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Towards Patient-Specific Carbohydrate Counting Accuracy: An *In Silico* Study

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Abstract. Type 1 diabetes mellitus patients on intensive insulin therapy use advanced carbohydrate counting to proper dose prandial insulin. Therefore, the patient's ability to accurately estimate the meal's carbohydrate content is paramount. However, despite its significance, several studies show that the patient's ability to estimates the meal's carbohydrate content is far from ideal and identify the need for continuous education on carbohydrate counting. In this context, the authors have proposed in previous works an analytic method to determine the maximum error to the carbohydrate counting regarding each patient's insulin-to-carb ratio and the insulin sensitivity factor. This maximum can be of great significance to design patient-specific educational programs and to define learning outcomes according to the specific characteristics of each patient. This work presents a methodology and conditions to assess the previously proposed method, using the FDA-approved University of Virginia(UVA)/Padova Type 1 Diabetes Simulator.

INTRODUCTION

Advanced carbohydrate counting has been used by Type 1 Diabetes Mellitus (T1DM) patients as a meal planning tool to improve glycemic control. Fu et al. [1], in their systematic review and meta-analysis, found that patients using advanced carbohydrate counting experienced a significant reduction in their HbA1c concentration compared with those using other diet management approaches. Besides, Koontz et al. [2], in their study to assess carbohydrate and insulin-dosing knowledge in youth with T1DM, demonstrated that youth's ability to estimate accurately the carbohydrate content of meals correlates with low HbA1c levels. Therefore, it is reasonable to conclude that well-trained patients on carbohydrate counting achieve the best results regarding reducing HbA1c levels. In this context, to maximize the time-on-target and consequently lower the HbA1c level, the authors proposed in [3] a new analytic method to determine the maximum error that each patient can make when estimating the carbohydrate content of each meal. The main idea of the proposed method is the following, the error on the meals carbohydrate estimates lead to a non-optimal preprandial insulin bolus and, consequently, to an off-target postprandial glycemic level. The difference between the postprandial blood glucose value and the target value depends not only on the meal's carbohydrate estimates error but also on the patient insulin sensitivity factor and the insulin-to-carbohydrate ratio. Therefore, knowing the hypoglycemia and the hyperglycemia limits its possible to compute the maximum carbohydrate counting error allowed for each patient and use it to design patient-specific educational programs and established proper and measurable learning outcomes. Nevertheless, to make this a reality it is necessary to validate the method proposed in [3], which will be undertaken in two phases. The first phase involves in-silico preclinical trials using the FDA-approved University of Virginia(UVA)/Padova Type 1 Diabetes Mellitus Simulator (T1DMS), and the second phase requires the assessment with real patients. This paper describes the reasoning to be used in the first phase.

The in-silico preclinical trials include the T1DMS adult population under intensive insulin therapy using multiple daily insulin injections on a basal-bolus scheme. Patient-specific basal rates will be set by the T1DMS, and the prandial bolus will be calculated using Equation 1, considering the insulin-on-board negligible, like what happens with most real patients on the same scheme. The carbohydrates intake for each meal will be affected by a random

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error dependent on the patient-specific limit calculated using the method proposed in [3]. Following, are presented and discussed the conditions that must be fulfilled to validate the previously described scenario.

MATHEMATICAL METHODS

Patients on intensive insulin therapy use Equation 1 to determine the correction bolus to be administrated before each meal:

$$B = \frac{CHO}{ICR} + \frac{G - G_T}{ISF} - IOB, \tag{1}$$

where B[U] is the bolus insulin, CHO[g] are the carbohydrates intake planned for that meal, G[mg/dL] is the preprandial blood glucose, G_T [mg/dL] is the blood glucose target, IOB[U] (Insulin-on-Board) is the insulin remaining active from the previously administrated boluses, and ICR[g/U] and ISF [mg/dL/U] are the insulin-to-carbohydrate ratio and the insulin sensitivity factor, respectively [4, 5]. Consider the CHO and the IOB absolute errors given by $\Delta CHO = |CHO - C\hat{H}O|$ and $\Delta IOB = |IOB - I\hat{O}B|$, respectively, where $C\hat{H}O$ and $I\hat{O}B$ are the carbohydrates and insulin-on-board estimates considered by the patient and $|\cdot|$ is the absolute value. From [3], the absolute error on the carbohydrate estimates so that the patient does not have cases of hypo and hyperglycemia, supposing that $IOB = I\hat{O}B = 0$, must respect the following condition:

$$\Delta CHO \leq \frac{ICR}{ISF} \min\left\{G_T - G_{Hypo}, G_{Hyper} - G_T\right\}, \tag{2}$$

where G_{Hyper} and G_{Hypo} are the hyperglycemia and hypoglycemia limits, respectively.

Next, we will deduce the upper limit for ΔCHO considering $\Delta IOB \neq 0$. Taking into account the estimates $C\hat{H}O$ and $I\hat{O}B$, there is an absolute error on B given by $\Delta B = |B - \hat{B}|$, where $\hat{B} = C\hat{H}O/ICR + (G - G_T)/ISF - I\hat{O}B$. Therefore, we have:

$$\Delta B = \left| \frac{CHO - C\hat{H}O}{ICR} - \left(IOB - I\hat{O}B\right) \right|. \tag{3}$$

The absolute error in the bolus, ΔB, will act as an unplanned correction bolus, and therefore leading to an off-target postprandial blood glucose ($G_{postprandial}$) and an absolute error given by

$$\Delta G_{postprandial} = \left| G_{postprandial} - G_T \right| = \Delta B \cdot ISF. \tag{4}$$

For the patient does not have episodes of hypo and hyperglycemia, then $\Delta G_{postprandial}$ has to verify $\Delta G_{postprandial} \leq \min\{G_T - G_{Hypo}, G_{Hyper} - G_T\}$. Taking this into account and replacing Equation 3 in Equation 4 we obtain:

$$\left| \frac{CHO - C\hat{H}O}{ICR} - \left(IOB - I\hat{O}B\right) \right| \leq \frac{1}{ISF} \min\left\{G_T - G_{Hypo}, G_{Hyper} - G_T\right\}, \tag{5}$$

once $ISF > 0$. Since the following inequality occurs:

$$\left| \frac{CHO - C\hat{H}O}{ICR} - \left(IOB - I\hat{O}B\right) \right| \leq \frac{\Delta CHO}{ICR} + \Delta IOB,$$

once $ICR > 0$, then it is enough consider that

$$\Delta CHO \leq \frac{ICR}{ISF} \min\left\{G_T - G_{Hypo}, G_{Hyper} - G_T\right\} - ICR \cdot \Delta IOB \tag{6}$$

to respect Equation 5. Note that Equation 6 translates to Equation 2 when the patient correctly estimates the IOB, i.e., $\Delta IOB = 0$.

Finally, considering $I\hat{O}B = 0$ in Equation 6, we obtain that

$$\Delta CHO \leq \frac{ICR}{ISF} \min\left\{G_T - G_{Hypo}, G_{Hyper} - G_T\right\} - ICR \cdot IOB, \tag{7}$$

once $IOB \geq 0$. Thus, to validate Equation 2 , it is necessary to determine the conditions that make Equations 2 and 7 approximately equivalents, i.e., we need to find the conditions that make the IOB negligible. To do so, it is necessary to find an estimate of the real value of IOB in the form

$$IOB = \sum_{i=1}^{n} B_i \cdot d\left(t_{B_i}\right), \tag{8}$$

where n is the number of boluses, B_i, previously administrated at time $t_{B_i} \in (t_{meal} - DIA, t_{meal})$, DIA is the duration of insulin action [6], and $d(t_{B_i})$ is the rate of remaining insulin in the body from each previous insulin bolus B_i at the actual meal time, t_{meal}, given by the decay curves presented in [7]:

$$d\left(t\right) = 1 - \frac{a_3 \cdot k_{1,DIA}}{k_{2,DIA}\left(a_1 - a_2\right)} \left(\frac{e^{-\frac{a_1\left(t_{meal} - t\right)}{k_{1,DIA}}} - 1}{a_1} - \frac{e^{-\frac{a_2\left(t_{meal} - t\right)}{k_{1,DIA}}} - 1}{a_2} \right), \tag{9}$$

where $k_{1,DIA}$, $k_{2,DIA}$, a_1, a_2 and a_3 are real constants that are properly chosen on the basis of the time of decay that depends of the insulin properties [8, 9]. Note that, by Equations 1 and 7, for we have $B > 0$ and $\Delta CHO \geq 0$, the IOB have to respect the constraints $IOB < CHO/ICR + (G - G_T)/ISF$ and $IOB \leq \min\{G_T - G_{Hypo}, G_{Hyper} - G_T\}/ISF$. Therefore, the conditions that is necessary to consider to use Equation 2 to prove that the patient is controlled are:

Condition 1: Choose the interval between meals wide enough so that the remaining insulin in the body is residual.

Condition 2: Considering a healthy diet plan, choose to ingest few carbohydrates so that the insulin bolus is as small as possible.

Condition 3: Consider CHO errors, $CHO - \hat{CHO}$, made by the patient following the Normal (Gaussian) distribution with zero mean and the standard deviation $\sigma = ICR/(m \cdot ISF) \cdot \min\{G_T - G_{Hypo}, G_{Hyper} - G_T\}$ for a positive real number m sufficiently large so that

$$P\left(\Delta CHO > \frac{ICR}{ISF} \min\left\{G_T - G_{Hypo}, G_{Hyper} - G_T\right\}\right) = 2\left(1 - \Phi\left(m\right)\right) \tag{10}$$

is sufficiently small, where P is the probability and Φ is the cumulative distribution function of the standard normal distribution. Thus, we will have the normal behavior of a patient in the measurement of carbohydrates with error that respects Equation 2 and how much more the patient is smarter in carbohydrates counting, more small is

$$P\left(\Delta CHO > \frac{ICR}{ISF} \min\left\{G_T - G_{Hypo}, G_{Hyper} - G_T\right\} - ICR \cdot IOB\right), \tag{11}$$

mainly if IOB is small.

Condition 4: Know the maximum relative frequency that the patient is not controlled, $f_{r_{max}}$, given approximately by Equation 11 with $IOB = IOB_{\max}$, i.e.,

$$f_{r_{\max}} \approx 2\left(1 - \Phi\left(m - \frac{m \cdot ISF \cdot IOB_{\max}}{\min\left\{G_T - G_{Hypo}, G_{Hyper} - G_T\right\}}\right)\right), \tag{12}$$

to compare with the percentage of the non-controlled cases of the patient in the in-silico preclinical trials. The value $IOB_{\max}$ is the maximum of the insulin-on-board for the duration of the simulation.

DISCUSSION

In this section, we analyze and discuss the conditions described in the previous section so that Equation 2 can be verified through the FDA-approved University of Virginia(UVA)/Padova Type 1 Diabetes Simulator. For that, we consider the example of a patient with $ICR = 19.16$ g/U and $ISF = 43.85$ mg/dL/U. Also consider the blood glucose target $G_T = 100$ mg/dL, and the hypoglycemia and hyperglycemia limits $G_{Hypo} = 70$ mg/dL and $G_{Hyper} = 180$ mg/dL, respectively. Firstly, before each meal, we determine an estimate for the real IOB by using Equation 8. For that purpose, it is necessary to find the constants of Equation 9 according to the proper duration of insulin action. Since there are different rapid-acting insulins, for this example, we will consider $DIA = 6$ h, as suggested in [9, 10]. Thus, for that DIA, the approximate values for the real constants of the decay curve are described in Table I. To respect Condition 1, considering this decay curve, the optimal interval between meals have to be at least 6 hours. In this case, we obtain $IOB \approx 0$ U, and Equation 7 translates into Equation 2. However, an interval of 6 hours between meals is too large. Therefore, it is necessary to consider an acceptable dietary plan, as proposed in Table II. Note that for this plan, the IOB at mealtime is very small. It is about 5.4% of the previous bolus (i.e., $d(t_{meal} - 4) \approx 0.05445$), as described in Table II. In that case, the difference between the ΔCHOs obtained by using Equations 2 and 7 is less than 24%. That means that the cost of considering $IOB = 0$ is a reduction in the patient's ΔCHO, given by Equation 2, less than 24%. We can improve that by reducing the ingestion of carbohydrates at each meal, which will imply a decrease in the amount of insulin bolus ingested and as such in the amount of insulin-on-board (Condition 2). Also using Condition 3, we can overcome this difference. Considering a well-trained patient on carbohydrate counting (e.g., $P(\Delta CHO \leq ICR/ISF \cdot \min\{G_T - G_{Hypo}, G_{Hyper} - G_T\}) = 0.95$, i.e., taking $m = 1.96$ in Equation 10), thus using Condition 3, the probability obtained using Equation 11 is small and Equation 2 can be used instead Equation 7. Therefore, the use of Condition 3 highlights the need for continuous education on carbohydrate counting using patient-specific learning outcomes. Finally, we can validate the results obtained in the in-silico preclinical trials through Condition 4. By Equation 12, the maximum relative frequency that the patient is not controlled is $f_{r_{\max}} \approx 2(1 - \Phi(1.5)) \approx 0.134$. Therefore, to demonstrate the veracity of Equation 2 using the T1DMS, the patient's blood glucose must be on-target on approximately 86.6% of the cases, at least.

TABLE 1. Real constants of the decay curve considering $DIA = 6$ h .

$k_{1,DIA}$	$k_{2,DIA}$	a_1	a_2	a_3
0.32566	1.91493	0.42974	0.31932	0.81366

TABLE 2. Schedule of daily meals for the patient with the information of the insulin bolus and the IOB estimate in each meal.

	First meal	Second meal	Third meal	Fourth meal	Last meal
Time of day [Hours]	08:00 am	12:00 pm	04:00 pm	08:00 pm	12:00 am
Insulin Boluses [U]	2	3	2	3	1
IOB **estimates [U]**[a]	0.00	0.11	0.16	0.11	0.16

[a] All the estimate values obtain for IOB respect the condition $IOB \leq \min\{G_T - G_{Hypo}, G_{Hyper} - G_T\}/ISF = 30/43.85$.

CONCLUSION

Accurate carbohydrate counting is crucial for patients on intensive insulin therapy. In this regard, the authors have proposed a patient-specific method to find the maximum admissible error on meal carbohydrate content estimates. This paper presented and discussed the necessary conditions to validate the proposed method on an in-silico preclinical trial, using the FDA-approved University of Virginia(UVA)/Padova Type 1 Diabetes Simulator and considering the insulin-on-board negligible, like what happens with most real patients. Our findings corroborate the need for adequate dietary plans, as well as the need for continuous carbohydrate counting education, as stated in Conditions 1, 2, and 3. Therefore, the scenario to be used in the in-silico preclinical trials must consider that patients are well trained on carbohydrate counting and have adequate meal plans. Besides, using Condition 4, it is possible to establish a score for the blood glucose time-on-target that must be verified to validate the patient-specific carbohydrate counting accuracy. Future investigations will use these criteria to assess the proposed method.

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