A Correction Insulin Bolus Delivery Strategy for Decision Support Systems in Type 1 Diabetes*

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Abstract—Management of type 1 diabetes (T1D) requires affected individuals to perform multiple daily actions to keep their blood glucose levels within the safe rage and avoid adverse hypo-/hyperglycemic episodes. Decision support systems (DSS) for T1D are composite tools that implement multiple software modules aiming to ease such a burden and to improve glucose control. At the University of Padova, we are developing a new DSS that currently integrate a smart insulin bolus calculator for optimal insulin dosing and a rescue carbohydrate intake advisor to tackle hypoglycemia. However, a module specifically targeting hyperglycemia, that suggests the administration of corrective insulin boluses (CIB), is still missing. For such a scope, this work aims to assess a recent literature methodology, proposed by Aleppo et al., which provides a simple strategy for dealing with hyperglycemia. The methodology is tested retrospectively on clinical data of individuals with T1D. In particular, here we leveraged a novel in silico tool that first identifies a non-linear model of glucose-insulin dynamics on data, then uses such model to simulate and compare the glucose trace obtained by "replaying" the recorded scenario and the glucose trace obtained using the CIB delivery strategy under evaluation. Results show that the CIB delivery strategy significantly reduce the percentage of time spent in hyperglycemia (-15.63%) without inducing any hypoglycemic episode, demonstrating both safety and efficacy of its use. These preliminary results suggest that the CIB delivery strategy proposed by Aleppo et al. is a promising candidate to be included in our system to counteract hyperglycemia. Future work will extensively evaluate the methodology and will compare it against other competing approaches.

Clinical Relevance—This work shows that the literature methodology for correction insulin bolus delivery proposed by Aleppo et al. is a promising approach to mitigate hyperglycemia.

I. INTRODUCTION

Type 1 diabetes (T1D) is a chronic autoimmune disease characterized by the lack of insulin production in the pancreas and the consequent inability to keep the blood glucose (BG) concentration within the safe range, i.e., BG $\in$ [70, 180] mg/dl [1]. Standard T1D therapy consists of multiple daily injections of exogenous insulin boluses administered in an "open-loop" fashion to compensate BG fluctuations due to meal intakes, and tuned according to diet, subject physiology, and current BG concentration measured using fingerprick self-monitoring devices (SMBG) [2].

In the last decades, new technologies for diabetes, such as minimally invasive continuous glucose monitoring (CGM) sensors [3], allowed to partially relieve the burden of T1D management and to improve glycemic control. Additionally,

CGM sensors provide dynamical information on BG fluctuations and in particular its derivative (G_{der}), which can be exploited to develop new tools to support the patients' decision-making process. Following this rationale, new CGM-based algorithms have been recently proposed in the literature demonstrating to be successful in improving glucose control [4]. A particularly appealing possibility consists of merging these methodologies in a decision support system (DSS) [5], i.e., composite software tool that offer multiple functionalities to assist individuals in managing T1D by automatically analyzing data and providing personalized recommendations about the therapy.

Recently, our research group at the University of Padova started the development of a new DSS, namely the Padova Decision Support System (PDSS) [6]. To date, it incorporates two G_{der}-based state-of-the-art algorithms, i.e., a personalized insulin bolus calculator, which aims at providing optimal insulin dosing at mealtime [7], and a smart rescue carbohydrate intake advisor to counteract the shortcoming of dangerous hypoglycemic events (i.e., BG < 70 mg/dl) [8].

A current missing feature of PDSS is the ability of targeting prolonged postprandial hyperglycemia, i.e., BG > 180 mg/dl, by providing patients with a smart correction insulin bolus (CIB) delivery strategy.

For this reason, the aim being equipping PDSS with such a feature, in this work we assessed a G_{der}-based literature algorithm for its possible integration within the system. The methodology is assessed leveraging a novel in-silico framework [9] that allows retrospectively modifying data acquired in people with T1D. Obtained results are promising and suggest the potential integration of the methodology in the PDSS.

II. A LITERATURE ALGORITHM TO GENERATE CORRECTION INSULIN BOLUSES BASED ON G_{DER}

A. The standard correction insulin bolus delivery strategy

Standard T1D therapy contains suggestions on how to administer one or more CIB to tackle prolonged postprandial hyperglycemic events, with the aim of lowering BG and get it back in the safe range. However, CIB delivery is not unique, and practitioners' recommendations may differ both in terms of CIB dosing and timing [10].

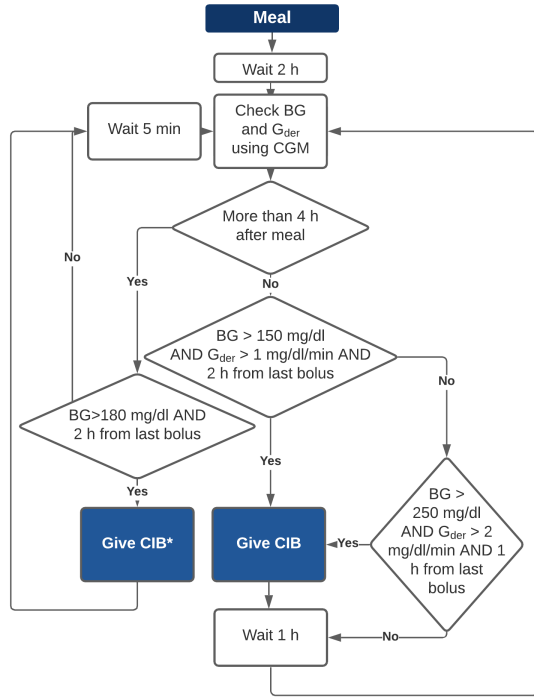Regarding CIB dosing, as a general rule of thumb, it can be obtained using the following simple formula [11]:

Figure 1. CIB delivery strategy as defined by Aleppo et al. [12]. BG stands for blood glucose, Gder stands for BG derivative, CGM stands for continuous glucose monitoring, CIB stands for correction insulin bolus.

$$CIB = \frac{G_C - G_T}{CF} - IOB \qquad (1)$$

where G_C (mg/dl) is the current BG concentration, provided by CGM, G_T (mg/dl) is the patient target BG level, CF (mg/dl/U) is the correction factor, a patient-specific therapy parameter usually tuned by physician to accommodate the peculiar patient physiology, and IOB (U) is the so-called insulin-on-board, i.e., an estimate of the amount of exogenous insulin that has been previously assumed by the patient but that has not been assimilated by the organism yet.

As far as CIB delivery timing is concerned, at the best of our knowledge, there are no fixed rules. However, a generally accepted indication is to wait at least 2 hours after a mealtime bolus before taking any corrective actions, since additional administrations of insulin in that time-window can often result in a subsequent hypoglycemia due to the high IOB.

A clear issue with the standard CIB delivery strategy is that it does not account for BG dynamics. To stress this aspect, let us consider the following representative situation. Two hours after a mealtime insulin bolus, a patient's BG is 200 mg/dl while his G_{der} is -2 mg/dl/min. Standard insulin therapy would suggest that in this scenario, a CIB should be delivered. However, it is intuitive to state that patient probably does not require such a CIB since G_{der} indicates that BG is rapidly falling, thus getting back to the safe range without requiring any additional corrective, and potentially dangerous, actions.

B. The Aleppo's methodology for CIB delivery

The aim being formulating a CIB delivery strategy able to account for G_{der} information, Aleppo et al. [12], proposed a simple heuristic based on their clinical experience. This strategy follows a precise scheme (reported in Fig. 1), which defines both CIB timing and dosing.

In details, to control postprandial BG after a meal, patients are required to wait two hours, and then check BG concentration and G_{der} values using CGM, and finally take one of these two actions:

- If more than 4 hours have passed since the last meal, BG > 180 mg/dl, and more than 2 hours have passed since the last bolus, take a CIB computed as:

$$CIB^* = CIB + f(CF, G_{der}) \qquad (2)$$

where $f(\cdot)$ (U) is a deterministic function depending on CF and G_{der} (see Table I for the detail on $f(\cdot)$ given CF and G_{der});

- If less than 4 hours have passed since the last meal, if BG > 150 mg/dl, G_{der} > 1 mg/dl/min, and more than 2 hours have passed since the last bolus, or BG > 250 mg/dl, G_{der} > 2 mg/dl/min, and more than 1 hour has passed since the last bolus, take a CIB computed using (1) and wait 1 hour before checking CGM again.

TABLE I. $F(\cdot)$ VALUES GIVEN CF AND G_{DER}

G_{der} (mg/dl/min)	CF (mg/dl/U)	$f(\cdot)$ (U)
> 3	< 25	+ 4.5
	25 − 50	+ 3.5
	50 − 75	+ 2.5
	> 75	+ 1.5
2 − 3	< 25	+ 3.5
	25 − 50	+ 2.5
	50 − 75	+ 1.5
	> 75	+ 1.0
1 − 2	< 25	+ 2.5
	25 − 50	+ 1.5
	50 − 75	+ 1.0
	> 75	+ 0.5
-1 − 1	< 25	0
	25 − 50	
	50 − 75	
	> 75	
-2 − -1	< 25	- 2.5
	25 − 50	- 1.5
	50 − 75	- 1.0
	> 75	- 0.5
-3 − -2	< 25	- 3.5
	25 − 50	- 2.5
	50 − 75	- 1.5
	> 75	- 1.0
< -3	< 25	- 4.5
	25 − 50	- 3.5
	50 − 75	- 2.5
	> 75	- 1.5

III. ASSESSMENT OF THE METHODOLOGY

A. Dataset

The assessment of the methodology was performed on data collected during a randomized crossover trial in patients with T1D [13]. In details, data were collected over a 2-month period where patients were randomized either to 2 months of

closed-loop therapy, using an artificial pancreas, from dinner to waking up, plus open-loop therapy during the day, or to 2 months of all-day open-loop therapy. The study was done in accordance with the Declaration of Helsinki and was approved by the institutional ethics review board at each site. All patients provided verbal and written informed consent.

Being the methodology under assessment targeting patients undergoing the open-loop therapy, we used only data collected during the all-day open-loop phase. From these data, we extracted the meal and related postprandial intervals lasting 8 hours. Then, in order to minimize the sources of variability and bias, we discarded those intervals containing rescue carbohydrate intakes or correction boluses. Finally, we retained only those intervals that presented, at least, one hyperglycemic event.

The resulting dataset consisted of 77, 8-hours long, portions of data each containing the information on meal intake, exogenous insulin infusion, and CGM measurements.

B. In silico framework and assessment criteria

In order to evaluate the CIB delivery strategy of Aleppo et al. on already acquired data, we resorted to a model-based methodology [9]. This approach consisted of two main phases: in the first phase, a model of glucose-insulin regulation in T1D population, whose inputs are carbohydrate intakes and exogenous insulin, and the output is the BG trace, was identified for each selected portion of data. Then, the identified model was used to simulate the postprandial glucose concentration that would have been obtained by adopting the CIB delivery strategy under examination.

Briefly, the identified model core was the Bergman et al. [14] minimal one, which describes the impact of plasma insulin action on plasma glucose. The model has been expanded by adding a model of subcutaneous insulin infusion [15], to describe how exogenous insulin diffuses to plasma, and a model of oral glucose assumption, to describe the impact of meal carbohydrate intakes on BG [16]. Then, the model was fitted on data in a Bayesian setup using Markov Chain Monte Carlo, avoiding any undesired non-identifiability issues, to obtain a point estimate of unknown model parameters. Details on the identification setup as well as model equations can be found in [9].

For each of the 77 portions of data, we designed two 8-hours long in-silico experiments. In the first scenario (scenario A), we simulated the BG trace obtained using the actual insulin input as reported in the data, thus without any CIB delivery. In the second scenario (scenario B), we simulated the BG trace resulting from the adoption of [12].

Finally, we quantified glycemic control in scenario A and B in terms of percentage of time that the BG trace spent in hyperglycemia (T_{Hyper}), hypoglycemia (T_{Hypo}), and in the safe target range (T_{Target}), i.e., three metrics that are widely used for such a purpose [17]. Difference between scenario A and scenario B was considered statistically significant according to the rank sum test with a 5% significance level.

IV. RESULTS

Fig. 2 presents an example of BG traces obtained in scenario A and scenario B in a representative subject. Top

panel reports the actual CGM data (in red), the BG profile resulting from the application of the original input data (in black), and the BG trace obtained using the original input data but with the addition of a correction bolus as suggested by the Aleppo et al. algorithm (in blue). It can be appreciated that, by administering a CIB of 2.67 U when patient's BG reach the hyperglycemic threshold at around 1:00 AM, it is possible to strongly mitigate the post-dinner hyperglycemic event without inducing any dangerous hypoglycemic event. In particular, resulting T_{Hyper}, and T_{Target} in scenario A and scenario B are 59.38% vs. 84.38%, 40.62% vs. 15.62%.

In Table II, we report the distributions of T_{Hypo}, T_{Hyper}, and T_{Target} in terms of median and interquartile range obtained in scenario A and scenario B for all considered portions of data. Considering T_{Hyper}, the algorithm allows to significantly improve ($p < 0.05$) the glycemic outcomes through the population. In details, average $\Delta T_{Hyper} = T_{Hyper}$(scenario B) - T_{Hyper}(scenario A) is -15.63%. Moreover, it can be noticed that no hypoglycemic episodes are induced by the algorithm being T_{Hypo} 0.00% in both scenarios. Finally, T_{Target} significantly improved by ΔT_{Target} = 12.50%.
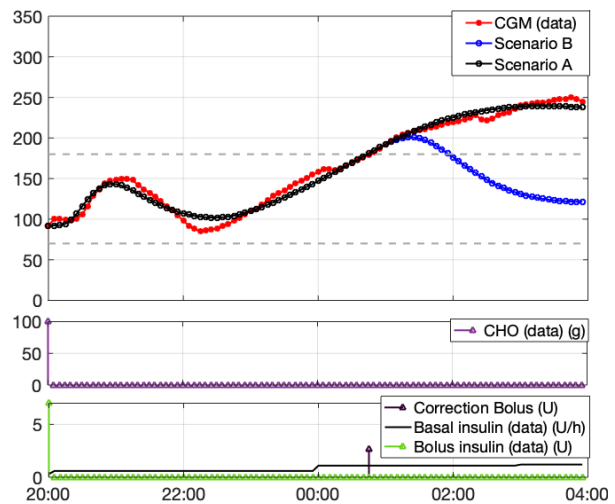

Figure 2. Example of BG traces obtained in in a representative subject. In the top panel, the CGM data (dotted red line) and the respective BG profiles obtained in scenario A (dotted black line) and scenario B (dotted blue line). In the center panel, the CHO data (violet stem). In the bottom panel, the insulin data (basal in solid black line, bolus in green stem) and the CIB generated by [12] (in black stem).

TABLE II.   OVERALL RESULTS

Scenario	T_{Hypo} (%)	T_{Hyper} (%)	T_{Target} (%)
A	0.00 [0.00, 0.00]	48.96 [45.83, 49.68]	51.04 [50.00, 52.35]
B	0.00 [0.00, 0.00]	33.33 [31.25, 36.25]	63.54 [62.40, 65.58]
p-value	1.00	< 0.05	< 0.05

V. CONCLUSIONS

DSS for T1D, such as the one that we are developing at the University of Padova, are tools able to proactively help patients in managing the therapy and its daily burden. In this

work, we focused on the possibility of integrating into PDSS a new module that targets hyperglycemia by recommending the administration of CIB. To do so, we evaluated a literature strategy for CIB delivery, recently proposed by Aleppo et al., that leverages the information on BG dynamics, and its G_{der}. By mean of a novel in-silico framework, we validated the algorithm on retrospective data of real subjects with T1D.

The preliminary validation of the methodology showed that the CIB strategy of [12] is a simple yet promising one. In particular, the obtained results indicated that the methodology was effective in mitigating post-prandial hyperglycemia in the considered scenarios. Moreover, the additional infused exogenous insulin did not induce any hypoglycemic episode, demonstrating the safety of the approach. For these reasons, we can conclude that [12] is a particularly promising candidate methodology to be included in a potential new PDSS module for hyperglycemic treatment.

However, further work is still necessary to offer a robust validation. In fact, in this setup, statistically significant improvements do not mean that there is a correspondent clinically relevant difference. This will start by performing the same validation strategy we proposed in this work on other clinical datasets using the same retrospective assessment methodology, to evaluate how much the results we obtained can be generalized. The validation will furtherly focus on an extensive comparison of the CIB delivery strategy of [12] against other methodologies available in the literature, such as [18] and [19]. This step will allow identifying the best approach for the scope and evidence possible margins of improvements.

Future work will also deal with the tuning and refinement of the best identified methodology. First, it will be tweaked by replacing the current BG concentration in (1) and (2), i.e., G_C, with the estimated future BG level provided by state-of-the-art glucose prediction algorithms [20]. Then, we will explore the possibility of leveraging machine learning to personalize the whole approach in order to fit the patient-specific physiology [21]. Finally, we will assess in silico how this methodology will cope with the other modules of the PDSS, and ultimately validate the whole system by mean of an ad-hoc clinical trial.

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