Postprandial Glucose Regulation via KNN meal classification in Type 1 Diabetes

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***Abstract*—Blood glucose concentration control is a classic negative feedback problem with insulin secreted by the pancreas as a control variable. Type 1 Diabetes is a chronic metabolic disease caused by a cellular-mediated autoimmune destruction of the pancreas beta-cells, so exogenous insulin administration is needed to regulate the glycaemia. Postprandial glucose regulation is typically based on the knowledge of an estimation of the ingested carbohydrates, of the Carbohydrate-to-insulin ratio, of the correction factor, of the insulin still active and of a measure of the glycaemia just before the meal. Despite the use of this information meal compensation is yet a key unsolved issue. In this paper a new approach based on machine-learning methodologies is proposed to improve postprandial glucose regulation. The proposed approach uses the multiple K-Nearest Neighbors classification algorithm to predict postprandial glucose profile due to the nominal therapy and to suggest a correction to time and/or amount of the meal bolus. This approach has been successfully validated on the adult in silico population of the UVA/PADOVA simulator, which has been accepted by the Food and Drug Administration as a substitute to animal trials.**

***Index Terms*—Machine Learning, Biological system, Pattern recognition and classification**

I. INTRODUCTION

TYPE 1 Diabetes (T1D) is a chronic metabolic disease associated with high Blood Glucose (BG) concentration (BG $>$ 180 mg/dl), known as hyperglycemia. In order to guarantee the supply of glucose to the cells, the body has to maintain BG concentration within the euglycemic range [70-180] mg/dl using the insulin secreted by the pancreas. T1D results from a cellular-mediated autoimmune destruction of the pancreas beta-cells, so exogenous insulin administration is needed to regulate glycaemia [1]. The conventional therapy to treat T1D consists of a basal insulin delivery, which is conceptually a piecewise constant insulin infusion, and of an insulin bolus, which is an impulse-like infusion used to compensate the glucose rise due to a meal [2], [3], [4]. The postprandial (PP) regulation is one of the most critical problem in BG control, in particular when an Open-Loop (OL) therapy is adopted. In fact, an underestimated bolus could lead to hyperglycemia, while an overestimated bolus could induce hypoglycemia. In order to improve meal compensation during PP periods, an augmented OL therapy based on machine-learning methodologies is proposed in this work. This approach uses the K-Nearest Neighbors (KNN) classification algorithm [5], [6] to predict the PP glucose profile due to the nominal OL therapy and, then, it adapts the meal bolus accordingly. Since the BG trend in the PP period is characterized by two features, the amplitude of the excursions and the shape of the profile, a Multiple Classifier System (MCS) is implemented with a parallel architecture, where each base classifier is devoted to predict one PP feature. The outputs of the two base classifiers are combined by an integration strategy to obtain a complete prediction.

The new approach is tested in silico by using the 2013 version of the UVA/PADOVA Simulator [7]. The 100 in silico adults considered in this work are characterized by intra- and inter-day variability of insulin sensitivity [8], different distributions of Carbohydrate-to-insulin Ratio (CR) at different day time and dawn phenomenon [9]. This letter is organized as follows. The description of the MCS architecture and of the base classifiers is given in Section II, where also the training procedure and results in terms of classifier predictions are discussed. In Section III the proposed augmented therapy based on KNN classifiers is formulated, and the testing scenario with the outcome metrics are introduced. In Section IV the final results are reported in comparison with the OL therapy. Section V reports the conclusions.

II. MEAL CLASSIFICATION

A. Open-Loop therapy

The conventional treatment of T1D patients is an OL therapy defined as follows:

$$i(t) = i_b(t) + i_B(t) \tag{1}$$

where i_B is the insulin bolus in correspondence to the meal at time t, and i_b (U/h) is the basal insulin, which is defined as a piecewise constant function with respect to t. The OL therapy includes a feed-forward action, which exploits the knowledge of external disturbances, namely the meals, to compensate in advance their effects by adapting the insulin bolus doses, as follows:

$$i_B(t_m) = \frac{\hat{d}(t_m)}{CR(t_m)} + \frac{y(t_m) - y_0}{CF(t_m)} - IOB(t_m) \tag{2}$$

where $\hat{d}$ (g) is the estimated amount of ingested carbohydrates at time t_m, CR (g/U) and CF (mg/dl/U) are the patient

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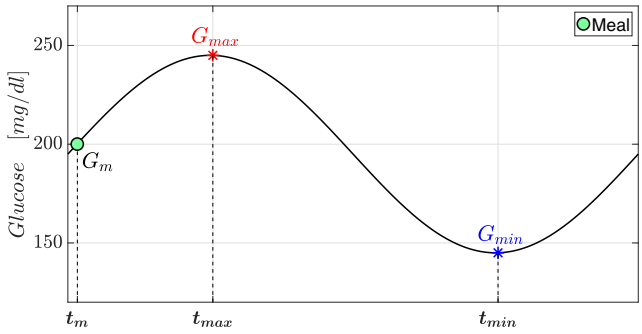

Fig. 1. An example of glucose trend where G_m, G_{min}, G_{max} are the glucose value at meal time, the minimum value of glucose, and the maximum value of glucose, respectively and t_m,t_{min}, t_{max} are meal time, the time instants when G_{min} and G_{max} values are reached, respectively.

$\mathbf{C_e}$	Description
$\mathbf{C_e^{-2}}$	$G_{max} < G_{high}$ and $G_{min} < G_{hypo}$
$\mathbf{C_e^{-1}}$	$G_{max} < G_{hyper}$ and $G_{hypo} < G_{min} < G_{low}$
$\mathbf{C_e^{0}}$	$G_{max} < G_{high}$ and $G_{min} < G_{low}$
$\mathbf{C_e^{+1}}$	$G_{max} > G_{high}$ and $G_{low} < G_{min} < G_{high}$
$\mathbf{C_e^{+2}}$	$G_{max} > G_{hyper}$ and $G_{min} > G_{high}$

TABLE I
EXCURSION CLASSIFICATION

$\mathbf{C_s}$	Description
$\mathbf{C_s^{-2}}$	$t_u < t_o$ and t_o,$t_u > 0$
$\mathbf{C_s^{-1}}$	$t_o n.d.$ and $t_u > 0$
$\mathbf{C_s^{0}}$	t_u, $t_o n.d.$
$\mathbf{C_s^{+1}}$	$t_u n.d.$ and $t_o > 0$
$\mathbf{C_s^{+2}}$	$t_o < t_u$ and t_o,$t_u > 0$

TABLE II
SHAPE CLASSIFICATION

time variant carbohydrate-to-insulin ratio and correction factor, respectively, y (mg/dl) is the glycaemia measured just before the meal, y_0 (mg/dl) is the patient glucose target, and IOB (Insulin-On-Board) represents the insulin still active in the system at time t_m [10].

B. Multiple Classifier Scheme

The effect of a meal on the glucose response can be characterized by two main PP variables, the amplitude of the maximum excursions and the shapes of glucose profile. The first is a measure of the glucose variability in the PP period and it is strictly related to the minimum and maximum values reached in the PP period; while the second is an information related to the times in which these values are reached. If these PP variables are predictable, the PP glucose response can be improved by properly modifying i_B. The first aim of this work is to identify a relation between measurable quantities, called input features, given at meal time and the two PP variables characterizing the future meal response. An example of glucose trend after a meal is presented in Figure 1, where the parameters characterizing the curve are:

- G_{min} and G_{max}, the minimum and maximum values of glucose, respectively;
- t_{min} and t_{max}, the time instants when G_{min} and G_{max} values are reached, respectively;
- G_m, the glucose at meal time t_m.

Since G_{min} and G_{max} define completely the excursion, while the shape is more related to t_{min} and t_{max}, the two PP variables can be considered separately by identifying two independent base classifiers, C_e and C_s, respectively. The PP variables result mutually complementary, so a Multiple Classifier System (MCS), where each predictable variable has its own classifier algorithm, is proposed. Given a single set of input features known at t_m, each base classifier will select its own subset for the classification.
The outputs of two base classifiers are combined following a parallel MCS architecture. The goal of this scheme is the improvement of the accuracy of the final prediction by exploiting the classifier diversity. Indeed, since the classifiers make different misclassification errors on different test samples, diversity improves the classification accuracy. Of course, the drawback is the need to train multiple classifiers. The combination strategy of the two base classifiers is performed by integration, namely both the classifiers contribute to the final output [11].

1) Excursion Classifier (C_e): In order to define the first classifier, the combinations of G_{max} and G_{min} have to be associated to a finite set of classes. Hence, five classes are defined on the basis of proper glucose thresholds:

- C_e^{-2}: glucose trend characterized by hypoglycemia
- C_e^{-1}: glucose trend associated with hypoglycemia risk
- C_e^{0}: glucose trend in the desired target
- C_e^{+1}: glucose trend associated with hyperglycemia risk
- C_e^{+2}: glucose trend characterized by hyperglycemia.

Denoting with G_{high}, G_{low} the upper and lower bounds of the desired glucose range, and with G_{hyper}, G_{hypo} the glucose limits that defines hyperglycemia and hypoglycemia events, the excursion classification is described in Figure 2 and summarized in Table I.

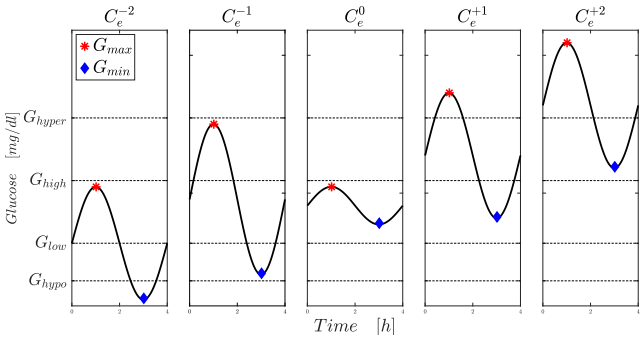

Fig. 2. The five classes of the *Excursion Classifier* C_e. The red stars represent G_{max}, and the blue diamonds represent G_{min}.

2) Shape Classifier (C_s): The second classifier aims to distinguish the meal responses on the base of glucose shape and in particular on the presence of significant undershoot and/or overshoot. Denoting a significant undershoot as

$$G_{min} < G_m - \Delta G_{th} \tag{3}$$

and a significant overshoot as

$$G_{max} > G_m + \Delta G_{th} \tag{4}$$

with ΔG_{th} a glucose threshold to be tuned, the shape classifier maps the input features to five categories of possible PP glucose shapes defined as follows:

- C_s^{-2}: meal response characterized by a significant undershoot at time t_u followed by a significant overshoot at time t_o
- C_s^{-1}: meal response characterized by a significant overshoot at time t_o ;
- C_s^{0}: meal response without significant undershoot and overshoot
- C_s^{+1}: meal response characterized by a significant undershoot at time t_u
- C_s^{+2}: meal response characterized by a significant overshoot at time t_o followed by a significant undershoot at time t_u

If undershoot (overshoot) are not present, t_u (t_o) are not defined (n.d.). The shape classes are described in Figure 3 and summarized in Table II.

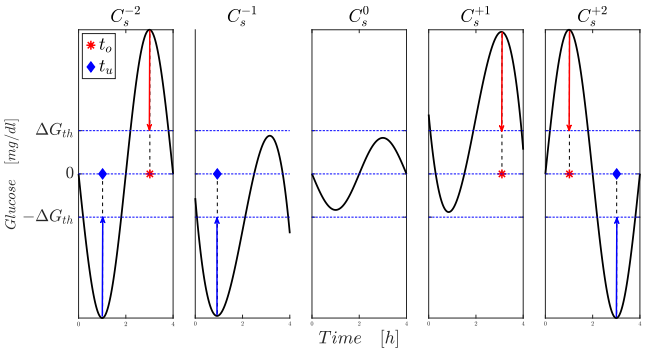

Fig. 3. The five classes of the *Shape Classifier* C_s. The red stars represent t_o, and the blue diamonds represent t_u. The red lines represent a significant overshoot, and the blue lines represents a significant undershoot.

C. KNN Classifier

The two classifiers developed in this work use a KNN algorithm to perform the classification. KNN algorithms are supervised non-parametric learning algorithms that learn the relationship between input and output observations. A new input instance is classified by assigning the output class of the K most similar neighbors, where similarity is defined according to a distance metric [5]. KNN algorithm is highly efficient for pattern recognition [6], [12] and well fits the purpose of glucose patterns classification. In order to train the classifiers, a single space set of possible input features has been defined for both the classifiers. These inputs features are selected from a set of parameters known at t_m consisting of BG, carbohydrate content (CHO), CR, IOB, i_b, i_B, amount of carbohydrate intake calculated in the interval $[t_m - 6h, t_m]$ (preCHO), Day Time (DT) with respect to midnight and the Day Period Classification (DPC). The DPC is a categorical variable defined as: morning [5:00am-12:00pm], afternoon [12:00pm-7:00pm] and evening [7:00pm to 5:00am]. For each classifier, the selection of the input features is performed via an ANOVA test to determine the parameters subset statistically correlated with the considered classifier, where a statistical correlation is considered significant at the level 0.05. Other factors, like stress, physical activity, etc., not usually available at meal time have been excluded from the analysis.

In addition to the input features, two other elements characterize the classifier: the dataset used in the training procedure, called training set, and the number of neighbors, N_n. In this work, the Condensed Nearest Neighbors (CNN) rule [13] is used to optimize the training set by selecting a subset of the samples contained in the original set. However, the training data can be affected by a sample error which can cause a decrease in performance; also N_n affects the prediction performance of the classifier. So, the training procedure is repeated an exhaustive number of times N_r with different training sets and different N_n. The selection of the classifier aims to maximize the probability of correctly predicting hypoglycemia. Then, each classifier prediction is associated to a posteriori probability of success, called score, and the standard KNN algorithm selects the one with the maximum score. Considering that a misclassification of the classes $C_x^{-2}, C_x^{+2}, x \in \{e, s\}$ represents a risk of hyper or hypoglycemia, respectively, in this work the classifier C_x is made more conservative by exploiting this score. Let's consider the critical case of a C_e^{-2} prediction, the classifier C_e maintains this prediction only if the difference between the score of C_e^{-2} and C_e^{-1} is above a safety threshold ϵ, otherwise the C_e prediction is changed to C_e^{-1} in order to apply a more conservative action. The same approach is used with $C_e^{+2}, C_s^{-2}, C_s^{+2}$ prediction, while the other predictions remain unchanged.

In addition to the training set, a validation set is needed to assess the classifier performance. In order to avoid the overfitting problem, training and validation sets are constrained to be independent, but with the same distribution probability.

D. Results

1) UVA/PADOVA simulator: The Universities of Virginia and Padova (UVA/PADOVA) have developed a large nonlinear compartmental model able to simulate the glucose-insulin dynamics of the diabetic population [7]. Different dynamics for different subjects are modeled through different sets of metabolic parameters of this model to describe the inter-subject variability of the diabetic population. Three "virtual populations" (children, adolescents and adults), each composed of 100 subjects, were included in the UVA/PADOVA simulator. This simulator was accepted by the Food and Drug Administration (FDA) as a substitute to animal trials for testing insulin therapies in T1D patients.

2) Datasets and classifier settings: The proposed approach aims to obtain a unique classifier valid for the entire T1D population. The training and validation sets are generated by using a four-day scenario. This scenario includes 18 meals: 4 breakfasts (between 7:00am and 8:30am), 6 snacks (2 in the morning, 3 in the afternoon and 1 in the evening), 4 lunches (between 12:30pm and 2:00pm) and 4 dinners (between 8:00pm and 8:30pm). The total amount of 1800 meal data over the 100 patients are split in two parts: half pertaining to the training set and half to the validation set. In order to

avoid overfitting or sample error, the number of repetition of the procedure N_r is set to 200.
The algorithm parameters are set to $\Delta G = 30$ [mg/dl], $G_{high} = 150$ [mg/dl], $G_{low} = 100$ [mg/dl], $G_{hyper} = 200$ [mg/dl], $G_{hypo} = 70$ [mg/dl], $\epsilon = 0.20$.

3) Outcome metrics: Denoting with C_x^n a generic class of a generic classifer C_x, some preliminary definitions are introduced below:

- True Positive (TP): sample belonging to class C_x^n classified correctly
- True Negative (TN): sample not belonging to class C_x^n classified correctly
- False Positive (FP): sample not belonging to class C_x^n but classified as belonged to C_x^n
- False Negative (FN): sample belonging to class C_x^n but classified as not belonged to C_x^n
- True Positive Rate (TPR) and False Positive Rate (FPR) measure the proportion of positives that are correctly classified and positives that are wrongly classified, respectively and they are defined as follows:

$$TPR = \frac{TP}{TP + FN}, \qquad FPR = \frac{FP}{TN + FP}.$$

Defining the Receiver Operator Characteristic (ROC) as the curve describing the relation between TPR and FPR, the perfomance of the classifiers are evaluated through the Area Under the curve of ROC (AUROC) [14]. Classifiers have a good performance with AUROC value more than 0.5, while AUROC equal to 0.5 means that the classifier behaves exactly as a random variable.

4) Discussion: The results of the two ANOVA tests are shown in Figure 4 and 5. Figure 4 shows the boxplots related to C_e: the input features statistically correlated with the classes of C_e are BG and i_B. The boxplot associated to BG is entirely below the adopted significance threshold; i_B presents a few outliers exceeding the threshold, but the performance are significantly better than the other parametrs. Figure 5 shows the boxplots related to C_s: BG, DCP, and DT are chosen for C_s because the boxplots are entirely below the threshold.
The AUROC values of the selected C_e and C_s are reported in Table III and IV, respectively. This index presents satisfactory performance with values between 0.60 and 0.90 for all the classes of both classifiers apart for C_s^{-2}. The critical AUROC value associated to this class can be explained by the poor representation of C_s^{-2}. This limitation is acceptable, considering that the event occurs occasionally during clinical trials and that the simulated dataset distribution has been choosen to be homogeneous with the real data.

III. CLASSIFIER-AUGMENTED OPEN-LOOP

The availability of a classifier able to predict the PP glucose dynamics at the meal time allows to modify in advance the OL therapy in order to avoid both hypoglycemia and hyperglycemia. In general, a condition of hyperglycemia can be reduced by increasing the meal bolus, while a condition of hypoglycemia can be prevented, or at least mitigated, by

$\mathbf{C_e}$	AUROC
$\mathbf{C_e^{-2}}$	0.84
$\mathbf{C_e^{-1}}$	0.77
$\mathbf{C_e^{0}}$	0.75
$\mathbf{C_e^{+1}}$	0.69
$\mathbf{C_e^{+2}}$	0.88

TABLE III
C_e AUROC

$\mathbf{C_s}$	AUROC
$\mathbf{C_s^{-2}}$	0.50
$\mathbf{C_s^{-1}}$	0.69
$\mathbf{C_s^{0}}$	0.60
$\mathbf{C_s^{+1}}$	0.64
$\mathbf{C_s^{+2}}$	0.77

TABLE IV
C_s AUROC

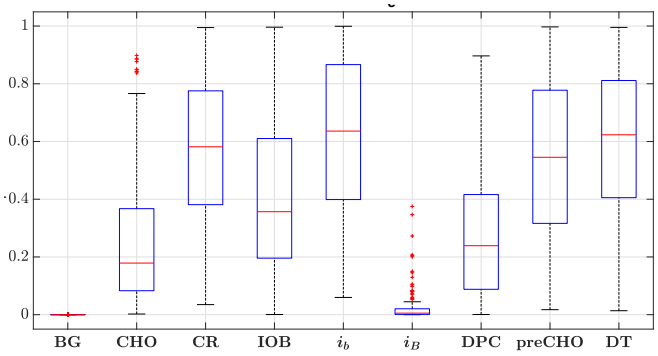

Fig. 4. Boxplots associated to ANOVA test of C_e

decreasing it. If both conditions occur sequentially, the insulin bolus has to be properly adapted on the basis of the time and the severity of each condition. If one single phenomenon is predominant, the bolus is modified only in terms of insulin amount, otherwise both the time and the amount of the bolus have to be adapted. Following these criteria, the Classifier-Augmented (CA) open-loop therapy proposed in this work exploits the information of both classifiers, trained offline, to modify the meal bolus, i_B. In particular, the classifier C_s defines the variation of the time, while C_e defines the range of the insulin variations. Then, the final adaptation of the bolus is the result of the integration of C_s and C_e.
Defining C_{sm} and C_{em} the classifier prediction of C_s and C_e at meal time t_m, respectively, the insulin bolus adapted by the CA strategy, i_B^{CA}, can be defined as follows:

$$i_B{}^{CA}(t_m) = \alpha\, i_B(t_m) + \beta\, i_B(t_m - \tau) \tag{5}$$

where the values of α, β used for each bolus depend on

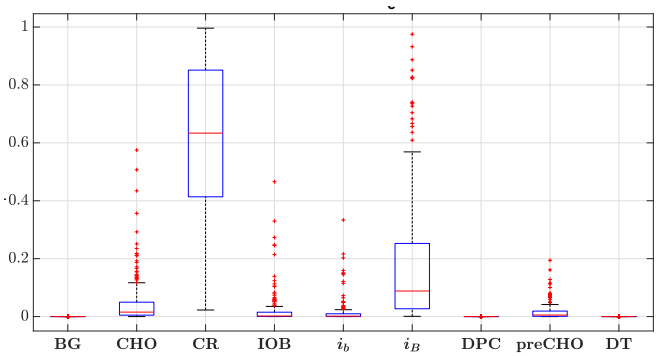

Fig. 5. Boxplots associated to ANOVA test of C_s

C_e \ C_s	C_s^{-2}	C_s^{-1}	C_s^{0}	C_s^{+1}	C_s^{+2}
C_e^{-2}	α=0.2, β=0.3	α=0.2, β=0,	α=0.4, β=0,	α=0.8, β=0,	α=0.3, β=0.2
C_e^{-1}	α=0.5, β=0.5	α=0.6, β=0,	α=0.8, β=0,	α=0.7, β=0,	α=0.5, β=0.5
C_e^{0}	α=0.8, β=0	α=0.8, β=0,	α=1, β=0,	α=1.2, β=0,	α=1.2, β=0
C_e^{+1}	α=0.5, β=0.8	α=1, β=0,	α=1.2, β=0,	α=1.4, β=0,	α=1.2, β=0.2
C_e^{+2}	α=0.7, β=1	α=1.4, β=0,	α=1.4, β=0,	α=1.7, β=0,	α=1.4, β=0.6

TABLE V
α AND β VALUES FOR PATIENTS OF CATEGORY A.

C_e \ C_s	C_s^{-2}	C_s^{-1}	C_s^{0}	C_s^{+1}	C_s^{+2}
C_e^{-2}	α=0.3, β=0.2	α=0.3, β=0,	α=0.5, β=0,	α=0.8, β=0,	α=0.4, β=0.1
C_e^{-1}	α=0.6, β=0.4	α=0.8, β=0,	α=1, β=0,	α=0.9, β=0,	α=0.8, β=0.2
C_e^{0}	α=0.8, β=0	α=0.9, β=0,	α=1, β=0,	α=1.1, β=0,	α=1.2, β=0
C_e^{+1}	α=0.8, β=0.4	α=1, β=0,	α=1, β=0,	α=1.2, β=0,	α=1.1, β=0.2
C_e^{+2}	α=0.9, β=0.8	α=1.2, β=0,	α=1.2, β=0,	α=1.4, β=0,	α=1.2, β=0.2

TABLE VI
α AND β VALUES FOR PATIENTS OF CATEGORY B.

C_{sm} and C_{em}. In particular, a first set of values for each possible combination of these classifiers has been defined as reported in Table V (Category A). A second more conservative category (Category B) has been defined in order to manage patients very sensitive to drastic change of their therapy, see Table VI. Finally, a third category (Category C) has been defined by setting $\alpha = 1$ and $\beta = 0$, in order to manage critical situations. The values of α and β have been tuned on a subset of meals taken from different patients able to represent the 25 possible combinations of classes reported in tables V and VI. The assignment of each patient to one category is performed by a trial and error procedure. In particular, each patient undergoes to a 16-day scenario composed of 4 periods of 4 days: the first in OL, the second with Category A and the fourth with Category B, divided by a washout period in OL. The introduction of hypotreatments in the protocol guarantees patient safety. Patients are assigned to Category C if both Categories A and B increase significantly the number of hypotreatments or no improvements of T_a (time above 180 mg/dl) and T_b (time below 70 mg/dl) are achieved. The assignment to Category A and B is performed minimizing both T_a and T_b or alternatively only one of them, giving priority to T_b. If the improvements between the two categories are similar, the category A is preferred. The parameter $\tau = 20$ [min] is set constant for all the patients. Since the classifier training is performed offline, the computational time required for the online implementation of the algorithm is negligible.

A. Simulation settings

The proposed CA algorithm is tested on the 100 in silico adult patients of the UVA/PADOVA simulator with a 4-day scenario. The testing scenario starts at 0:00 am and involves 16 meals: 4 breakfasts (between 7:00am and 8:00am), 4 snacks (1 in the morning, 2 in the afternoon and 1 in the evening), 4 lunches (between 12:30pm and 1:00pm) and 4 dinners (between 7:00pm and 8:30pm). Hypotreatments (ht) of 15g are administrated to the patient in case of hypoglycemia (BG $<$ 65 mg/dl).

B. Performance metrics

In order to evaluate the effectiveness of an insulin therapy, some performance metrics have been adopted. The following outcome indices follow the consensus statement for artificial pancreas trials described in [15]. They include average (A) and standard deviation (SD) of glucose (mg/dl), time in target, or percentage of time spent in euglycemic range [70-180] mg/dl (T_r), time in tight target or percentage of time spent in tight range [70-140] mg/dl (T_{tr}), time above target or percentage of time spent in hyperglycemia (T_a), time below target or percentage of time spent below 70 mg/dl (T_b), percentage of time spent below 60 mg/dl (T_{b60}), the Root Mean Square Error (RMSE) respect a glucose reference of 120 (mg/dl), and the Total Daily Insulin (TDI) delivered to the patient. These metrics are computed overall (O), during night (N, 0:00pm - 6:00am), and as an average of all the PP periods (4h). Median [25th; 75th] 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.

IV. RESULTS

The performance metrics obtained with the OL and CA strategies evaluated on the entire population on the testing scenario are reported in Table VII. Interesting improvements are obtained by the new technique for all the 100 patients in the PP period, period mainly affected by the meal bolus changes. The CA is able to improve the time in target by 2.1% and in tight target by 11.6%, to lower the average glucose by 5.4% and to reduce the time spent above the target by 36.7% with respect the OL therapy. The increase of the times spent below the target remains limited: T_b initially 2.9% reaches 3.2% while T_{b60} from 1.5% increases to 1.8%. The RMSE is decreased by 5.4% with and increment of the TDI of 2.9 (U). All these results are statistically significant. The same observations can be drawn overall, where the CA is able to

		O	N	PP
A (mg/dl)	OL	**144.57 [134.86, 155.84] [142.38,148.63]**	**148.59 [137.59, 168.59] [148.49,157.77]**	**145.73 [134.84, 154.13] [142.20,148.78]**
	CA	**139.05**^{a} **[132.11, 148.43] [137.98,143.29]**	**144.76**^{a} **[133.95, 161.91] [142.75,151.62]**	**137.82**^{a} **[131.45, 148.92] [137.01,142.72]**
SD (mg/dl)	OL	**34.46 (± 12.54) [31.97,36.95]**	**19.06 [13.59, 26.83] [18.25,22.20]**	**35.08 [24.68, 41.42] [31.52,36.71]**
	CA	**35.80**^{a} **(± 12.64) [33.29,38.30]**	**22.58**^{a} **[15.75, 30.31] [20.87,25.00]**	**35.07**^{c} **[25.80, 42.70] [32.26,37.32]**
T_t (%)	OL	**80.61 [65.47, 92.74] [75.41,83.55]**	**89.00 [64.38, 100.00] [77.51,88.30]**	**80.80 [65.82, 92.57] [74.26,82.61]**
	CA	**84.64**^{a} **[68.61, 94.57] [77.78,85.46]**	**93.11**^{a} **[74.62, 100.00] [82.03,92.72]**	**82.47**^{a} **[68.86, 94.84] [77.18,85.02]**
T_{tt} (%)	OL	**38.84 (± 18.43) [35.19,42.50]**	**31.58 [11.94, 53.13] [27.54,39.28]**	**38.75 (± 18.33) [35.12,42.39]**
	CA	**42.83**^{a} **(± 17.09) [39.44,46.22]**	**41.78**^{a} **[21.27, 57.76] [35.13,45.79]**	**43.25**^{a} **(± 17.61) [39.75,46.74]**
T_a (%)	OL	**13.31 [4.30, 28.94] [12.91,20.48]**	**9.16 [0.00, 35.62] [11.63,22.25]**	**14.39 [4.86, 27.90] [13.51,21.17]**
	CA	**10.53**^{a} **[2.77, 23.54] [10.51,16.77]**	**4.67**^{a} **[0.00, 24.79] [5.54,17.51]**	**9.11**^{a} **[3.66, 23.69] [10.81,17.38]**
T_b (%)	OL	**2.92 [0.00, 5.53] [2.57,3.98]**	**0.00 [0.00, 0.00] [0.00,0.00]**	**2.87 [0.00, 5.57] [2.22,4.08]**
	CA	**3.64**^{a} **[1.41, 6.72] [3.33,4.84]**	**0.00**^{a} **[0.00, 0.00] [0.00,0.00]**	**3.17**^{a} **[0.87, 6.99] [3.07,4.83]**
T_{b60} (%)	OL	**1.81 [0.00, 3.45] [1.54,2.66]**	**0.00 [0.00, 0.00] [0.00,0.00]**	**1.48 [0.00, 3.82] [1.50,2.69]**
	CA	**2.37**^{a} **[0.00, 4.77] [2.13,3.43]**	**0.00**^{b} **[0.00, 0.00] [0.00,0.00]**	**1.82**^{a} **[0.00, 5.24] [2.08,3.52]**
RMSE	OL	**42.64 [31.94, 56.21] [40.52,47.44]**	**36.15 [27.01, 56.05] [37.25,45.62]**	**42.50 [34.09, 54.17] [40.94,47.79]**
	CA	**40.37**^{a} **[30.71, 53.89] [38.81,45.55]**	**34.79**^{a} **[26.08, 50.66] [34.03,41.96]**	**40.21**^{a} **[30.63, 52.73] [38.78,45.47]**
TDI (U)	OL	**53.76 [44.45, 68.83] [52.21,59.03]**	**8.65 [7.21, 10.30] [8.36,9.35]**	**38.74 [31.49, 48.45] [37.58,42.49]**
	CA	**55.87**^{a} **[45.40, 69.57] [54.86,62.16]**	**8.75**^{a} **[7.64, 10.76] [8.72,9.74]**	**39.86**^{a} **[32.46, 50.74] [39.45,44.74]**

TABLE VII

OL STRATEGY VS NEW CA APPROACH ON 100 IN SILICO PATIENTS. CONFIDENCE INTERVALS ARE REPORTED. THE SIGNIFICANT RESULTS ARE HIGHLIGHTED IN BOLD. P-VALUE (p) SIGNIFICANCE LEVELS ARE: $a := p < 0.001,\ b := p < 0.01,\ c := p < 0.05$

improve the times in target (5% and 10.3% for the tight target), to lower the average glucose by 3.8% and to reduce the time spent above the target by 20.9%. The increase of the time spent below the target remains limited. The RMSE is decrease by 5.3% with and increment of TDI of 3.9 (U). All these results are statistically significant.

V. CONCLUSIONS

This letter presents a multiple KNN classification algorithm to predict PP glucose profile due to the nominal therapy. A potential application is proposed to compute corrections to time and/or amount of the meal bolus. Satisfactory results have been obtained in terms of reduction of the average glucose and of hyperglycemia, and in terms of increment of the time in target with limited increase of hypoglycemia. Future work will be devoted to the individualization of the corrections, to the online adaptation of the classifiers to the specific patient and to exploit the classifiers prediction in a closed-loop context.

REFERENCES

[1] D. Nathan, P. Cleary, J. Backlund, S. Genuth, J. Lachin, T. Orchard, P. Raskin, B. Zinman, D. Control, and DCCT/EDIC Study Research-Group, "Intensive diabetes treatment and cardiovascular disease in patientswith type 1 diabetes," *New England Journal of Medicine*, vol. 353, no. 25, 2005.

[2] 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*, vol. 7, no. 1, pp. 48–57, 2005.

[3] 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*, vol. 17, no. 13, pp. 1194–1213, 2007.

[4] 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*, vol. 18, no. 3–4, pp. 258–265, 2008.

[5] N. S. Altman, "An introduction to kernel and nearest-neighbor nonparametric regression," *The American Statistician*, vol. 46, no. 3, pp. 175–185, 1992.

[6] N. Bhatia *et al.*, "Survey of nearest neighbor techniques," *arXiv preprint arXiv:1007.0085*, 2010.

[7] 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*, vol. 8, no. 1, pp. 26–34, 2014.

[8] 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*, vol. 17, no. 1, pp. 1–7, 2015.

[9] C. Toffanin, R. Visentin, M. Messori, F. Di Palma, L. Magni, and C. Cobelli, "Towards a run-to-run adaptive artificial pancreas: In silico results," *IEEE Trans Biomed Eng*, 2017.

[10] 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*, vol. 5, no. 5, p. A237, 2003.

[11] T. K. Ho, J. J. Hull, and S. N. Srihari, "Decision combination in multiple classifier systems," *Ieee Transaction on patter analysis and machine intelligence*, vol. 16, no. 1, pp. 66 – 75, 1994.

[12] A. Kataria and M. Singh, "A review of data classification using k-nearest neighbour algorithm," *International Journal of Emerging Technology and Advanced Engineering*, vol. 3, no. 6, pp. 354–360, 2013.

[13] P. Hart, "The condensed nearest neighbors rule," *IEEE Transaction Information Theory*, vol. 14, no. 3, pp. 515–516, 1968.

[14] C. M. Florkowski, "Sensitivity, specificity, receiver-operating characteristic (ROC) curves and likelihood ratios: Communicating the performance of diagnostic tests," *Diabetes Care*, vol. 29, no. 1, pp. 83–87, 2008.

[15] D. M. Maahs, B. A. Buckingham, J. R. Castle, A. Cinar, E. R. Damiano, E. Dassau, J. H. DeVries, and F. J. Doyle III et al., "Outcome measures for artificial pancreas clinical trials: A consensus report," *Diabetes Care*, vol. 39, no. 7, pp. 1175–1179, 2016.