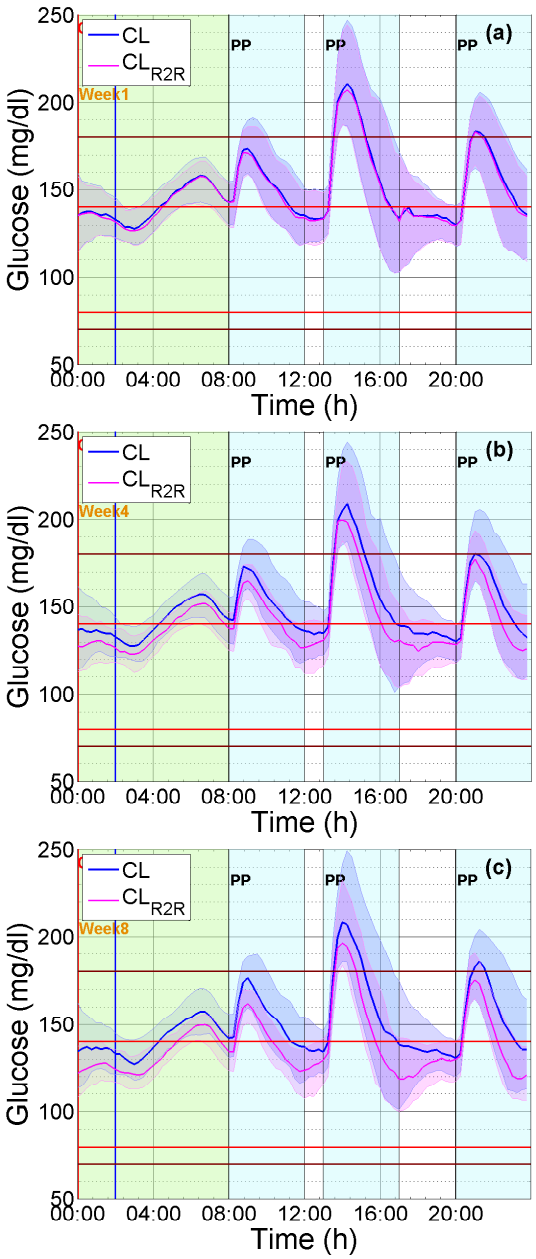

Fig. 2. Comparison of average glucose time courses in CL (blue) vs CL_{R2R} (magenta) on Week 1 (a), Week 4 (b), and Week 8 (c) of *Scenario 1*. Continuous lines are the median across patients, with $[25^{th}, 75^{th}]$ percentiles as shading.

V. CONCLUSION

Making an AP adaptive is key for long-term real life outpatient studies. An adaptive MPC algorithm based on R2R has been presented and has shown in silico the great potential to capture intra- and inter-day glucose variability. In silico one- and two-month simulations have been performed by using the FDA-accepted University of Virginia/Padova T1D simulator enriched by three novel features: intra- and inter-day variability of insulin sensitivity, different distributions of CR at breakfast, lunch and dinner, and dawn phenomenon. The R2R CGM based strategy uses the % of time spent below 70 mg/dl, the % of time spent above 180 mg/dl, and

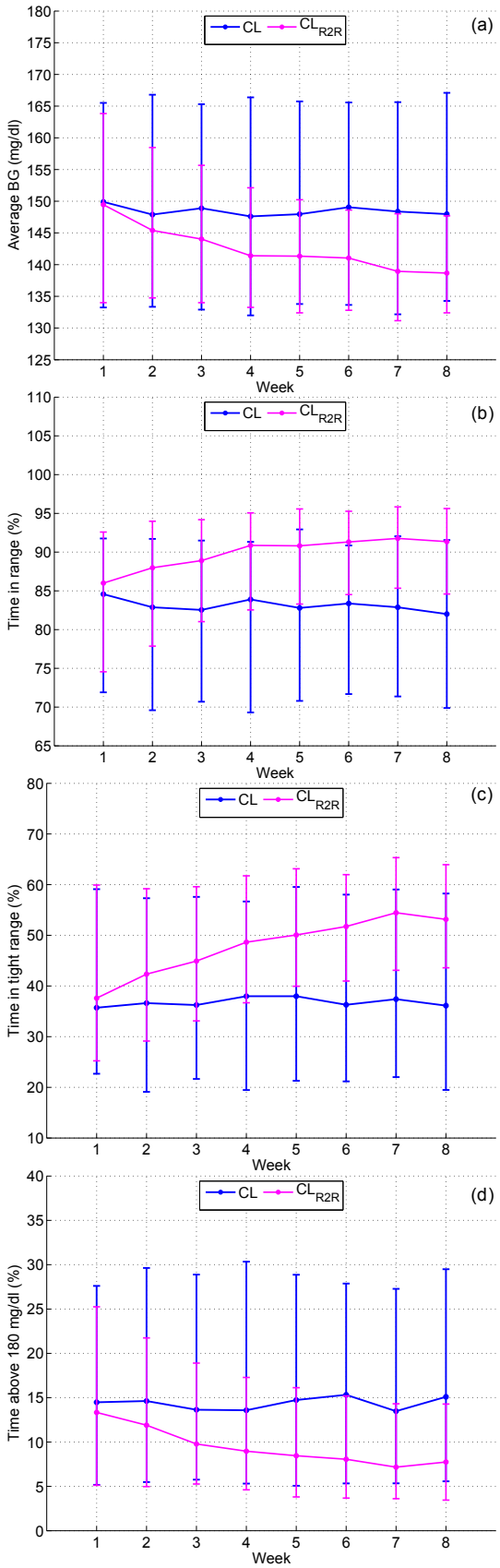

Fig. 3. Performance metrics of CL (blue), and CL_{R2R} (magenta) along the 8 weeks of *Scenario 1*: median (dots) $[25^{th}, 75^{th}]$ percentiles (bars) of the average BG (a), time in range (b), time in tight range (c) and time above 180 mg/dl (d) on 100 virtual patients.

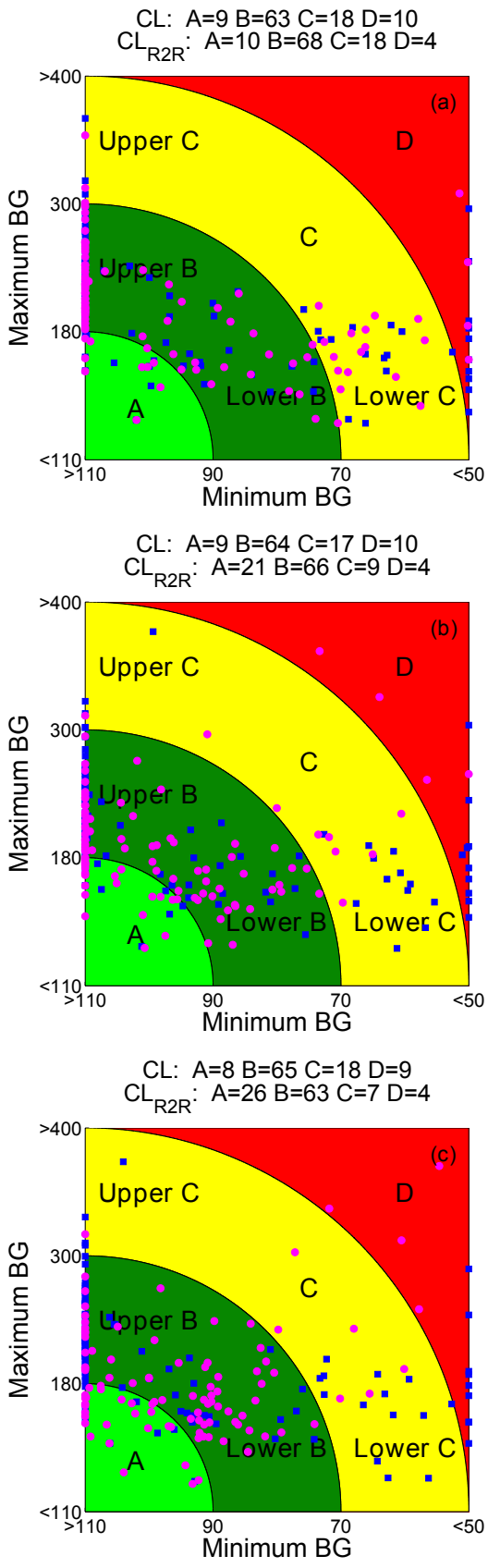

Fig. 4. CVGA of CL (blue square) vs CL_{R2R} (magenta circle) on Week 1 (a), Week 4 (b), and Week 8 (c) of *Scenario 1*. Each point represents the coordinates (x is the 2.5 percentile and y is the 97.5 percentile of glucose values) associated to a single patient.

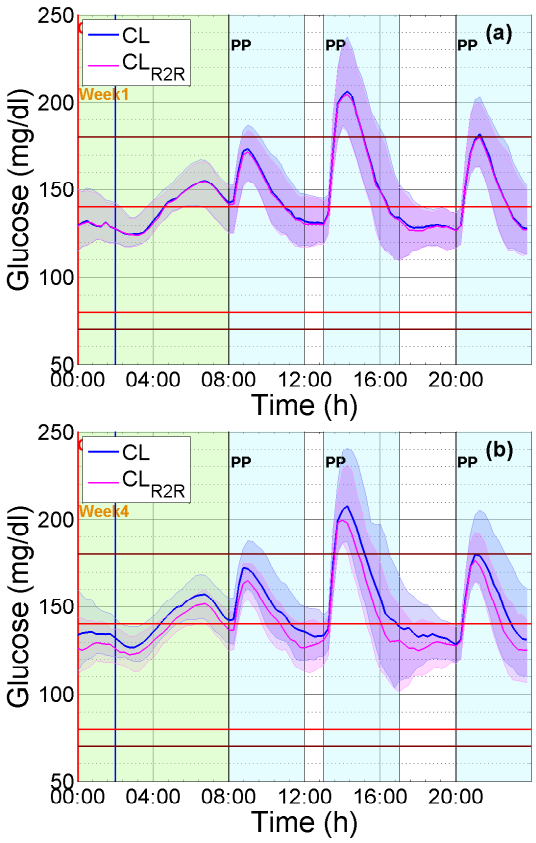

Fig. 5. Comparison of average glucose time courses in CL (blue) vs CL$_{R2R}$ (magenta) on Week 1 (a), and Week 4 (b) of *Scenario 2*. Continuous lines are the median across patients, with $[25^{th}, 75^{th}]$ percentiles as shading

the distance of average glucose from a target to adapt the basal insulin delivery during the night and and the CR during the day. Priority is given to avoid hypoglycemia, so that a switching strategy is derived. Both overnight and postprandial glucose control have been improved with no increase of hypoglycemia events by the adaptive MPC R2R strategy.
These encouraging in silico results achieved in a realistic one month conditions pave the way to an in vivo test of the proposed adaptive strategy with potential benefits for T1D subjects.

References

[1] C. Cobelli, E. Renard, and B. P. Kovatchev. Artificial pancreas: Past and present and future. *Diabetes*, 60(11):2672–2682, 2011.

[2] N.H. White, W. Sun, P.A. Cleary, R.P. Danis, M.D. Davis, D.P. Hinsworth, L.D. Hubbard, J.M. Lachin, and D.M. Nathan. Prolonged effect of intensive therapy on the risk of retinopathy complications in patients with type 1 diabetes mellitus: 10 years after the diabetes control and complications trial. *Arch Ophthalmol*, 126(12):1707–1715, 2008.

[3] R.M. Bergenstal, W.V. Tamborlane, A. Ahmann, J.B. Buse, G. Dailey, S.N. Davis, C. Joyce, B.A. Perkins, J.B. Welsh, and S.M. Willi et al. Sensor-augmented pump therapy for a1c reduction (star 3) study results from the 6-month continuation phase. *Diabetes Care*, 34(11):2403–2405, 2011.

[4] R.M. Bergenstal, D.C. Klonoff, S.K. Garg, B.W. Bode, M. Meredith, R.H. Slover, A.J. Ahmann, J.B. Welsh, S.W. Lee, F.R. Scott, and F.R. Kaufman. Threshold-based insulin-pump interruption for reduction of hypoglycemia. *New England Journal of Medicine*, 369(3):224–232, 2013.

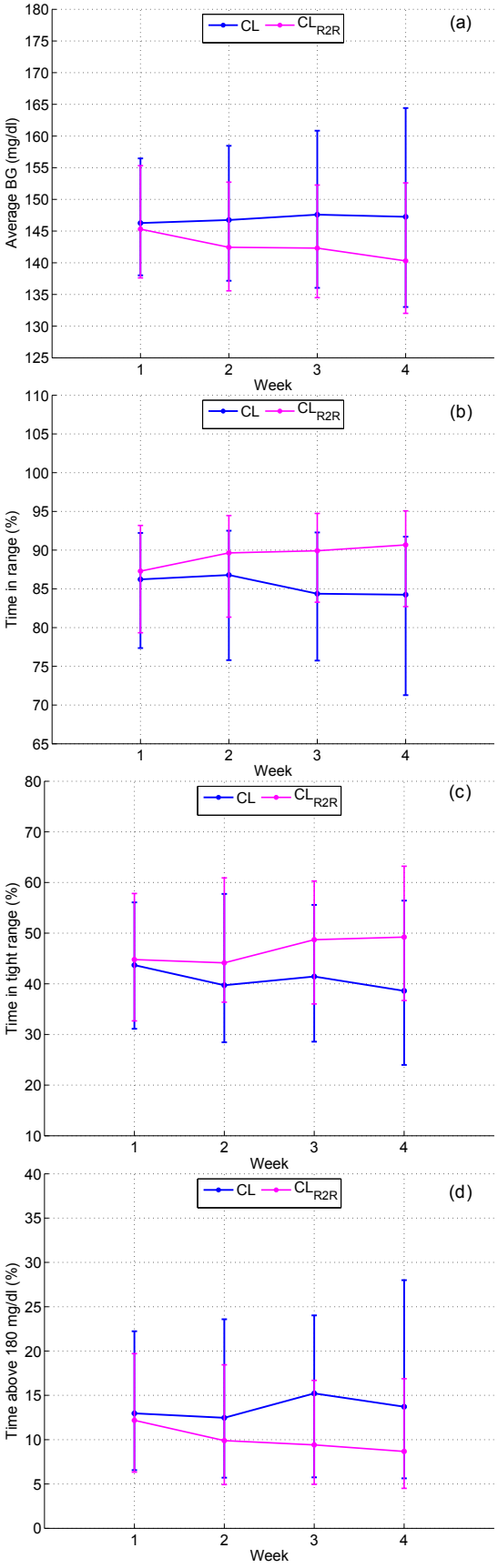

Fig. 6. Performance metrics of CL (blue), and CL$_{R2R}$ (magenta) along the 4 weeks of *Scenario 2*: median (dots) $[25^{th}, 75^{th}]$ percentiles (bars) of the average BG (a), time in range (b), time in tight range (c) and time above 180 mg/dl (d) on 100 virtual patients.

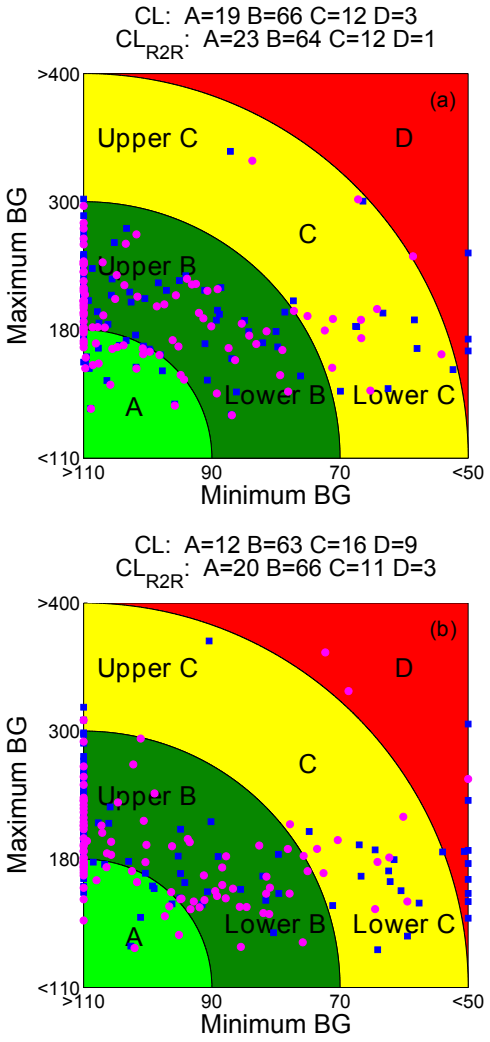

Fig. 7. CVGA of CL (blue square) vs CL$_{R2R}$ (magenta circle) on Week 1 (a), and Week 4 (b) of *Scenario 2*. Each point represents the coordinates (x is the 2.5 percentile and y is the 97.5 percentile of glucose values) associated to a single patient.

[5] S. D. Patek, L. Magni, E. Dassau, C. Hughes-Karvetski, C. Toffanin, G. De Nicolao, S. Del Favero, M. Breton, C. Dalla Man, E. Renard, H. Zisser, F. J. Doyle, C. Cobelli, and B. P. Kovatchev. Modular closed-loop control of diabetes. *IEEE Transactions on Biomedical Engineering*, 59(11):2986–2999, 2012.

[6] P. Soru, G. De Nicolao, C. Toffanin, C. Dalla Man, C. Cobelli, L. Magni, and on behalf of the AP@home consortium. Mpc based artificial pancreas: Strategies for individualization and meal compensation. *Annual Reviews in Control*, 36(1):118–128, 2012.

[7] C. Toffanin, M. Messori, F. Di Palma, G. De Nicolao, C. Cobelli, and L. Magni. Artificial pancreas: Model predictive control design from clinical experience. *Journal of Diabetes Science and Technology*, 7(6):1470–1483, 2013.

[8] P. Keith-Hynes, B. Mize, A. Robert, and J. Place. The diabetes assistant: a smartphone-based system for real-time control of blood glucose. *Electronics*, 3(4):609–623, 2014.

[9] M. Breton, A. Farret, D. Bruttomesso, S. Anderson, L. Magni, S. Patek, C. Dalla Man, J. Place, S. Demartini, S. Del Favero, C. Toffanin, C. Hughes-Karvetski, E. Dassau, H. Zisser, F. J. Doyle III, G. De Nicolao, A. Avogaro, C. Cobelli, E. Renard, B. Kovatchev, and on behalf of The International Artificial Pancreas (iAP) Study Group. Fully integrated artificial pancreas in type 1 diabetes: Modular closed-loop glucose control maintains near normoglycemia. *Diabetes*, 61(9):2230–2237, 2012.

[10] Y. M. Luijf, J. H. DeVries, K. Zwinderman, L. Leelarathna, M. Nodale, K. Caldwell, K. Kumareswaran, D. Elleri, J. M. Allen, M. E. Wilinska, M. L. Evans, R. Hovorka, W. Doll, M. Ellmerer, J. K. Mader, E. Renard, J. Place, A. Farret, C. Cobelli, S. Del Favero, C. Dalla Man, A. Avogaro, D. Bruttomesso, A. Filippi, R. Scotton, L. Magni, G. Lanzola, F. Di Palma, P. Soru, C. Toffanin, G. De Nicolao, S. Arnolds, C. Benesch, and L. Heinemann. Day and night closed-loop control in adults with type 1 diabetes mellitus: a comparison of two closed-loop algorithms driving continuous subcutaneous insulin infusion versus patient self-management. *Diabetes Care*, 36(12):3882–3887, 2013.

[11] S. Del Favero, D. Bruttomesso, F. Di Palma, G. Lanzola, R. Visentin, A. Filippi, R. Scotton, C. Toffanin, M. Messori, S. Scarpellini, P. Keith-Hynes, B. P. Kovatchev, J. H. DeVries, E. Renard, L. Magni, A. Avogaro, C. Cobelli, and on behalf of the AP@home Consortium. First use of model predictive control in outpatient wearable artificial pancreas. *Diabetes Care*, 37(5):1212–1215, 2014.

[12] S. Del Favero, J. Place, J. Kropff, M. Messori, P. Keith-Hynes, R. Visentin, M. Munaro, D. Bruttomesso, S. Galasso, F. Boscari, C. Toffanin, F. Di Palma, G. Lanzola, S. Scarpellini, A. Ferret, B. Kovatchev, L. Magni, A. Avogaro, J. H. DeVries, C. Cobelli, E. Renard, and on behalf of the AP@home Consortium. Multicentre outpatient dinner/overnight reduction of hypoglycemia and increased time of glucose in target with a wearable artificial pancreas using multi-modular model predictive control algorithm in adults with type 1 diabetes. *Diabetes and Obesity and Metabolism*, 17(5):468–476, 2015.

[13] J. Kropff, S. Del Favero, J. Place, C. Toffanin, R. Visentin, M. Monaro, M. Messori, F. Di Palma, G. Lanzola, A. Farret, F. Boscari, S. Galasso, P. Magni, A. Avogaro, P. Keith-Hynes, B. P. Kovatchev, D. Bruttomesso, C. Cobelli, J. H. DeVries, E. Renard, L. Magni, and for the AP@home consortium. Evening and night closed-loop glucose control in patients with type 1 diabetes under free living conditions: a randomized cross-over trial. *The Lancet Diabetes & Endocrinology*, In Press, 2015.

[14] F. H. El-Khatib, J. Jiang, and E. R. Damiano. Adaptive closed-loop control provides blood-glucose regulation using dual subcutaneous insulin and glucagon infusion in diabetic swine. *Journal of Diabetes Science and Technology*, 1(2):181–192, 2007.

[15] M. Eren-Oruklu, A. Cinar, L. Quinn, and D. Smith. Adaptive control strategy for regulation of blood glucose levels in patients with type 1 diabetes. *Journal of Process Control*, 19(8):1333–1346, 2009.

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

[17] H. Zisser, L. Jovanovič, F. J. Doyle III, P. Ospina, and C. Owens. Run-to-run control of meal-related insulin dosing. *Diabetes Technology & Therapeutics*, 7(1):48–57, 2005.

[18] C. Owens, H. Zisser, L. Jovanovič, B. Srinivasan, D. Bonvin, and F. J. Doyle. Run-to-run control of blood glucose concentrations for people with type 1 diabetes mellitus. *IEEE Transactions on Biomedical Engineering*, 53(6):996–1005, 2006.

[19] C. C. Palerm, H. Zisser, W. Bevier, L. Jovanovič, and F.J. Doyle III. Prandial insulin dosing using run-to-run control application of clinical data and medical expertise to define a suitable performance metric. *Diabetes Care*, 30(5):1131–1136, 2007.

[20] C. C. Palerm, H. Zisser, L. Jovanovič, and F. J. Doyle III. A run-to-run framework for prandial insulin dosing: handling real-life uncertainty. *International Journal of Robust and Nonlinear Control*, 17(13):1194–1213, 2007.

[21] C. C. Palerm, H. Zisser, L. Jovanovič, and F. J. Doyle III. A run-to-run control strategy to adjust basal insulin infusion rates in type 1 diabetes. *Journal of Process Control*, 18(3–4):258–265, 2008.

[22] Y. Wang, E. Dassau, and F. J. Doyle. Closed-loop control of artificial pancreatic beta-cell in type 1 diabetes mellitus using model predictive iterative learning control. *IEEE Transactions on Biomedical Engineering*, 57(2):211–219, 2010.

[23] Y. Wang, H. Zisser, E. Dassau, L. Jovanovic, and F.J. Doyle III. Model predictive control with learning-type set-point: Application to artificial pancreatic β-cell. *AIChE Journal*, 56(6):1510–1518, 2010.

[24] P. Herrero, P. Pesl, M. Reddy, N. Oliver, P. Georgiou, and C. Toumazou. Advanced insulin bolus advisor based on run-to-run control and case-based reasoning. *IEEE Journal of Biomedical and Health Informatics*, 3(19):1087–1096, 2015.

[25] J. Tuo, H. Sun, D. Shen, H. Wang, and Y. Wang. Optimization of insulin pump therapy based on high order run-to-run control scheme. *Comput Methods Programs Biomed*, 120(3):123–134, 2015.

[26] P. Herrero, P. Pesl, J. Bondia, M. Reddy, N. Oliver, P. Georgiou, and C. Toumazou. Method for automatic adjustment of an insulin bolus calculator: In silico robustness evaluation under intra-day variability. *Computer methods and programs in biomedicine*, 1(119):1–8, 2015.

[27] C. Toffanin, M. Messori, C. Cobelli, and L. Magni. Automatic adaptation of basal therapy for type 1 diabetic patients: a run-to-run approach. *Biomedical Signal Processing and Control*, 31:539–549, 2017.

[28] L. Magni, M. Forgione, C. Toffanin, C. Dalla Man, G. De Nicolao, B. Kovatchev, and C. Cobelli. Run-to-run tuning of model predictive control for type i diabetic subjects: an in silico trial. *Journal of Diabetes Science and Technology*, 3(5):1091–1098, 2009.

[29] C. Dalla Man, F. Micheletto, D. Lv, M. Breton, B. Kovatchev, and C. Cobelli. The uva/padova type 1 diabetes simulator: New features. *Journal of Diabetes Science and Technology*, 8(1):26–34, 2014.

[30] R. Visentin, C. Dalla Man, Y. C. Kudva, A. Basu, and C. Cobelli. Circadian variability of insulin sensitivity: Physiological input for in silico artificial pancreas. *Diabetes Technology & Therapeutics*, 17(1):1–7, 2015.

[31] L. Hinshaw, C. Dalla Man, D. K. Nandy, A. Saad, A. E. Bharucha, J. A. Levine, R. A. Rizza, R. Basu, R. E. Carter, C. Cobelli, Y. C. Kudva, and A. Basu. Diurnal pattern of insulin action in type 1 diabetes: Implications for a closed-loop system. *Diabetes*, 62(7):2223–2229, 2013.

[32] P. C. Davidson, H. R. Hebblewhite, B. W. Bode, R. D. Steed, N. S. Welch, and M. C. Greenlee et al. Statistically based csii parameters: correction factor and cf (1700 rule) and carbohydrate-to-insulin ratio and cir (2.8 rule) and and basal-to-total ratio. *Diabetes Technology & Therapeutics*, 5(5):A237, 2003.

[33] A. Mallad, L. Hinshaw, C. Dalla Man, C. Cobelli, R. Basu, Y.C. Kudva, and A. Basu. Dawn phenomenon in type 1 diabetes: Dual tracer approach to measure effect size and tracer recycling. *Diabetes Technology Therapeutics*, 17(8):587–595, 2015.

[34] G. Perriello, P. De Feo, E. Torlone, C. Fanelli, F. Santeusanio, P. Brunetti, and G.B. Bolli. Dawn phenomenon in type 1 diabetes: Dual tracer approach to measure effect size and tracer recycling. *Diabetes*, 34(1):21–28, 1991.

[35] D. M. Maahs, B. A. Buckingham, J. R. Castle, A. Cinar, E. R. Damiano, E. Dassau, J. H. DeVries, F. J Doyle III, S. C. Griffen, A. Haidar, L. Heinemann, R. Hovorka, T. W. Jones, C. Kollman, B. Kovatchev, B. L. Levy, R. Nimri, D. ONeal, M. Philip, E. Renard, S. J. Russell, S. A. Weinzimer, H. Zisser, and J. W. Lum. Outcome measures for artificial pancreas clinical trials: A consensus report. *Diabetes Care*, 39(7):1175–1179, 2016.

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

		Week 1		
		D&N	N	PP
A (mg/dl)	CL	151.35 (± 23.60) [146.66,156.03]	140.40 [129.06, 152.11] [137.78,144.50]	162.55 (± 32.04) [156.19,168.91]
	CL_{R2R}	150.05^a (± 21.35) [145.82,154.29]	139.62^a [129.26, 151.08] [137.10,143.22]	161.23^a (± 29.28) [155.42,167.04]
SD (mg/dl)	CL	30.74 [24.44, 36.27] [29.20,32.65]	14.17 [11.37, 19.16] [13.82,16.43]	33.10 [27.29, 41.12] [32.24,36.15]
	CL_{R2R}	30.10^a [24.24, 34.94] [28.51,31.77]	14.12 [11.55, 19.43] [13.87,16.43]	32.66^a [26.82, 38.70] [31.62,35.15]
T_r (%)	CL	84.57 [71.91, 91.76] [77.64,84.18]	100.00 [96.27, 100.00] [96.87,99.48]	70.89 [48.60, 84.74] [60.77,70.96]
	CL_{R2R}	86.00^a [74.56, 92.59] [79.82,85.67]	100.00^a [96.99, 100.00] [97.81,99.90]	73.41^a [52.49, 86.06] [64.01,73.49]
T_{tr} (%)	CL	35.71 [22.67, 59.12] [34.16,44.56]	47.53 (± 29.48) [41.68,53.38]	26.58 [9.67, 44.34] [23.50,32.98]
	CL_{R2R}	37.61^a [25.22, 59.92] [35.97,46.06]	49.36^a (± 28.56) [43.70,55.03]	28.12^a [11.50, 45.15] [24.81,34.38]
T_a (%)	CL	14.49 [5.17, 27.61] [13.94,20.53]	0.00 [0.00, 2.64] [0.00,1.74]	28.37 [9.94, 51.40] [25.99,36.82]
	CL_{R2R}	13.34^a [5.12, 25.26] [12.88,18.74]	0.00^a [0.00, 1.76] [0.00,1.55]	26.57^a [9.86, 47.51] [24.33,34.40]
T_{a250} (%)	CL	0.00 [0.00, 1.55] [0.00,1.39]	0.00 [0.00, 0.00] [0.00,0.00]	0.00 [0.00, 3.10] [0.00,2.79]
	CL_{R2R}	0.00^a [0.00, 1.12] [0.00,1.09]	0.00 [0.00, 0.00] [0.00,0.00]	0.00^a [0.00, 2.23] [0.00,2.18]
% Bolus (%)	CL	40.53 [34.65, 45.15] [38.56,41.20]	0.00 [0.00, 0.00] [0.00,0.00]	60.43 [53.71, 64.71] [57.85,61.39]
	CL_{R2R}	40.37 [35.25, 44.98] [38.69,41.30]	0.00 [0.00, 0.00] [0.00,0.00]	61.13^c [54.95, 65.17] [58.32,61.74]
% Basal (%)	CL	59.47 [54.85, 65.35] [58.80,61.43]	100.00 [100.00, 100.00] [100.00,100.00]	39.57 [35.29, 46.29] [38.60,42.15]
	CL_{R2R}	59.63 [55.02, 64.75] [58.69,61.31]	100.00 [100.00, 100.00] [100.00,100.00]	38.87^c [34.83, 45.05] [38.26,41.68]
TDI (U)	CL	51.54 [44.01, 64.09] [51.37,56.92]	11.16 [9.48, 13.28] [10.84,11.98]	36.64 (±9.74) [34.71,38.57]
	CL_{R2R}	51.95^a [44.29, 65.53] [51.75,57.70]	11.39^a [9.66, 13.56] [11.00,12.21]	36.85 (±10.01) [34.86,38.83]
		Week 4		
		D&N	N	PP
A (mg/dl)	CL	150.88 (± 23.29) [146.26,155.50]	141.94 (± 16.14) [138.74,145.14]	161.96 (± 32.27) [155.56,168.36]
	CL_{R2R}	143.62^a (± 15.10) [140.62,146.61]	134.84^a (± 9.93) [132.87,136.81]	154.41^a (± 21.95) [150.05,158.76]
SD (mg/dl)	CL	30.78 [24.56, 36.01] [28.86,32.53]	14.08 [10.94, 18.79] [13.72,16.35]	32.27 [27.23, 39.95] [31.93,35.85]
	CL_{R2R}	27.57^a [23.53, 32.81] [26.50,29.34]	14.62 [10.93, 17.91] [13.76,16.23]	31.07^a [25.77, 36.09] [29.65,32.65]
T_r (%)	CL	83.89 [69.30, 91.33] [77.76,84.33]	100.00 [97.09, 100.00] [97.49,99.73]	70.23 [48.05, 83.99] [61.22,71.37]
	CL_{R2R}	90.86^a [82.54, 95.06] [87.17,90.66]	100.00^a [99.82, 100.00] [99.40,100.00]	82.27^a [66.58, 90.73] [75.63,82.38]
T_{tr} (%)	CL	40.02 (± 23.02) [35.46,44.59]	46.90 (± 28.93) [41.16,52.64]	27.58 [9.29, 44.90] [23.13,33.18]
	CL_{R2R}	49.99^a (± 17.90) [46.44,53.55]	58.62^a (± 22.53) [54.15,63.09]	38.95^a [21.19, 51.53] [32.72,41.08]
T_a (%)	CL	13.58 [5.32, 30.34] [13.56,20.24]	0.00 [0.00, 1.94] [0.04,1.49]	26.96 [10.26, 51.95] [25.24,36.54]
	CL_{R2R}	8.97^a [4.61, 17.28] [8.73,12.13]	0.00^a [0.00, 0.00] [0.00,0.00]	17.05^a [8.95, 33.42] [16.69,23.58]
T_{a250} (%)	CL	0.00 [0.00, 2.07] [0.00,1.16]	0.00 [0.00, 0.00] [0.00,0.00]	0.00 [0.00, 4.15] [0.00,2.32]
	CL_{R2R}	0.00^a [0.00, 0.30] [0.00,0.29]	0.00 [0.00, 0.00] [0.00,0.00]	0.00^a [0.00, 0.61] [0.00,0.59]
% Bolus (%)	CL	39.98 [34.56, 43.80] [38.25,40.93]	0.00 [0.00, 0.00] [0.00,0.00]	60.19 [53.14, 64.41] [57.32,60.86]
	CL_{R2R}	39.84 [35.31, 44.76] [38.41,40.98]	0.00 [0.00, 0.00] [0.00,0.00]	60.43 [54.90, 65.08] [58.53,61.36]
% Basal (%)	CL	60.02 [56.20, 65.44] [59.06,61.75]	100.00 [100.00, 100.00] [100.00,100.00]	39.81 [35.59, 46.86] [39.14,42.67]
	CL_{R2R}	60.16 [55.24, 64.69] [59.02,61.59]	100.00 [100.00, 100.00] [100.00,100.00]	39.57 [34.92, 45.10] [38.64,41.47]
TDI (U)	CL	52.05 [43.98, 65.04] [51.68,57.27]	11.19 [9.63, 13.36] [10.88,12.04]	36.89 (± 10.00) [34.91,38.88]
	CL_{R2R}	56.49^a [46.31, 72.28] [54.64,61.87]	11.90^a [10.08, 14.36] [11.59,13.00]	39.07^a (± 11.97) [36.70,41.45]
		Week 8		
		D&N	N	PP
A (mg/dl)	CL	147.97 [134.27, 167.09] [145.47,154.88]	142.59 (± 17.58) [139.11,146.08]	163.11 [138.83, 182.89] [154.99,168.04]
	CL_{R2R}	138.67^a [132.39, 147.70] [137.22,141.98]	132.60^a (± 9.91) [130.63,134.56]	148.33^a [137.11, 159.92] [145.13,152.67]
SD (mg/dl)	CL	30.80 [24.67, 37.12] [29.43,33.07]	13.87 [10.92, 19.27] [13.78,16.52]	33.56 [27.75, 40.30] [32.38,36.27]
	CL_{R2R}	27.03^a [23.35, 33.83] [26.59,29.86]	14.84 [12.45, 19.24] [14.34,16.82]	30.76^a [26.11, 37.10] [29.88,33.30]
T_r(%)	CL	82.01 [69.88, 91.56] [77.06,83.67]	100.00 [94.87, 100.00] [96.33,99.55]	67.67 [49.30, 85.32] [60.68,70.79]
	CL_{R2R}	91.35^a [84.59, 95.62] [88.45,91.93]	100.00^a [99.87, 100.00] [99.78,100.00]	84.34^a [70.61, 92.29] [78.57,84.98]
T_{tr}0 (%)	CL	36.12 [19.49, 58.25] [33.88,43.79]	46.68 (± 29.64) [40.80,52.56]	27.76 [9.09, 41.55] [22.66,32.80]
	CL_{R2R}	53.15^a [43.59, 63.95] [50.14,56.85]	62.22^a (± 20.78) [58.10,66.35]	42.22^a [27.62, 54.22] [37.78,45.26]
T_a (%)	CL	15.10 [5.56, 29.50] [14.15,20.83]	0.00 [0.00, 3.39] [0.04,2.48]	27.60 [10.41, 50.70] [26.02,36.92]
	CL_{R2R}	7.74^a [3.45, 14.28] [7.27,10.68]	0.00^a [0.00, 0.00] [0.00,0.00]	15.17^a [6.73, 28.36] [13.98,20.49]
T_{a250} (%)	CL	0.00 [0.00, 2.83] [0.00,1.72]	0.00 [0.00, 0.00] [0.00,0.00]	0.00 [0.00, 5.65] [0.00,3.44]
	CL_{R2R}	0.00^a [0.00, 0.05] [0.00,0.27]	0.00 [0.00, 0.00] [0.00,0.00]	0.00^a [0.00, 0.11] [0.00,0.55]
% Bolus (%)	CL	40.51 [34.78, 43.48] [38.40,41.03]	0.00 [0.00, 0.00] [0.00,0.00]	60.73 [53.71, 64.07] [57.59,61.03]
	CL_{R2R}	39.80 [35.81, 43.83] [38.43,41.05]	0.00 [0.00, 0.00] [0.00,0.00]	60.15 [55.85, 64.27] [58.59,61.29]
% Basal (%)	CL	59.49 [56.52, 65.22] [58.97,61.60]	100.00 [100.00, 100.00] [100.00,100.00]	39.27 [35.93, 46.29] [38.97,42.41]
	CL_{R2R}	60.20 [56.17, 64.19] [58.94,61.57]	100.00 [100.00, 100.00] [100.00,100.00]	39.85 [35.73, 44.15] [38.71,41.41]
TDI (U)	CL	51.87 [44.25, 64.70] [51.57,57.06]	11.21 [9.62, 13.31] [10.88,12.02]	36.79 (± 9.83) [34.84,38.74]
	CL_{R2R}	60.78^a [47.45, 75.19] [57.18,64.52]	12.30^a [10.25, 15.33] [11.95,13.56]	40.63^a (± 12.21) [38.20,43.05]

TABLE II

PERFORMANCE METRICS OF CL VS CL_{R2R} AFTER ONE WEEK (WEEK 1), ONE MONTH (WEEK 4) AND TWO MONTHS (WEEK 4) WITH *Scenario 1*. ^{a} P-VALUE $< .001$, ^{b} P-VALUE $< .01$, ^{c} P-VALUE $< .05$.

	Scenario 2 after 4 weeks	Scenario 1 after 4 weeks	Scenario 1 after 8 weeks
CR_B	15.4 [7.96, 25.07] [14.05, 19.33]	15.57 [7.69, 27.34] [14.86, 21.35]	23.79 [12.84, 36.12] [21.21, 29.41]
CR_L (%)	28.59 [14.61, 40.28] [24.99, 32.47]	32.43 [18.87, 44. 8] [27.96, 36.47]	46.05 [24.15, 59.32] [37.52, 49.61]
CR_D (%)	30.5 [15.37, 43.2] [25.8, 34.27]	32.99 [15.28, 47.36] [27.58, 36.69]	43.64 [22.87, 60.66] [37.33, 48.54]
$Basal$ (%)	7.94 [3.13, 24.05] [10.1, 17.32]	10.71 [3.27, 27.28] [10.65, 19.08]	15.76 [6.14, 36.93] [16.03, 26.88]

TABLE III

PERCENTAGES OF VARIATION DUE TO THE USE OF THE R2R ALGORITHM IN TERM OF MEDIAN $[25^{th}, 75^{th}]$ PERCENTILES [CONFIDENTIAL INTERVALS].

		Week 1		
		D&N	N	PP
A (mg/dl)	CL	148.30 (± 16.25) [145.08,151.52]	136.50 [131.11, 147.83] [136.00,141.73]	159.65 (± 23.80) [154.92,164.37]
	CL_{R2R}	146.97^a (± 14.76) [144.05,149.90]	136.10^a [130.62, 146.51] [135.49,140.66]	158.16^a (± 22.07) [153.78,162.54]
SD (mg/dl)	CL	30.41 [24.54, 34.68] [28.30,31.69]	14.07 [10.71, 19.52] [13.76,16.40]	32.58 [27.15, 39.82] [31.63,35.29]
	CL_{R2R}	29.51^a [24.24, 33.71] [27.72,30.95]	13.94^c [10.79, 19.41] [13.77,16.36]	31.94^a [26.92, 38.37] [31.05,34.55]
T_r (%)	CL	86.22 [77.36, 92.21] [82.26,87.16]	100.00 [98.57, 100.00] [98.96,100.00]	74.14 [57.16, 84.92] [67.22,75.77]
	CL_{R2R}	87.29^a [79.34, 93.19] [83.94,88.28]	100.00^a [98.82, 100.00] [99.00,100.00]	76.10^a [62.10, 86.74] [70.06,77.82]
T_{tr} (%)	CL	44.61 (± 18.15) [41.00,48.21]	53.76 [33.49, 67.12] [47.32,58.20]	28.03 [19.01, 43.66] [26.89,34.47]
	CL_{R2R}	46.09^a (± 17.54) [42.61,49.57]	55.32^a [36.04, 67.85] [49.00,59.45]	30.57^a [20.24, 44.81] [28.46,35.86]
T_a (%)	CL	12.96 [6.57, 22.23] [11.85,16.78]	0.00 [0.00, 0.92] [0.00,0.72]	25.70 [12.50, 40.96] [22.44,31.33]
	CL_{R2R}	12.19^a [6.35, 19.71] [10.88,15.33]	0.00^a [0.00, 0.73] [0.00,0.61]	22.35^a [12.14, 37.51] [20.78,28.85]
T_{a250} (%)	CL	0.00 [0.00, 0.23] [0.00,0.24]	0.00 [0.00, 0.00] [0.00,0.00]	0.00 [0.00, 0.47] [0.00,0.49]
	CL_{R2R}	0.00^a [0.00, 0.06] [0.00,0.14]	0.00 [0.00, 0.00] [0.00,0.00]	0.00^a [0.00, 0.12] [0.00,0.29]
% Bolus (%)	CL	40.45 [35.36, 44.94] [38.75,41.45]	0.00 [0.00, 0.00] [0.00,0.00]	61.32 [55.39, 65.48] [58.29,61.69]
	CL_{R2R}	40.60 [35.41, 45.09] [38.92,41.50]	0.00 [0.00, 0.00] [0.00,0.00]	61.41^c [55.96, 65.34] [58.66,61.97]
% Basal (%)	CL	59.55 [55.06, 64.64] [58.54,61.25]	100.00 [100.00, 100.00] [100.00,100.00]	38.68 [34.52, 44.61] [38.31,41.71]
	CL_{R2R}	59.40 [54.91, 64.59] [58.49,61.08]	100.00 [100.00, 100.00] [100.00,100.00]	38.59^c [34.66, 44.04] [38.03,41.33]
TDI (U)	CL	51.11 [43.60, 64.31] [50.83,56.15]	11.03 [9.48, 13.21] [10.73,11.87]	36.14 (± 9.24) [34.31,37.98]
	CL_{R2R}	51.49^a [44.08, 65.08] [51.35,57.07]	11.15^a [9.47, 13.32] [10.85,12.04]	36.55^a (± 9.56) [34.66,38.45]
		Week 4		
		D&N	N	PP
A (mg/dl)	CL	150.06 (± 21.54) [145.79,154.33]	141.26 (± 15.03) [138.28,144.24]	158.93 [139.59, 181.48] [154.10,166.12]
	CL_{R2R}	143.11^a (± 15.33) [140.07,146.16]	134.84^a (± 9.89) [132.87,136.80]	149.69^a [136.87, 166.02] [147.74,156.06]
SD (mg/dl)	CL	30.42 [24.48, 35.62] [28.68,32.37]	14.18 [10.73, 18.76] [13.76,16.39]	32.49 [26.67, 39.77] [31.84,35.72]
	CL_{R2R}	27.89^a [23.46, 32.79] [26.50,29.26]	14.66 [11.20, 17.96] [13.78,16.26]	31.22^a [26.14, 35.48] [29.68,32.57]
T_r (%)	CL	84.24 [71.28, 91.74] [79.13,85.11]	100.00 [97.97, 100.00] [97.24,99.69]	71.93 [51.39, 84.58] [62.79,72.90]
	CL_{R2R}	90.68^a [82.71, 95.06] [87.39,90.70]	100.00^a [99.97, 100.00] [99.72,100.00]	82.28^a [66.38, 90.52] [75.98,82.59]
T_{tr} (%)	CL	41.21 (± 21.74) [36.90,45.53]	48.17 (± 27.94) [42.63,53.71]	28.01 [11.16, 44.50] [24.16,33.72]
	CL_{R2R}	50.32^a (± 17.94) [46.76,53.88]	58.85^a (± 22.22) [54.44,63.26]	38.99^a [20.85, 51.73] [32.90,41.51]
T_a (%)	CL	13.71 [5.64, 27.99] [12.83,18.97]	0.00 [0.00, 1.63] [0.00,1.06]	26.82 [10.96, 48.57] [24.26,35.01]
	CL_{R2R}	8.67^a [4.51, 16.88] [8.50,11.87]	0.00^a [0.00, 0.00] [0.00,0.00]	16.71^a [8.74, 32.87] [16.28,23.06]
T_{a250} (%)	CL	0.00 [0.00, 1.23] [0.00,0.94]	0.00 [0.00, 0.00] [0.00,0.00]	0.00 [0.00, 2.47] [0.00,1.88]
	CL_{R2R}	0.00^a [0.00, 0.03] [0.00,0.25]	0.00 [0.00, 0.00] [0.00,0.00]	0.00^a [0.00, 0.07] [0.00,0.50]
% Bolus (%)	CL	39.48 (±6.72) [38.15,40.81]	0.00 [0.00, 0.00] [0.00,0.00]	60.30 [54.53, 64.62] [57.66,61.06]
	CL_{R2R}	39.51 (±6.33) [38.25,40.76]	0.00 [0.00, 0.00] [0.00,0.00]	60.59 [55.84, 64.40] [58.65,61.35]
% Basal (%)	CL	60.52 (±6.72) [59.19,61.85]	100.00 [100.00, 100.00] [100.00,100.00]	39.70 [35.38, 45.47] [38.94,42.34]
	CL_{R2R}	60.49 (±6.33) [59.24,61.75]	100.00 [100.00, 100.00] [100.00,100.00]	39.41 [35.60, 44.16] [38.65,41.34]
TDI (U)	CL	51.87 [43.81, 64.67] [51.40,56.86]	11.08 [9.66, 13.31] [10.83,11.98]	35.70 [28.77, 44.42] [34.39,38.40]
	CL_{R2R}	56.19^a [46.85, 71.18] [54.59,61.63]	11.88^a [10.22, 14.08] [11.48,12.85]	36.83^a [29.54, 50.14] [36.10,41.14]

TABLE IV

PERFORMANCE METRICS OF CL VS CL_{R2R} AFTER ONE WEEK (WEEK 1) AND ONE MONTH (WEEK 4) WITH *Scenario 2*.
^{a} P-VALUE $< .001$, ^{b} P-VALUE $< .01$, ^{c} P-VALUE $< .05$.