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Improving the management of hyperglycemia in type 1 diabetes therapy: an algorithm for the suggestion of corrective insulin boluses based on future glucose prediction

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Abstract. Type 1 diabetes (T1D) is a chronic disease characterized by elevated blood glucose (BG) levels, due to the absence of insulin secretion by pancreatic β-cells. People affected by T1D, must adhere with a life-long therapy which aims to maintain BG concentration within the safe range of [70−180] mg/dL. The standard therapy, which consists of multiple burdensome daily actions, can be inefficient and difficult to implement in the long-term, thus negatively affecting patient's quality of life. In this context, decision support systems (DSSs) based on minimally-invasive continuous glucose monitoring (CGM) sensors, which allow measuring BG almost continuously for several days, play a key role in improving T1D management. In particular, DSSs are software tools which can assist individuals with T1D by suggesting appropriate therapeutic actions as carbohydrates intake and insulin injections. The availability of algorithms that can accurately predict future BG levels would facilitate proactive therapeutic interventions, further improving glucose control and patients well-being. In this paper, we present a novel algorithm for DSSs that suggests the administration of corrective insulin boluses (CIBs) leveraging a CGM-based predictive model aimed to forecast the future CGM concentration. The effectiveness of the proposed algorithm has been assessed retrospectively on a dataset consisting of 30 T1D patients recorded in real-life conditions and the performance has been compared with that of a recent state-of-art heuristic-based strategy for hyperglycemia correction. Results indicate that the proposed algorithm for CIB suggestion decreases the time in hyperglycemia (34.77% vs 39.42%) and increases the percentage of time spent in euglycemia (64.33% vs 59.16%) with statistical significance, additionally lowering the overall risk for patients.

1 Introduction

Type 1 diabetes (T1D) is a chronic disease characterized by the autoimmune destruction of pancreatic β-cells, which are responsible for insulin production. Therefore, in people affected by T1D, blood glucose (BG) concentration often exceeds the safe range of [70−180] mg/dL: T1D requires a life-long therapy which consist of several daily actions such as BG self-monitoring, carbohydrate (CHO) estimation and exogenous insulin administrations. The therapy has to be accurately tuned: insulin underdosing increases risk of hyperglycemia, i.e., BG$\geq$180 mg/dL, which can lead to serious long-term consequences as neuropathy and cardiovascular disease; on the other side, insulin overdose can lead to hypoglycemia, i.e., BG$\leq$70 mg/dL, which is dangerous both in the short and long-term, causing seizures, loss of consciousness, coma and even death [1].

In the recent year, continuous glucose monitoring (CGM) sensors have been widely adopted by T1D patients to improve the management and ease the burden of the standard therapy [2]. CGM devices are minimally-invasive sensors which measure interstitial BG level at intervals of 1-5 minutes, for several days. Furthermore, these sensors can provide patients with information about their glucose trend (rate of change, ROC) and generate visual/acoustic alerts if their glycemia falls outside the safe range. The integration of CGM sensors with continuous subcutaneous insulin infusion (CSII) pumps, smart insulin pens, and dedicated mobile applications has facilitated the development of decision support systems (DSSs) [3]. These are software tools that can automatically collect and analyze data from CGM sensors and CSII pumps to generate customized recommendations, such as corrective insulin boluses (CIB) and hypotreatments, aimed at enhancing BG control.

According to current guidelines [4], a CIB is computed using the standard formula [5]:

$$CIB = \frac{G - G_T}{C_F} - IOB \tag{1}$$

where G (mg/dL) is the actual BG value, G_T (mg/dL) is the patient target BG value (e.g., 120 mg/dL), C_F (mg/dL/U) is the correction factor, i.e., how much 1 U of insulin lowers BG, and IOB (U) is the insulin-on-board, i.e., the amount of insulin still present in the blood from previous administrations. In literature, several heuristic algorithms which suggest insulin bolus correction have been published [6, 7, 8, 9], which add or subtract a fixed quantity of insulin to standard CIB computed with Equation (1) mainly depending on ROC and patient's C_F.

Despite the above-mentioned guidelines are proved to achieve encouraging results, they mainly focus on the current BG level and trend, being unable to suggest proactive actions that can limit the frequency and duration of hyperglicemia. Therefore, the issue of improving postprandial BG control remains open. In this context, one possible key element that can enhance current strategies for CIB suggestion could be predicting and using the future BG concentration rather than the actual value. In fact, a wide literature exists proving that the real-time BG forecasting not only is possible but also can be accurately achieved [10, 11]. Knowing with an anticipation of e.g. 20 or 30 minutes if BG is crossing the hyperglycemic threshold will allow the patient to take preventive targeted measures to counteract the onset of critical impending episodes, considerably improving T1D management.

To address this gap, we present a novel algorithm in this paper that suggests preventive CIBs using an adaptive auto-regressive model to predict future BG concentrations, combined with patient-specific physiological information. We aim to retrospectively evaluate the effectiveness of our proposed approach against state-of-art CIB suggestion methods using a dataset consisting of T1D patients who were monitored in real-life conditions.

2 Data and Methods

2.1 The proposed approach for preventive CIB suggestion: rAR-CIB

The proposed approach is summarized in the flowchart presented in Figure 1 and is based on a predictive model of future glucose concentrations. The algorithm works as follows:

1. waits two hours after a meal;
2. at every new CGM value, forecasts the future glucose concentration with a prediction horizon (PH) of 30 minutes exploiting a suitable predictive model;
3. if the predicted glycemia G_{pred} is above the hyperglycemic threshold, i.e., 180 mg/dL, and the ROC of glucose concentration is positive:

- suggests a CIB according to:

$$CIB = \frac{G_{pred} - G_T}{C_F} - IOB \tag{2}$$

- waits at least a patient-specific t_{pers} time before suggesting another CIB

4. otherwise, returns to 2.

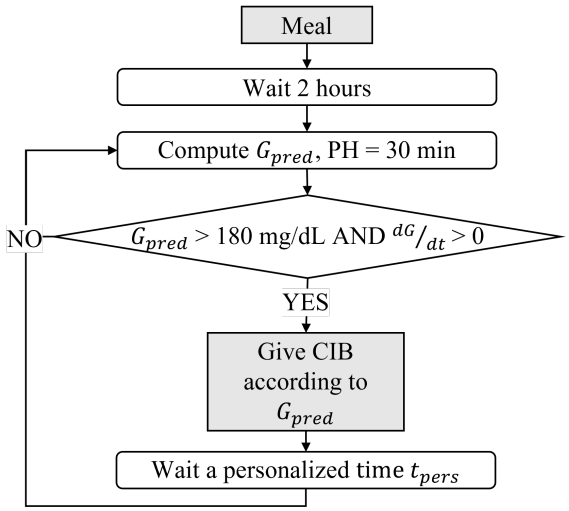

Figure 1: rAR-CIB flowchart. Abbreviations: predicted glycemia (G_{pred}), prediction horizon (PH), corrective insulin bolus (CIB), personalized timing (t_{pers}).

BG forecasting algorithms The BG predictive algorithm of step 2. is a personalized recursive autoregressive model (rAR), which employs as input information only the CGM datastream as in [12, 13]. Each time a new CGM sample is recorded, model parameters are updated according to a well established recursive scheme [14]. In fact, the recursive estimation approach for parameters' identification represent a natural option to handle intra-patient variability and the slow changes over time in patient metabolism.

Personalized timing between CIB As regard the patient-specific 'time-between-boluses', from now on called t_{pers}, it is forced to be greater than 60 min and lower than 120 min (interquartile range [60, 91.5, 120] min) and it is retrieved from patient's personal glucose-insulin dynamics. More in details, it is calculated as 150% of the patient-specific delay of insulin action, i.e., the time in which insulin rate of appearance in plasma reaches its maximum value, retrieved from a white-box model of glucose-insulin dynamics based on the maximal physiological model of the UVa/Padova T1D Simulator [15].

State-of-the-art approach As comparator, we implemented the heuristic algorithm of Aleppo et al. [7] (AL). This approach adjusts the CIB amount specified in Equation (1) by incorporating a fixed quantity of insulin, either increasing or decreasing it based on factors such as ROC, C_F, and the current BG concentration, and specifically includes post-prandial recommendation.

2.2 Methodology Assessment

The two methodologies were evaluated using ReplayBG [16], a novel tool developed by our research group that retrospectively assesses the outcome of alternative therapy regimes on real-world T1D data. ReplayBG works in two steps. In the first step, a nonlinear model of the glucose-insulin dynamic is identified using individual's CHO intakes, insulin infusions, and CGM data as input. The identified model is then used in the second step to simulate the glucose profile that would have been obtained by adopting the CIB therapy advised by the algorithms.

2.3 Dataset

The dataset used was obtained from the Control To Range 3 (CTR3) study [17], which includes data about CGM and self-monitoring blood glucose readings, injected boluses, basal insulin, ingested CHO, as well as personal patient information as gender, age, body weight, and therapy's parameters. From the data, we extracted daily traces with at least the 3 main meals and mean hyperglycemia duration of 3 hours. A total of 42 daily traces were then identified using ReplayBG framework, with a mean absolute relative difference below 13% compared to the original CGM data. For the second step (i.e., simulation phase) of ReplayBG we cleared the CIBs injected by the patient in order to test our new strategy. These data will now be referred to as baseline.

2.4 Evaluation metrics

For each individual and algorithm, we calculated time in range (TIR, i.e., [70≤BG≤180] mg/dL), time above range (TAR), time below range (TBR) as temporal metrics; number of generated CIB (CIB) and total daily insulin injected (INS) as CIB metrics; the glycemia risk index (GRI) [18] for glucose control evaluation; and hyperglycemic events duration (HyperD) as hyperglycemic metric. We used the Student test to evaluate statistical significance, if the normality distribution assumption was not rejected, and the Wilcoxon signed-rank test otherwise, with a significance level of 5%.

3 Results

Figure 2 shows the glucose simulated traces via ReplayBG obtained for baseline (dotted line), and AL (green line) and rAR-CIB (red line) approaches for CIB suggestion in a representative subject, characterized with a t_{pers} =74 min as time between consecutive CIBs.

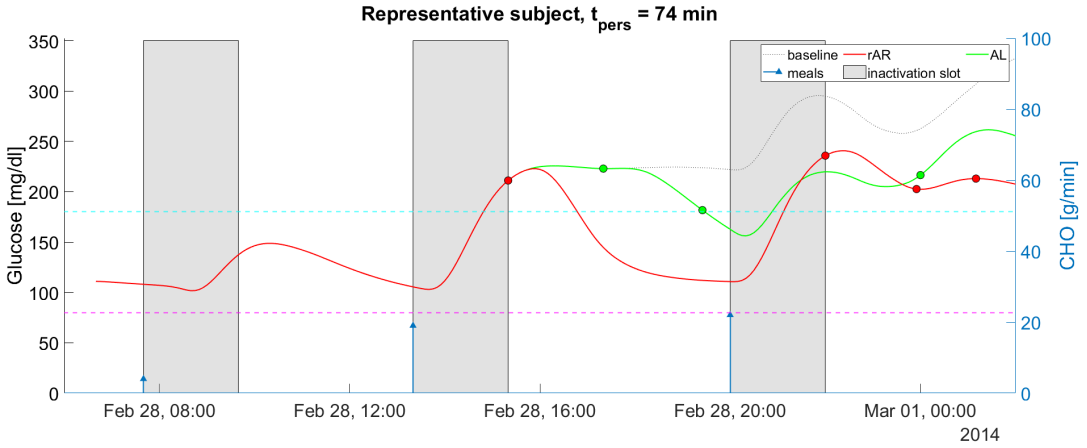

Figure 2: Application of AL and rAR-CIB algorithms via ReplayBG on a representative subject. The dotted line is the glycemic traces obtained with no CIBs (baseline); the green line is the glycemic trace resulting from AL guidelines and the red line is the glycemic trace resulting from rAR-CIB algorithm. CIBs are reported as green dots and red dots for AL and rAR-CIB, respectively. Meals are shown with the blue arrows in the bottom of the plot. The common inactivation slot of two hours after the meal of the aforementioned methodologies are highlighted.

As can be observed, the dotted line, representing the simulation in which CIB have not been administered, shows a large part of the simulated trace (57.94%) above the hyperglycemic threshold, highlighted with a cyan dotted line, which means a high risk level for the patient (GRI=67.98). Following AL guidelines, 3 CIBs (green dots) are generated: 2.16U at time 17:20 and 1.29U at 19:25 in order to take back glycemia in the euglycemic range after lunch, and 1.95U at 00:00, reducing TAR to 50.64% and GRI to 46.01.

rAR-CIB algorithms, suggests 4 CIBs (red dots) instead: one of 2.25U just after the inactivation slot after lunch, at time 15:20, which rapidly drives glycemia below 180 mg/dL; and 3 after

dinner, where glycemia is particularly high: 2.41U at time 22:00, 1.53U at 23:55 and 1.95U at 01:10, further reducing TAR to 35.62%. Despite the increased number of boluses suggested (one bolus more), GRI for rAR-CIB algorithm is reduced by 38.06% compared to AL guidelines.

In Table 1 the overall results calculated among the 42 traces are reported for baseline, AL guidelines and rAR-CIB algorithm in terms of median and [25^{th}-75^{th}] ranges.

Table 1: Comparison between baseline, AL and rAR-CIB approaches. Metrics are reported as median, [25^{th}, 75^{th}].

	TIR [%]	**TAR** [%]	**TBR** [%]	**GRI** [unit]	**HyperD** [min]	**CIB** [unit]	**INS** [U]
baseline	52.29 [39.56, 61.59]	46.57 [38.41, 60.44]	0 [0, 0]	52.71 [36.33, 67.98]	260 [212.5, 333.1]	-	-
AL	59.16 [46.58, 68.98]	39.42 [22.41, 48.48]	0 [0, 0]	42.14 [28.79, 62.96]	217.5 [175, 252.5]	2 [2, 2]	5.45 [3.68, 8.78]
rAR-CIB	64.33* [55.98, 76.50]	34.77* [22.73, 39.56]	0 [0, 0]	36.07* [27.52, 52.28]	195* [147.5, 227.5]	3* [2, 3]	7.63* [4.04, 12.44]

* significant variation between AL and rAR-CIB

Compared to baseline, in which no CIBs are delivered, both approaches improve the overall glycemic control. In fact, both AL and rAR-CIB significantly reduce TAR and hyperglycemia duration, resulting also in statistically significant improvement in TIR and GRI.

Comparing the two strategies instead, rAR-CIB acts in advance compared to AL, resulting in a promising strategy: TAR and HyperD are significantly improved (from 39.42% to 34.37%, and from 217.5 min to 195 min, for AL and rAR-CIB respectively), significantly reducing GRI by 14.40%. It should be noted that rAR-CIB algorithm involves one bolus/day more than AL as well as a statistically significant increase of the injected insulin. However, this necessary increment entails the significant improvement of TIR (from 59.16% to 64.33%) and does not affect patient TBR. In fact, the algorithm considers patient-specific plasmatic insulin absorption delay and adjusts the suggested bolus by subtracting IOB, which ensures that the undesired consequence of hypoglycemia is mitigated: TBR for our proposed algorithm remains null.

4 Discussion and Conclusion

In this paper we propose rAR-CIB, a novel CIB-suggesting algorithm which utilizes a CGM-only predictive model for the preventive suggestion of therapy actions interspersed by a personalized time retrieved from patient's glucose-insulin dynamics. The proposed strategy outperforms one of the most recent heuristic approach by: i) significantly reducing both hyperglycemia duration and TAR (by 10.34% and 5.05%, respectively); ii) statistically improving TIR (+5.17%) and GRI (from 42.14 to 36.07) and iii) enhancing TBR.

To assess the methodologies, we leveraged the CTR3 closed-loop dataset. However, since our objective is to create an open-loop algorithm, we replaced the time-varying basal insulin of the data with the mean across the entire data traces for each subject before the physiological model identification step via ReplayBG. This replacement aimed to simulate the effect of a long-acting insulin bolus typically administered in the morning for patients following multiple daily injections therapy. By doing so, we could determine the optimal open-loop therapy that emulates the original data. It is important to acknowledge this limitation of the study, and we plan to address it in future research when larger datasets recorded in free-living conditions and under open-loop setups become available. Future work will also examine more elaborated predictive algorithms which employ additional input such as insulin injections and CHO intake.

In conclusion, rAR-CIB is a practical valuable alternative to the state-of-art heuristic-based strategy for suggesting CIBs. Moreover, it is well-suited for integration into an insulin bolus calculator module of a DSS, especially with a specific focus on CIBs.

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