Proceedings of the 19th World Congress
The International Federation of Automatic Control
Cape Town, South Africa. August 24-29, 2014

Automatic adaptation of basal therapy for Type 1 diabetic patients: a Run-to-Run approach

Chiara Toffanin * **Alice Sandri** * **Mirko Messori** *
Claudio Cobelli ** **Lalo Magni** *

* *Department of Architecture and Civil Engineering, University of Pavia, Pavia, Italy, (e-mail: chiara.toffanin@unipv.it)*
** *Department of Systems and Information Engineering, University of Padova, Padova, Italy*

Abstract: Type 1 diabetic patients require adjustments of their basal therapy due to insulin requirement changes. A very promising automatic approach is based on the so called Run-to-Run (R2R) strategy, which adjusts the insulin therapy based on the performance measured during the previous run, usually of 1 day. Previous R2R approaches were based on few blood glucose measurements. In this paper the use of a subcutaneous-continuous glucose monitoring is exploited in order to obtain more relevant clinical performance indices such as the percentage of time spent by the glycaemia below 70 mg/dl, above 180 mg/dl and the mean glucose. Different priority is given to hypo and hyperglycemia control and in particular the primary goal is to reduce the time below 70 mg/dl, to reduce the time above 180 mg/dl and to reach the mean glucose target. In doing so a switching control law is achieved. A procedure for the convergence analysis of a linear version of the proposed R2R approach is introduced by resorting to the Lyapunov theory for piecewise affine systems. Performance is studied for both nonlinear and linear algorithm by means of an extensive *in-silico* trial performed on 100 adults patients of the UVA/Padova simulator with a random variation of patient insulin sensitivity. After a week the time spent below 70 mg/dl (initially equal to 8.3%) was reduced to 1.52% using the nonlinear R2R and to 1.36% using the linear R2R, the time in range [70-180] mg/dl was increased by 20.2% and 19.8%, respectively.

Keywords: Run-to-Run, automatic adaptation, stability, piecewise affine system

1. INTRODUCTION

Type 1 diabetes mellitus (T1DM) is a disease characterized by an elevated blood glucose (BG) levels, called *hyperglycemia* (BG $>$ 180 mg/dl), caused by an absolute deficiency of insulin secretion. In order to avoid prolonged hyperglycaemia which is associated with a series of long-term complications, people with T1DM need exogenous insulin delivery. Intensive treatment with insulin injections reduces the risk of chronic complications, but can increase *hypoglycemia* (BG $<$ 70 mg/dl) risks that can be very dangerous. The goal for T1DM patients is therefore to maintain BG within a strict glucose range ([70-180] mg/dl), called *euglycemic range*.
The availability of a new generation of Continuous Glucose Monitoring (CGM) and subcutaneous insulin infusion allows to improve glycemic control based on the so-called sensor-augmented insulin-pump therapy (Bergenstal et al. [2010]), which is a pump based therapy supervised and adapted by the patient using the continuous measurements provided by the CGM. The pump therapy (hereafter Conventional Therapy (CT)) is composed by a basal insulin, which is conceptually a piecewise constant insulin injection, and an insulin bolus, which is an impulse-like injection used to compensate the glucose rise due to the meal.
This paper deals with the automatization of basal adaptation based on CGM exploring the use of Run-to-Run (R2R) approach. The R2R is a learning-type control algorithm (Wang et al. [2009]) introduced in the chemical process industry where the process variability is high and the requirements are strict; this algorithm learns information about the control quality from the current run and changes the control variable to apply in the next run, in order to improve a specific performance index.
A first generation of R2R strategies that use only few daily BG showed good performance when applied to the glucose control problem for T1DM patients (Owens et al. [2006], Palerm et al. [2007a,b, 2008]). In this case, the patterns of meal intake, glucose measurement, and insulin delivery repeat themselves in 24 h cycles, so a 24h R2R approach can be the right choice to manage these uncertainties. Several versions of the R2R strategy were used to adatpt day-by-day the basal insulin (Palerm et al. [2008]) or the meal bolus (Doyle et al. [2001], Zisser et al. [2005], Owens

⋆ This work was supported by the Fondo per gli Investimenti della Ricerca di Base project Artificial Pancreas: In Silico Development and In Vivo Validation of Algorithms for Blood Glucose Control funded by Italian Ministero dell'Istruzione, dell'Universita' e della Ricerca.

et al. [2006], Palerm et al. [2007a,b]) and were successfully tested both *in-silico* and *in-vivo*.
In this paper, the additional information provided by the CGM is used to explore a new R2R algorithm based on well accepted performance indices like the percentage of time spent below 70 mg/dl, the percentage of time spent above 180 mg/dl and distance of the average glucose from a target. Priority is given to the reduction of the percentage of time spent below 70 mg/dl, so that a switching control law is derived. A nonlinear and a linear version of the algorithm are proposed. An algorithm to verify the convergence of a linear version of the proposed algorithm is introduced by resorting to the Lyapunov theory for the piecewise affine (PWA) systems (Gang [2005]). Finally, the performance of the nonlinear and linear R2R approaches are compared with the CT that does not consider basal adaptation on 100 *in-silico* adults patients of the UVA/Padova simulator (Dalla Man et al. [2013]) with a random variation of patient insulin sensitivity.

2. RUN-TO-RUN STRATEGY

The general idea behind a R2R approach is to update, at each run, the controlled variable in order to improve as much as possible a performance index.
In clinical practice the common index of a good glycemic control is the glycated hemoglobin (HbA1c): higher values of HbA1c indicate a poor control of blood glucose levels (Rohlfing et al. [2002], Davidson [2004], Heisler et al. [2005]). This parameter is measured in laboratory and used primarily to identify the average plasma glucose concentration over prolonged periods of time (months). For these reasons it can not be used in a R2R context where the run has typically a duration of one day.
The first R2R approaches for T1DM used a few BG fingerstick measurements (see e.g. Doyle et al. [2001], Zisser et al. [2005], Owens et al. [2006], Palerm et al. [2007a,b, 2008]). However, the introduction of CGM sensors that measure countinuosly the subcutaneous glucose concentration, and the necessity to evaluate also short period trials, has motivated the definition of short period performance indices, that are now well accepted in clinical research to evaluate control quality. The main ones are the percentage of time spent in range, the percentage of time spent below the range, the percentage of time spent above the range and the average BG.
In this work these performance indices are exploited in the R2R algorithm. The major concern of a T1DM patient is to avoid hypoglycaemia, hence the updating law was 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 BG to the desired target. Note that if this secondary law is too aggressive an oscillatory behavior can be obtained. This must be avoided with a suitable tuning of the algorithm.

2.1 New algorithm

In the R2R algorithm proposed in this work, the run period is set equal to 24h which corresponds with the circadian rhythmicity of the patient's variations.

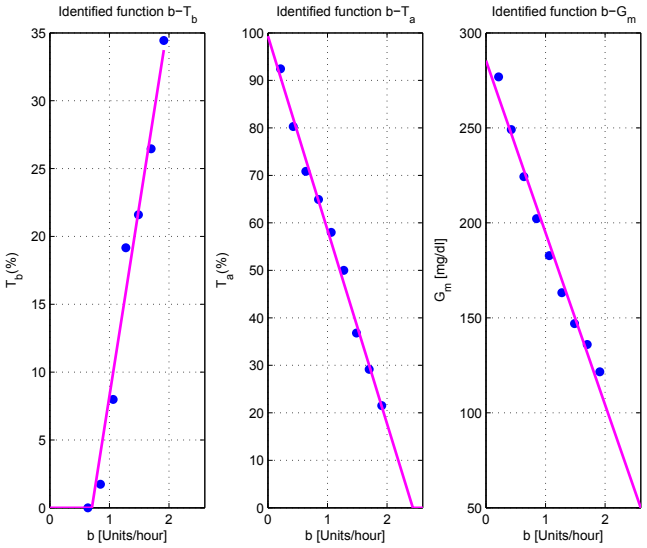


Fig. 1. Plot of the three identified curves (magenta) obtained from simulated data (blue) of a generic virtual patient of the UVA/Padova simulator: T_b, T_a and G_m are well approximated by a linear function of the basal insulin b.

At run k, the updating law is defined as follows

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

where b is the basal insulin, the variable updated by the algorithm, the constants k_1, k_2, k_3 are the R2R gains, G_T is the glycemic target and T_b, T_a, G_m are the R2R performance indices. In particular, T_b is the percentage of time spent below 70 mg/dl, T_a is the percentage of time spent above 180 mg/dl and G_m is average subcutaneous glucose concentration. The variation of the basal insulin, at each run, is proportional to the basal rate applied at the previous run and to the performance indices computed during the last interval. Hence, the resulting system is a switching nonlinear system driven by the value of T_b.

2.2 Stability analisys

Due to the switching structure of the updating law (1), the classic stability analysis of R2R algorithms (see Francois et al. [2003], Owens et al. [2006]) can not be applied. In order to study the stability properties, it is helpful to note that the signal T_b, T_a and G_m depend on the value of the basal rate. In particular, performing an *in-silico* test with the UVA/Padova simulator (Dalla Man et al. [2013]) on 100 virtual patients, it has been noted that the following PWA models can well describe these relations (see Fig. 1):

$$T_b(k) = \begin{cases} k_b(b(k) - \bar{b}_b) & \text{if } b(k) > \bar{b}_b \\ 0 & \text{otherwise} \end{cases} \quad (2)$$

$$T_a(k) = \begin{cases} k_a(b(k) - \bar{b}_a) & \text{if } b(k) < \bar{b}_a \\ 0 & \text{otherwise} \end{cases} \quad (3)$$

$$G_m(k) = k_G b(k) - G_G \quad (4)$$

where the parameters k_b, $\bar{b}_b$, k_a, $\bar{b}_a$, k_G and G_G have to be identified for each single patient.
In order to identify these models, several experiments with different basal values in the interval $[b_i^{min}, b_i^{max}]$ with a fix step δb_i have been performed taking constant all the other external quantities that can affect the performance indices. Each index has been computed for every basal value and used to identify a piecewise linear model through a linear interpolation (see Fig. 1).
However, by including the identified linear functions (2), (3), (4) in (1), the study of the stability of the system remains difficult in view of the nonlinearity of (1).
On the contrary, several stability results are available for PWA systems (Johansson [1998],Gang [2005]). Hence, in order to obtain a R2R algorithm whose convergence can be verified, the following linear R2R law is proposed:

$$b(k+1) = \begin{cases} b(k) - \bar{b}k_1 T_b(k) & \text{if } T_b(k) > 0 \\ b(k) + \bar{b}\left(k_2 T_a(k) + k_3 \dfrac{(G_m(k) - G_T)}{G_T}\right) & \text{if } T_b(k) = 0 \end{cases}, \quad \text{with } b(0) = \bar{b} \tag{5}$$

where $\bar{b}$ is the initial basal therapy of the patient.
In Section 3 an *in-silico* comparison of the control performance achieved with the nonlinear R2R (1) and the linear one (5) is reported.
Combining the identified linear functions (2), (3), (4) with (5), the system can be written as

$$b(k+1) = \begin{cases} (1 - k_1\bar{b}k_b)b(k) + k_1\bar{b}k_b\bar{b}_b & \text{if } b(k) \in S_1 \\ \left(1 + k_2\bar{b}k_a + \dfrac{k_3\bar{b}k_G}{G_T}\right)b(k) - & \\ -k_2\bar{b}k_a\bar{b}_a - \dfrac{k_3\bar{b}(G_G + G_T)}{G_T} & \text{if } b(k) \in S_2 \\ \left(1 + \dfrac{k_3\bar{b}k_G}{G_T}\right)b(k) - \dfrac{k_3\bar{b}(G_G + G_T)}{G_T} & \text{if } b(k) \in S_3 \end{cases} \tag{6}$$

where $S_1 = \{b : b > \bar{b}_b\}$, $S_2 = \{b : b \leq \bar{b}_b \wedge b < \bar{b}_a\}$ and $S_3 = \{b : \bar{b}_a \leq b \leq \bar{b}_b\}$. Note that if $\bar{b}_a > \bar{b}_b$ zone S_3 is empty, which means that it is not possible to reach the 100% of time in target.
The convergence of the R2R algorithm (6) can now be proven using the results reported in Gang [2005], where a method based on a piecewise Lyapunov function is used to test the stability of a discrete time PWA system.
In order to fulfill the hypotheses required to apply the stability results reported in Gang [2005] (the equilibrium must be on the boundary of the region), the region S_3 must be splitted in two regions (S_3, S_4) and system (6) can be rewritten in the following way:

$$x(t+1) = A_l x(t) + a_l, \text{ for } x \in S_l \quad l = 1, 2, \ldots, m \tag{7}$$

where

$$x(t) = b(k) - b_{eq}, \quad b_{eq} = \frac{G_G + G_T}{k_G}, \quad m = 4,$$
$$A_1 = 1 - k_1\bar{b}k_b, \quad A_2 = 1 + k_2\bar{b}k_a + \frac{k_3\bar{b}k_G}{G_T},$$
$$A_3 = A_4 = 1 + \frac{k_3\bar{b}k_G}{G_T},$$
$$a_1 = k_1\bar{b}k_b(\bar{b}_b - b_{eq}),$$
$$a_2 = k_2\bar{b}k_a(b_{eq} - \bar{b}_a) + \frac{k_3\bar{b}}{G_T}(k_G b_{eq} - G_G - G_T),$$
$$a_3 = a_4 = 0.$$

$\{S_l\}_{l\in\{1,2,3,4\}} \subseteq \Re$ denotes a partition of the state space into four closed interval, in particular $S_1 = \{x : x > \bar{b}_b - b_{eq}\}$, $S_2 = \{x : x \leq \bar{b}_b - b_{eq} \wedge x \leq \bar{b}_a - b_{eq}\}$, $S_3 = \{x : \bar{b}_a - b_{eq} \leq x \leq 0\}$ and $S_4 = \{x : 0 \leq x \leq \bar{b}_b - b_{eq}\}$. Hence, it is possible to formulate the following stability theorem, where $L_0 = \{3, 4\}$ is the set of indices for subspaces that contain the origin, $L_1 = \{1, 2\}$ the set of indices for the subspaces that do not contain the origin, $\Omega = \{l, j | x(t) \in S_l, x(t+1) \in S_j, j \neq l\}$ and

$$\bar{A}_l = \begin{bmatrix} A_l & a_l \\ 0 & 1 \end{bmatrix}, \quad \bar{E}_l = [E_l \;\; e_l]$$

with

$$E_1 = \begin{bmatrix} 1 \\ 0 \end{bmatrix}, E_2 = \begin{bmatrix} -1 \\ -1 \end{bmatrix}, E_3 = \begin{bmatrix} -1 \\ 0 \end{bmatrix}, E_4 = \begin{bmatrix} 0 \\ 1 \end{bmatrix}$$

$$e_1 = \begin{bmatrix} -\bar{b}_b + b_{eq} \\ 0 \end{bmatrix}, e_2 = \begin{bmatrix} \bar{b}_b - b_{eq} \\ \bar{b}_a - b_{eq} \end{bmatrix}, e_3 = e_4 = \begin{bmatrix} 0 \\ 0 \end{bmatrix}$$

Theorem 1. (Gang [2005]) Consider the piecewise linear system (7). If there exist symmetric matrices P_l, $l \in L_0$, $\bar{P}_l$, $l \in L_1$, U_l, W_l and Q_{lj} such that U_l, W_l and Q_{lj} have nonnegative entries and the following LMIs are satisfied:

$$0 < P_l - E_l^T U_l E_l, \qquad l \in L_0 \tag{8}$$
$$A_l^T P_l A_l - P_l + E_l^T W_l E_l < 0, \qquad l \in L_0 \tag{9}$$
$$0 < \bar{P}_l - \bar{E}_l^T U_l \bar{E}_l, \qquad l \in L_1 \tag{10}$$
$$\bar{A}_l^T \bar{P}_l \bar{A}_l - \bar{P}_l + \bar{E}_l^T W_l \bar{E}_l < 0, \qquad l \in L_1 \tag{11}$$
$$A_l^T P_j A_l - P_l + E_l^T Q_{lj} E_l < 0, \;\; l, j \in \Omega \cap L_0 \tag{12}$$
$$\bar{A}_l^T \bar{P}_j \bar{A}_l - \bar{P}_l + \bar{E}_l^T Q_{lj} \bar{E}_l < 0, \;\; l, j \in \Omega \cap L_1 \tag{13}$$
$$\bar{A}_l^T \bar{P}_j \bar{A}_l - \bar{P}_l + \bar{E}_l^T Q_{lj} \bar{E}_l < 0, \; \begin{matrix} l, j \in \Omega, \\ l \in L_1, j \in L_0 \end{matrix} \tag{14}$$
$$\bar{A}_l^T \bar{P}_j \bar{A}_l - \bar{P}_l + \bar{E}_l^T Q_{lj} \bar{E}_l < 0, \; \begin{matrix} l, j \in \Omega, \\ l \in L_0, j \in L_1 \end{matrix} \tag{15}$$

where $\bar{P}_j = [1 \;\; 0]^T P_j [1 \;\; 0]$ for $j \in L_0$ in (14) and $\bar{P}_l = [1 \;\; 0]^T P_l [1 \;\; 0]$, for $l \in L_0$ in (15), then the origin of the piecewise linear system is exponentially stable, that is, $x(t)$ tends to the origin exponentially for every trajectory in the state space. □

If the region S_3, S_4 do not exist, the b_{eq} has to be recomputed as equilibrium of S_2 and the sets of indices changes in $L_0 = \{2\}$, $L_1 = \{1\}$, with $m = 2$.
Note that the convergence of the system depends on the R2R gains k_1, k_2, k_3. The Multi-Parametric Toolbox (MPT), introduced in Kvasnica et al. [2004], allows to find these Lyapunov functions for PWA systems and ensure its stability. Hence given k_1, k_2 and k_3 it is possible to verify the stability of the associated linear R2R algorithm.

3. IN-SILICO RESULTS

The main goal of this section is to find a tuning for the R2R algorithm guaranteeing the stability and good performance for any possible patient. In order to obtain

these results the widely accepted UVA/Padova simulator (Dalla Man et al. [2013]) equipped with a population of 100 adults *in-silico* patients is used. The gains of the algorithm have been fixed for all the patients to $k_1 = 0.15$, $k_2 = 0.175$ and $k_3 = 0.005$, and $G_T = 115$ mg/dl for both the linear and nonlinear algorithms. A deeply analysis of the quality of this choice has been performed on the entire *in-silico* population that is characterized by an intra-individual variability which well describe the one of real patients. The analysis has been conducted both in term of stability and of performance. After the indentification of the individual values of the parameters k_b, $\bar{b}_b$, k_a, $\bar{b}_a$, k_G and G_G for each *in-silico* patient was completed, the stability of the algorithm for each *in-silico* patient has been successfully verified using the MPT. The basal interval used to collect data was defined taking $b_{b_i}^{min} = 0.25 b_{bi}, b_{b_i}^{max} = 2 b_{bi}$ and $\delta b_{bi} = 0.25 b_{bi}$, where b_{bi} is the basal insulin provided by the simulator of the i-th patient.

The control performance were evaluated on a 15day scenario, simulated on the virtual population with a fixed 25% random ($\pm$) variation of insulin sensitivity, in order to represent possible uncertainties on individual insulin sensitivity and the day-by-day changes of insulin requirements. The protocol involves 3 meals a day at 7:00, 12:00 and 18:00 of 50g, 60g and 80g of carbohydrates, respectively. The protocol includes also a 16g administration, called *hypo treatment* (ht), if the BG falls below 65 mg/dl. The administration can be repeated only if 30 minutes have elapsed from the previous one. The CGM sensor is affected by the error noise described in Toffanin et al. [2013] which describes the total measurement error, including wearing issues in addition to noise and drift usually considered.

The simulations have been realized following the CT, the nonlinear R2R strategy (R2R_{Nl}) (1) or the linear R2R strategy (R2R_L) (5). The results are reported in Table 1 in term of Mean and Standard Deviation (SD) of BG, the percentage of time spent in euglycemic range [70-180] mg/dl (T_r), the percentage of time spent in tight range [80-140] mg/dl (T_{tr}), the percentage of time spent above 180 mg/dl (T_a), the percentage of time spent below 70 mg/dl (T_b), the percentage of time spent below 50 mg/dl (T_h), and the average number of hypo treatments per patient ($\#\overline{ht}$) occurred during the considered run. All these indices are computed globally (G), during the night (N, 23:00-8:00), and as an average relative to all post prandial (3h) periods (PP) of the specified day. In order to evaluate the statistical significance of the results, the p-value are computed for the comparisons between CT and R2R_{Nl} and between R2R_{Nl} and R2R_L.

Table 1 shows the comparison between Day 2 and Day 8, i.e. the first day in which the R2R algorithms have an effect and the results after a week using these algorithms. Since $u(0) = \bar{u}$, for $k = 1$ R2R_{Nl} and R2R_L coincide (see Day 2 in Table 1). In one step, the R2R algorithm reduced the times spent above 180 mg/dl by 15%, below 70 mg/dl by 48.6% and below 50 mg/dl by 73.8% with a moderate increase of average BG (0.2 mg/dl). The time in range and tight range were increased by 8.4% and 11%. The $\#\overline{ht}$, initially 3.51, were reduced by 55.6% with the R2R_{Nl} and by 84% with R2R_L. All these results are statistically significant (p-value < 0.001).

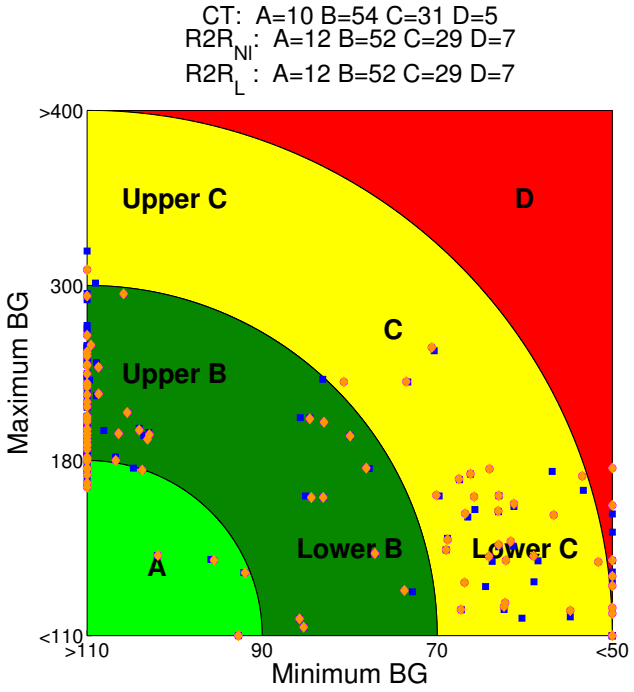
After a week the time spent below 70 mg/dl, initially equal to 8.3%, was reduced to 1.52% (p-value < 0.001) by the R2R_{Nl} and to 1.36% by the R2R_L, the increase of the time in range achieved by these algorithms is equal to 20.2% (p-value < 0.001) and 19.8%, respectively. Also the time in tight range was increased, for R2R_{Nl} by 26.2% (p-value < 0.001) and for R2R_L by 26.8%. The average BG was decreased by 5.7% (p-value < 0.001) and by 5.1%, respectively, while SD remained almost the same. The $\#\overline{ht}$ (equal to 3.5) were reduced by 89.1% with R2R_{Nl} and by 91.1% with R2R_L. After 2 weeks no further improvements were achieved (see Table 2). Note that in general the differences between R2R_{Nl} and R2R_L are not statistically significant, and when statistically significant the differences are very limited.

Table 1. Simulation results obtained with the CT, R2R_{Nl}, and R2R_L strategies. ^{a} p-value $< .001$, ^{b} p-value $< .01$, ^{c} p-value $< .05$

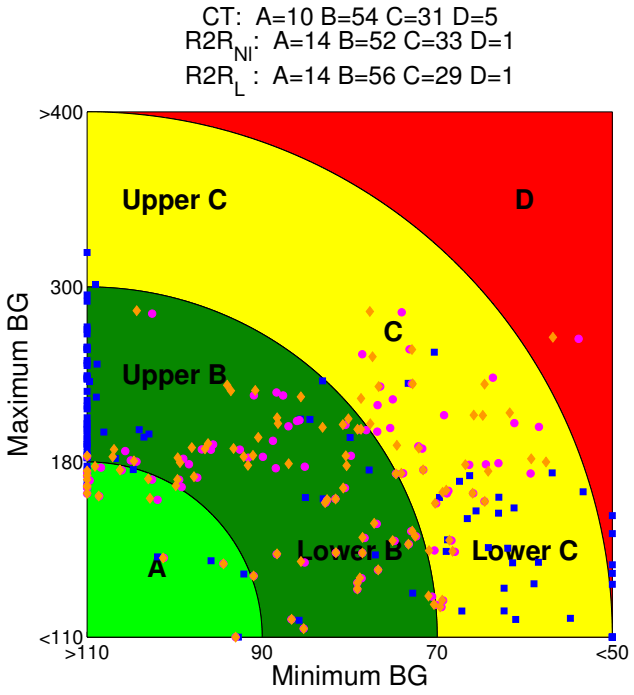
		Day 2			Day 8		
		G	N	PP	G	N	PP
Mean [mg/dl]	CT	131.88^c	104.17	159.03	131.86^b	104.19^b	158.96
	$R2R_{Nl}$	132.02	104.38	159.22	124.36	96.04	151.64
	$R2R_L$	132.02	104.38	159.22	125.15^a	96.78	152.48
SD [mg/dl]	CT	30.85^a	9.04	26.18	30.82	9.05	26.15
	$R2R_{Nl}$	30.57	9.42	25.68	31.19	9.44	26.58
	$R2R_L$	30.57	9.42	25.68	31.18^b	9.42	26.49
T_r (%)	CT	75.96^a	84.85	64.7	75.98^a	85.18^a	64.45^a
	$R2R_{Nl}$	82.33	88.5	70.51	91.37	95.78	82.29
	$R2R_L$	82.33	88.5	70.51	91.06^a	96.12	81.36
T_{tr} (%)	CT	49.04^a	70.3	31.39	49^a	70.34^c	31.24^b
	$R2R_{Nl}$	54.42	75.63	33.62	61.86	81.35	34.41
	$R2R_L$	54.42	75.63	33.62	62.19	83.85	34.03
T_a (%)	CT	15.76^a	0.86	32.1	15.76^a	0.85^c	32.11^c
	$R2R_{Nl}$	13.38	0.64	29.16	7.11	0.02	17.4
	$R2R_L$	13.38	0.64	29.16	7.57^a	0.02	18.41
T_b (%)	CT	8.28^a	14.29	3.2^b	8.27^a	13.96^b	3.44^c
	$R2R_{Nl}$	4.29	10.87	0.33	1.52	4.2	0.31
	$R2R_L$	4.29	10.87	0.33	1.38	3.85	0.23
T_h (%)	CT	3.55^b	4.12	1.77	3.5^b	4.19^b	1.68^b
	$R2R_{Nl}$	0.94	2.51	0.07	0	0	0
	$R2R_L$	0.94	2.51	0.07	0	0	0
$\#\overline{ht}$	CT	3.51^a	1.8	0.6	3.5^a	1.76^b	0.6
	$R2R_{Nl}$	1.56	1.25	0.05	0.38	0.34	0.04
	$R2R_L$	0.56	1.25	0.05	0.31	0.27	0.04

The performance was evaluated also using the Control Variability Grid Analysis (CVGA) introduced in Magni et al. [2008] and improved in (Soru et al. [2012]). A single point represents the couple of minimum and maximum BG values reached by the virtual patient during the considered day. In Fig. 2 the CVGAs relative to Day 2 (a) and 8 (b) confirm the good performance of the R2R algorithms already observed in Table 1. Note that on Day 2, two patients using the R2R approach fall in the D zone so that they reach a BG minimum lower than with CT, but the percentage of time spent under 70 mg/dl is negligible and overall the performance indices are improved. On Day 8 91% of the patients are in A and B zones and 0 in D. On Day 15 the performance are slightly improved: zone A decreases the number of patients by 2, C by 4 and B increases by 6 with the R2R_{Nl}, while with the R2R_L zone A decreases by 2, B increases by 3 and D goes to 0.

In Fig. 3 are represented the mean $\pm$ standard deviation of the glucose profiles of Day 2 (a) and Day 8 (b), respectively. The same conclusions can be hold: after 1 step of R2R (Day 2) the post-prandial below basal excursions,



(a)



(b)

Fig. 2. CVGA representing the results obtained using CT (blue square), R2R$_{Nl}$ (magenta circle), and R2R$_L$ (orange diamond) on Day 2 (a) and Day 8 (b) with the insulin sensitivity variation scenario. Each point represents the coordinates (x is a function of the minimum glucose value and y a function of the maximum value) associated with a single patient.

Table 2. Simulation results obtained with the CT, R2R$_{Nl}$, and R2R$_L$ strategies. ^{a} p-value $< .001$, ^{b} p-value $< .01$, ^{c} p-value $< .05$

		Day 8			Day 15		
		G	N	PP	G	N	PP
Mean [mg/dl]	CT	131.86^b	104.19^b	158.96	131.93^a	104.25^a	159.04^c
	$R2R_{Nl}$	124.36	96.04	151.64	122.84	94.15	150.26
	$R2R_L$	125.15^a	96.78	152.48	123.29^a	94.76	150.66
SD [mg/dl]	CT	30.82	9.05	26.15	30.83^c	9.05	26.16
	$R2R_{Nl}$	31.19	9.44	26.58	31.42	9.65	26.68
	$R2R_L$	31.18^b	9.42	26.49	31.33^b	9.54	26.62
T_r (%)	CT	75.98^a	85.18^a	64.45^a	75.95^a	84.8^a	64.69^a
	$R2R_{Nl}$	91.37	95.78	82.29	92.8	97.89	84.49
	$R2R_L$	91.06^a	96.12	81.36	92.73^b	98.1	84.11
T_{tr} (%)	CT	49^a	70.34^c	31.24^b	49.06^a	70.35	31.4^a
	$R2R_{Nl}$	61.86	81.35	34.41	63.3	80.53	35.46
	$R2R_L$	62.19	83.85	34.03	63.45	82.16	34.96
T_a (%)	CT	15.76^a	0.85^c	32.11^c	15.76^a	0.85^c	32.1^b
	$R2R_{Nl}$	7.11	0.02	17.4	6.46	0.04	15.4
	$R2R_L$	7.57^a	0.02	18.41	6.61^c	0.04	15.79
T_b (%)	CT	8.27^a	13.96^b	3.44^c	8.3^a	14.35^a	3.2^b
	$R2R_{Nl}$	1.52	4.2	0.31	0.74	2.07	0.11
	$R2R_L$	1.38	3.85	0.23	0.67	1.86	0.1
T_h (%)	CT	3.5^b	4.19^b	1.68^b	3.4^b	4.07^b	1.73^b
	$R2R_{Nl}$	0	0	0	0	0	0
	$R2R_L$	0	0	0	0	0	0
$\#\overline{ht}$	CT	3.5^a	1.76^b	0.6	3.43^a	1.71^a	0.59^c
	$R2R_{Nl}$	0.38	0.34	0.04	0.14	0.13	0.01
	$R2R_L$	0.31	0.27	0.04	0.08	0.07	0

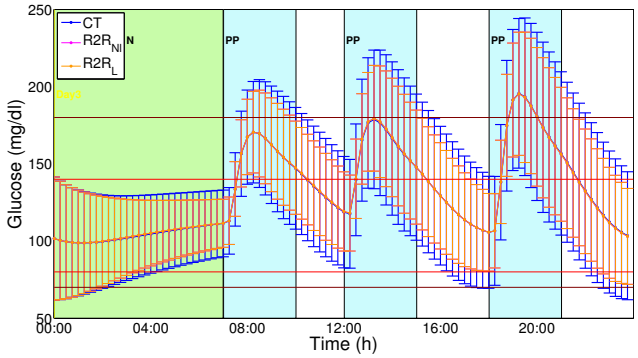
detected after lunch and dinner, are reduced (Fig. 3a); after 1 week (Day 8) the standard deviation computed on 100 patients is largely reduced (Fig. 3b) as well as the minimum and maximum BG, confirming the CVGA results of Fig. 2b.

4. CONCLUSION

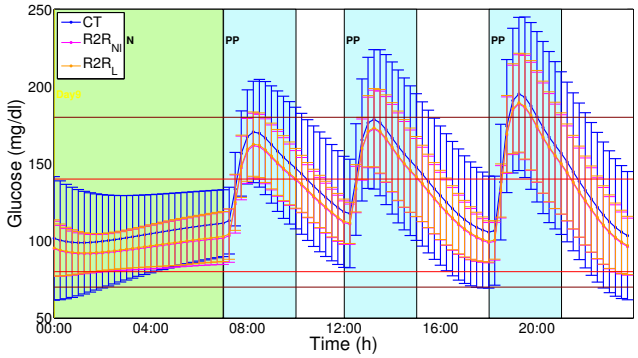
A new switching R2R strategy using the percentage of time spent below 70 mg/dl, above 180 mg/dl and distance of the average glucose from a target to update the basal insulin is proposed. This approach, differently from closed-loop artificial pancreas, does not require a real-time closed-loop connection avoiding all the related technological and safety issues. With respect to the previous R2R approaches, that use only few BG measurements, the use of a CGM allows an automatic adjustment based on a richer information. Algorithm convergence has been proven for a linear version by studying the stability of the associated piecewise affine system.

The performance studied on an extensive *in-silico* trial performed on 100 adults patients of the UVA/Padova simulator with a random variation of patient insulin sensitivity, is very promising already after one week. The hypoglycemia phenomena experienced with the CT are completely avoided by using the R2R and the hyperglycemia is reduced as well. The R2R algorithm shows good performance and stability in both its forms on the entire diabetic population.

Hence the proposed R2R algorithm could be safely used in real patients thanks to the well accepted capability of the UVA/Padova simulator to represent real population. From a methodological point of view the next step is to apply the R2R approach also to adapt the insulin boluses moving



(a)



(b)

Fig. 3. The figure shows for CT (blue), $R2R_{Nl}$ (magenta), and $R2R_L$ (orange) the mean (dots) and the variability ($\pm$ standard deviation) of the glucose profiles obtained in 100 virtual patients on Day 2 (a) and Day 8 (b) with the insulin sensitivity variation scenario. N, night; PP, postprandial period.

from a scalar problem to a multivariable one that however significantly increases the complexity of the problem in view of the interaction between basal and insulin boluses.

ACKNOWLEDGEMENTS

Thanks to Federico Di Palma for the valuable comments.

REFERENCES

R.M. Bergenstal, W.V. Tamborlane, A. Ahmann, J.B. Buse, G. Dailey, S.N. Davis, C. Joyce, T. Peoples, B.A. Perkins, J.B. Welsh, B. John et. al. Effectiveness of sensor-augmented insulin-pump therapy in type 1 diabetes. *New England Journal of Medicine*, 363(4): 311–320, 2010.

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.

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

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.

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.

C.C. Palerm and 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):258–265, 2008.

F.J. Doyle III, B. Srinivasan and D. Bonvin. Run-to-run control strategy for diabetes management. *Engineering in Medicine and Biology Society, 2001. Proceedings of the 23rd Annual International Conference of the IEEE*, 4:3159–3162, 2001.

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.

F. Gang Stability analysis of piecewise discrete-time linear systems. *Automatic Control, IEEE Transactions on*, 47(7):1108–1112, 2002.

C. Dalla Man, F. Micheletto, D. Lv, M. Breton, B.P. Kovatchev, and C. Cobelli. The UVA/Padova Type 1 Diabetes Simulator: New Features. *J Diabetes Sci Technol*, 8(1):26–34, 2014.

C.L. Rohlfing, H.M. Wiedmeyer, R.R. Little, J.D. England, A. Tennill and D.E. Goldstein. Defining the relationship between plasma glucose and HbA1c analysis of glucose profiles and HbA1c in the Diabetes Control and Complications Trial. *Diabetes care*, 25(2):275–278, 2002.

J.A. Davidson. Treatment of the patient with diabetes: importance of maintaining target HbA1c levels. *Current Medical Research and Opinion®*, 20(12):1919–1927, 2004.

M. Heisler, J.D. Piette, M. Spencer, E. Kieffer and S. Vijan. The relationship between knowledge of recent HbA1c values and diabetes care understanding and self-management. *Diabetes care*, 28(4):816–822, 2005.

G. Francois and B. Srinivasan and D. Bonvin. Convergence analysis of run-to-run control for a class of nonlinear systems. *American Control Conference, 2003. Proceedings of the 2003*, 4:3032–3037, 2003.

M. Johansson and A. Rantzer. Computation of piecewise quadratic Lyapunov functions for hybrid systems. *Automatic Control, IEEE Transactions on*, 43(4):555–559, 1998.

M. Kvasnica, P. Grieder, M. Baotić and M. Morari. Multi-parametric toolbox (MPT). *Hybrid systems: computation and control*, Springer:448–462, 2004.

C. Toffanin, M. Messori, F. Di Palma, G. De Nicolao, C. Cobelli, and L. Magni. Artificial Pancreas: MPC design from clinical experience. *J Diabetes Sci Technol*, 7(6): 1470–1483, 2013.

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

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 Review in Control*, 36:118–128, 2012.