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Risk of hypoglycemia in type 1 diabetes management: An in-silico sensitivity analysis to assess and rank the quantitative impact of different behavioral factors

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ABSTRACT

Background and Objective: In type 1 diabetes (T1D), a quantitative evaluation of the impact on hypoglycemia of suboptimal therapeutic decision (e.g. incorrect estimation of the ingested carbohydrates, inaccurate insulin timing, etc) is unavailable. Clinical trials to measure sensitivity to patient actions would be expensive, exposed to confounding factors and risky for the participants. In this work, a T1D patient decision simulator (T1D-PDS), realistically reproducing blood glucose dynamics in a large virtual population, is used to perform extensive in-silico trials and the so-derived data employed to implement a sensitivity analysis that ranks different behavioral factors based on their impact on a clinically meaningful parameter, the time below range (TBR). Methods: Eleven behavioral factors impacting on hypoglycemia are considered. The T1D-PDS was used to perform multiple 2-week simulations involving 100 adults, by testing about 3500 different perturbations for nominal behavior. A local linear approximation of the function linking the TBR and the factors were computed to derive sensitivity indices (SIs), quantifying the impact of each factor on TBR variations. Results: The obtained ranking quantifies importance of factors w.r.t. the others. Factors apparently related to hypoglycemia were correctly placed on the top of the ranking, including systematic (SI = 2.05%) and random (SI = 1.35%) carb-counting error, hypotreatment dose (SI = -1.21%), insulin bolus time w.r.t. mealtime (SI = 1.09%). Conclusions: The obtained SIs allowed to rank behavioral factors based on their impact on TBR. The behavioral factors identified as most influential can be prioritized in patient training.

1. Introduction

Due to endogenous insulin deficiency, individuals with type 1 diabetes (T1D) have to manually administer themselves insulin in order to mitigate the undesirable excursions of their blood glucose (BG) concentration outside the normal range, both in hyperglycemia (BG > 180 mg/dl) and in hypoglycemia (BG < 70 mg/dl) [1]. In particular, hypoglycemia is the most common side effect of insulin treatment, and represents the major barrier to achieving optimal control. In severe cases it can cause neurological or cardiovascular complications, or even death [2]. To keep BG concentration within the target range of [70–180] mg/dl, people with T1D need a lifelong therapy which requires several daily mental and manual operations.

For instance, in order to control the post-meal BG concentration rise caused by carbohydrates (CHO) intakes, T1D individuals need to take an insulin dose before meals, which should be computed by patients themselves based on the estimated CHO content (the so-called carb-count) of the meal, as well as measurement of pre-meal glucose concentration [3]. A second important example of operation frequently required to T1D individuals is BG monitoring, a task dealt with by employing portable or wearable glucose sensors, which, in presence of abnormal levels, can trigger the prompt adoption of suitable corrective countermeasures. In particular, when a hypoglycemic event occurs, subjects are recommended to consume 15 grams of fast-acting CHO to rise BG, the so-called hypotreatment, and to recheck their glycemic level after a certain period (usually 15 min) [4]. In case of hyperglycemia, subjects are recommended to timely inject an insulin correction bolus to lower their BG, whose dose is calculated based on the current glycemia, some patient specific parameters (i.e. the correction factor and the insulin on board) and, possibly, the glucose trend [5].

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Although individuals receive a specific training about how to correctly perform operations like the ones described above [3], it is difficult to avoid errors and/or to perfectly/timely adhere to therapeutic recommendations day to day. Errors or inaccuracies in performing these operations can cause a deterioration of glycemic control and an increase risk of hypoglycemia. For instance, miscalculating the meal CHO amount results in the so-called carb-counting errors, which can have a negative effect on post-meal glucose excursion [6–9]. Similarly, in the daily life it may happen that patients can delay or skip the reaction to a hypoglycemic alert [10], with a possible negative impact on their glycemic control.

The above described examples make it clear that there are a number of factors, related to what in this paper is called, for sake of reasoning, subject's behavior, that may have an impact on glycemic control. A quantitative measure of how much these "behavioral factors" impact on glycemic control and, specifically, on hypoglycemia would be very useful for healthcare providers, educators and also T1D subjects. Indeed, identify the most impactful factors would allow emphasizing the actions/decisions which may deserve special attention in training programs and in the daily management of diabetes. To the best of our knowledge, a quantitative analysis of how much the risk of hypoglycemia is sensitive to deviations from ideal/recommended treatment action and decisions has never been performed in the literature so far. In fact, designing a study on real patients to assess the impact of behavioral factors on hypoglycemia is very challenging because of the difficulty to isolate the contribution of a single behavioral factor from other (behavioral and confounding) factors, and also because of the potential health risks that treatment errors can drive to.

These limitations can be overcome by in-silico clinical trials [11,12], i.e. virtual clinical trials performed with computer simulations, which easily allow to manipulate the behavioral factors of interest, e.g. varying a single factor while fixing all the others, in order to isolate the impact of a single behavioral factor from the others. Moreover, in-silico clinical trials allow to repeat the same experiment multiple times on the same virtual subjects, while maintaining unaltered the surrounding conditions, even simulating high risk scenarios, but, notably, without any risk for real patients [13,14].

In this work, the well-established potential of in-silico clinical trials is exploited to quantify how much hypoglycemia is influenced by the patient behavior in T1D. Specifically, our goal is to design and implement a sensitivity analysis methodology to assess and rank, in-silico, the quantitative impact of different behavioral factors on glycemic control. To do that, we will setup extensive in-silico clinical trials by using a simulation model of T1D patient behavior [15] and physiology [16,17] and we will perform a local sensitivity analysis to assess how variations of the behavioral models' parameters impact on a widely used metric of the effectiveness of glycemic control: the time below range (TBR) [18]. Specifically, the local sensitivity analysis (that involves the derivation of linear approximation of TBR via multiple linear regression model and subsequent coefficients scaling), will produce a ranked list of behavioral factors, ordered according to their impact on hypoglycemia.

The paper is organized as follows. Section 2 reports a general description of the methodology we adopted to perform a multi-factor sensitivity analysis. Section 3 describes its application to the specific problem of measuring the impact of behavioral factors on TBR. The obtained results and their interpretation are reported in Section 4. Some conclusions end the work in Section 5.

2. The local multi-factor sensitivity analysis framework

Sensitivity analysis methods investigate how much the perturbation of an input of a function affects the output of that function. In this work, we are interested in quantifying how much the average time spent below the target range (TBR), i.e., the percent of time with BG < 70 mg/dL, is affected by small perturbations of behavioral factors. This problem is cast into a sensitivity analysis problem by introducing a function (unknown) that describes the dependency of the average TBR (scalar output) on the multiple behavioral factors under consideration (inputs). While an analytical expression for this function is missing, the function can be interrogated via simulations, that return the average TBR achieved with a given value of the behavioral factors (how these simulations have been performed to address our problem is later explained in Section 3).

Let us introduce the function $f : \mathbb{R}^k \rightarrow \mathbb{R}$, which relates the (scalar) output under study, y, to a set of factors which can influence it, $x_i, i = 1, 2, \dots, k$:

$$y = f(x_1, x_2, ..., x_k) \tag{1}$$

and let us denote with $\boldsymbol{x_0} = [x_{10} \dots, x_{k0}]^T$ the nominal values of these factors. The nominal output $y_0 = f(\boldsymbol{x_0})$, is obtained in response to the nominal inputs.

Assuming that f is sufficiently smooth, when the input factors are subject to a small perturbation $\boldsymbol{x} = \boldsymbol{x_0} + \Delta\boldsymbol{x}$, the corresponding output perturbation $y = f(\boldsymbol{x}) = y_0 + \Delta y$ can be computed using the first-order Taylor approximation of f:

$$\Delta y = f(\boldsymbol{x}) - y_0 \cong \nabla f(\boldsymbol{x})^T|_{\boldsymbol{x}=\boldsymbol{x_0}} \Delta\boldsymbol{x} \tag{2}$$

where $\nabla f(\boldsymbol{x})^T = [\frac{\partial f}{\partial x_1}, ..., \frac{\partial f}{\partial x_n}]$ is the gradient of f.

Since the explicit form of the function f is unknown in our problem, the gradient can not be computed analytically. Instead we search for an approximated linear relationship between the output perturbation and the inputs perturbation by solving a multiple linear regression model on data obtained by simulating multiple small perturbations of the factors.

In other words, a local linear approximation of the function f is derived by fitting a multiple linear regression model

$$\Delta y = \sum_{i=1}^{k} m_i \Delta x_i \tag{3}$$

to the data obtained by several interrogations of the function f for different perturbations of the input factors.

The regression coefficient m_i quantifies the impact of the i^{th} input on the output. However, these m_i coefficients are not comparable to each other, because the magnitude of each of them is also influenced by the range of variation of the associated factor and by its measurement unit.

To overcome this limitation, the normalized perturbation is considered instead of the absolute one. Specifically, for each considered input factor let us introduce the quantity ΔI_i:

$$\Delta I_i = x_{i,max} - x_{i,min} \qquad i = 1, ..., k \tag{4}$$

representing the plausible range of variation for that input factor x_i, $i = 1, ..., k$. Then, eq. (3) can be rewritten as:

$$\Delta y = \sum_{i=1}^{k} m_i \Delta I_i \frac{\Delta x_i}{\Delta I_i} = \sum_{i=1}^{k} \alpha_i \frac{\Delta x_i}{\Delta I_i} \tag{5}$$

providing an equivalent multiple linear regression model that uses as input the normalized input perturbation.

The new regression coefficients, α_i,

$$\alpha_i = m_i \Delta I_i \qquad i = 1, ..., k \tag{6}$$

are comparable among each other, as they share the same measurement unit, that is the measurement of the output y (in the case of TBR %), and refer to variables with comparable ranges of variation.

As such, these coefficients can be ranked based on their absolute value to determine which factor impacts more on the output. Indeed, the absolute value of these coefficients represents the magnitude of the related factors' impact on the output. In particular, a factor having no impact on the output will have a coefficient equal to zero. In the following, these coefficients will be referred to as sensitivity indices.

The sign of the sensitivity indices carries another fundamental information: when the sensitivity index is positive, an increase in the factor corresponds to an increase in the output; conversely, when the sensitivity index is negative, an increase in the factor corresponds to a decrease in the output.

2.1. Analogy with gradient descent optimization

To gain an alternative perspective on the proposed approach, let us focus on the problem of educating to hypoglycemia management a population of T1D subjects. This could be seen as an optimization problem, where clinicians attempt to minimize the occurrence of hypoglycemia in the population (measured by average TBR) by modifying a number of behavioral factors through education. The average TBR is therefore the cost function and the behavioral factors are the optimization variables.

As well known in optimization theory, iterative optimization algorithms often update the optimization variables in the direction of minus gradient of the cost function, as this is the direction that produces the locally steepest decrease in cost. Because of this, algorithms based on this idea are commonly known as steepest descent algorithms.

The local linear approximation in (3), derived above by least-square fitting, allows to estimate the gradient of the cost function and thus to inform the clinician on the steepest direction in the behavioral parameters space to reduce the average TBR in the population.

3. Sensitivity analysis to assess the impact of behavioral factors on hypoglycemia

The methodology described in Section 2 is applied to study the impact of behavioral factors on TBR. The data for the sensitivity analysis are generated by extensive in-silico clinical trials whose framework is described in Section 3.1. Section 3.2 reports a detailed explanation on how the 11 factors related to the behavior of T1D subjects in the therapy management considered in our analysis are simulated and perturbed. Then, the final simulated dataset employed in the sensitivity analysis is described in Section 3.3. Finally, details about the implementation of the sensitivity analysis on the simulated data are provided in Section 3.4.

3.1. Simulation strategy design

The data for the sensitivity analysis are generated by using the T1D patient decision simulator (T1D-PDS), a modular simulation tool that allows performing in-silico trials in T1D presented in Vettoretti et al. [15]. The T1D-PDS includes a core module, that models the glucose, insulin and glucagon pathophysiological dynamics and other modules describing BG monitoring devices (e.g. CGM) and insulin administration systems. A further module describes the patient's behavior in making treatment decisions, mimicking the behavior of a patient in the daily therapy management.

With respect to the version presented in [15], in this work multiple modules were updated based on published improvements that become available. Specifically, we adopted the most recent version available of the physiological core i.e. UVA/Padova simulator version s2017, [16]. With respect to the FDA accepted version (s2014), [17], used in [15], this version (i) includes the so-called down phenomena (ii) includes the intraday changes in insulin sensitivity (iii) instead of adopting constant CR and basal, considers piecewise constant patterns for the therapy parameters in each patient. The parameters match the expected insulin sensitivity variation. For what it concerns the CGM sensor, [15] employed a model described the Dexcom G4 sensor, while in this work, we consider a model of Dexcom G6, a more recent sensor, [19]. Finally, since the publication of [15], some further behavioral modules have been validated and published. In particular we introduced one module modelling the main meals amount and one modelling snack amount and timing, presented in [20].

The T1D-PDS is used to simulate the glycemic profile of 100 virtual subjects for 14 days each, mimicking an open-loop therapy based on non-adjunctive CGM use (i.e., therapy decisions made without confirmatory BG monitoring measurements [21]). As proposed in [20], for each subject, 3 main meals (i.e. breakfast, lunch and dinner) and a variable number of additional meal intakes (namely snacks) are considered for each day of simulation. Specifically, the amount of CHO eaten at breakfast, lunch and dinner are generated by using probability density function parametric models recently derived from clinical data by Camerlingo et al. [20]. In each day, lunch time is randomly sampled from a uniform distribution in 11.30 AM and 2.00 PM. Then, breakfast and dinner times are set accordingly, assuming that the intervals between breakfast and lunch and between lunch and dinner were the same, equal to Δmeal (one of the behavioral factors that will be perturbed). The snacks time and amount are instead simulated by employing the recently developed stochastic model of snacks consumption [20], which triggers one or more snacks during the day, based on glucose, meal, and insulin data collected over time, as well as participants' demographics characteristics. Overall, a number of 3 main meals plus 2.76 ± 2.03 (mean $\pm$ standard deviation) snacks are consumed daily by each subject. The daily amount (mean $\pm$ standard deviation) of breakfast, lunch and dinner over the population are 40.73 ± 4.90 g, 55.46 ± 7.56 g and 60.84 ± 10.47 g, respectively. Instead, a snack amount of 47.01 ± 15.47 g is consumed per day.

The carb-counting error, i.e., $\widetilde{CHO}$, is defined as the signed percentage difference between the estimated CHO amount, i.e., $\widehat{CHO}$, and the true CHO amount, i.e., CHO, of the meals, according to

$$\widehat{CHO} = CHO + \widetilde{CHO} \cdot CHO \tag{7}$$

where $\widetilde{CHO}$ is generated by using a Gaussian distribution with mean μ and standard deviation σ:

$$\widetilde{CHO} \sim N(\mu, \sigma) \tag{8}$$

The use of a relative error rather than an absolute error is supported by the finding in [7]. As discussed in the next section, mean μ and standard deviation σ will be used to describe the behavioral factors systematic and random carb-counting error respectively. Therefore they will assume values taken from a predefined range (detail in Section 3.2).

Therapy parameters (basal insulin infusion rate, correction factor, and carbohydrate-to-insulin ratio) were set according to the guidelines of Davidson et al. [22]). Post-prandial correction boluses and hypotreatments were generated to mitigate hyperglycemic and hypoglycemic events, respectively.

3.2. Behavioral factors investigated

The T1D-PDS is employed to reproduce in-silico the behavioral factors introduced in Section 1. In particular, a total of 11 behavioral factors are considered for the sensitivity analysis and described below.

1. Delay in responding to CGM hypo-alerts: the time, expressed in minutes, that elapses from the activation of the hypo-alert to the action of the T1D subject (i.e., check of his/her glucose level and, if needed, hypotreatment assumption).
2. Delay in responding to CGM hyper-alerts: the time, expressed in minutes, that elapses from the activation of the hyper-alert to the action of the T1D subject (i.e., check of his/her glucose level and, if needed, correction bolus injection).
3. Low CGM alert threshold: the glucose level (in mg/dl) which determines the activation of an alert for an incoming hypoglycemic episode.
4. High CGM alert threshold: the glucose level (in mg/dl) which determines the activation of an alert for an incoming hyperglycemic episode.

Table 1
Nominal value (2^{nd} column), range of variation (3^{rd} column) and maximum variation (last column) considered for each behavioral factor under study, reported in the 1^{st} column.

Behavioral factors x	Nominal value x_0	Range of variation $[x_{min}, ..., x_{max}]$	Maximum variation ΔI
Delay in responding to CGM hypo-alerts [min]	0	[0, 5, 10, ..., 25, 30]	30
Delay in responding to CGM hyper-alerts [min]	10	[0, 5, 10, ..., 25, 30]	30
Low CGM alert threshold [mg/dl]	80	[50, 55, 60, ..., 95, 100]	50
High CGM alert threshold [mg/dl]	200	[180, 200, ..., 320, 340]	160
Random carb-counting error [%]	20	[10, 15, 20, ..., 40, 45]	35
Systematic carb-counting error [%]	-5	[-20, -15, -10, ..., 5, 10]	30
Time between main meals [hours]	6	[5, 5.5, 6, 6.5, 7]	2
Insulin bolus time w.r.t. mealtime [min]	0	[-20, -15, -10, ..., 15, 20]	40
Hypotreatment dose [grams]	15	[10, 15, 20, ..., 30, 35]	25
Recheck time after hypotreatment [min]	20	[10, 15, 20, 25, 30]	20
Fake factor [hours]	/	[1, 2, 3, ..., 11, 12]	11

The nominal value for the fake factor is not defined.

5. Random carb-counting error: standard deviation of the carb-counting error distribution, i.e. parameter σ of eq. (8).
6. Systematic carb-counting error: mean of the carb-counting error distribution, i.e. parameter μ of eq. (8); it is a positive number if the subject overestimates the meal CHO, a negative number if he/she underestimates them.
7. Time between main meals: Δmeal parameter, expressed in hours, used to set the time that occurs between two consecutive main meals, i.e., breakfast-lunch and lunch-dinner.
8. Insulin bolus time compared to mealtime: the time, expressed in minutes, between the meal and the insulin bolus injection; it is a negative number if the bolus is taken before the meal, a positive number if it is taken after the meal.
9. Hypotreatment dose: the quantity, measured in grams, of fast-absorption CHO assumed by a subject to treat hypoglycemic episodes.
10. Recheck time after hypotreatment: the time, expressed in minutes, the subject waits to recheck his/her glucose level after an hypotreatment assumption.
11. Fake factor: an integer number randomly sampled among integer values ranging from 1 to 12 (for example, this factor could represent the number of daily calls the subject makes to family/friends).

Note that we include a "fake" factor in the analysis in order to check if our methodology correctly estimates a negligible impact for a factor that, by definition, does not influence the glycemic control.

For each behavioral factor, a nominal value and a range of variation were defined, based on empirical and clinical considerations. The former, which represents the working point around which the linearization is performed (i.e. the point x_0 of eq. (2)), should match the most common value assumed by the behavioral factor in the T1D population. The range of variation represents a plausible range of values that the behavioral factor may assume in the T1D population. Then, for each behavioral factor we defined a grid of possible values that explores the factor's range of variation and includes its nominal value. The granularity of the grid was defined in order to obtain a suitable trade-off between the number of values and the computational time. The nominal value and the grid of variation we defined for each behavioral factor are summarized in Table 1.

When data were available, they were employed to compute the average behavior of the population with the corresponding range of variation. Specifically, the values of systematic and random carb-counting errors were derived from a dataset of 50 T1D subjects who estimated the meal CHO amount of different meals (about 9 meals per subject) [8]. Data showed that, in the observed T1D population, the systematic carb-counting error is equal to -5.6% [-21.1%, 8.9%], while the random carb-counting error is equal to 21.9% [11.8%, 45.4%] (on median [10^{th} percentile, 90^{th} percentile]). We therefore used a nominal value [range of variation] of -5% [-20%, +10%] for the systematic error and 20% [10%, 45%] for the random error. As far as the CGM alert thresholds are concerned, their nominal value was set to commonly adopted values of 80 mg/dl and 200 mg/dl for low and high alert thresholds, respectively, [23]. The range of variation of the low alert was defined assuming an interval of +/-30 mg/dl around the nominal value, while the range of variation of the high alert was set based on the distribution of high alert setting used in the model of Vettoretti et al. [15].

The nominal value of the behavioral factor "Hypotreatment dose" was set to 15 g, as per suggestion of the guidelines [3]. More and less conservative settings are then explored in the sensitivity analysis.

For the nominal value and range of the remaining factors, educated guess were used since, to the best of knowledge, no model or clinical dataset where these variables are reliably monitored is available. The nominal value and the range of variation were set according to the recommended therapy guidelines [3], slightly deteriorated in order to picture a slight sub-optimal average behavior, and what we expect to be a reasonable variability around these values. The delay in responding to CGM alerts was assumed to vary in the interval 0–30 min, with a nominal value of 0 for the hypo-alerts and 10 min for the hyper-alerts. Note that we hypothesized a higher nominal value for the delay in responding to high alerts, compared to the delay in responding to low alert, because the response to high alert usually consists in the computation and the injection of an insulin bolus, actions on average requiring longer times than the consumption of hypotreatments in response to low alerts. Moreover, hypoglycemia is generally a more dangerous condition than hyperglycemia, so the response time to hypoglycemia is usually faster.

Finally, note that the nominal value for the fake factor is not necessary for the analysis, since the fake factor randomly varies independently from the other factors (it is never fixed to a nominal value while the other factors change, as we do for the other meaningful factors included in the sensitivity analysis).

3.3. Simulated dataset

A baseline simulation was performed by fixing each behavioral factor to its nominal value. Then, multiple simulations were performed by varying the behavioral factors within their grids of variation.

For each perturbation of the subjects' behavioral factors, the simulated BG profiles of all the 100 virtual subjects over 14 days were produces. It should be stressed that each perturbation of a behavioral factor usually affects the simulation of each subject in multiple portions. For each subject, TBR was computed as the percentage of time spent with BG below 70 mg/dl over the entire simulation length. The average TBR is then derived. In particular, for the nominal simulation we obtained a %TBR equal to 2.0 ± 1.69% (mean $\pm$ standard deviation) over the 100 subjects.

Exploring all possible combinations of behavioral factors' values would lead to a great number of simulations (more than one million), hardly performable in practice because of the requested computation time. To explore the factors' space with enough density, we performed three different simulation sets, characterized by different levels of factors' interaction:

Table 2
Impact of behavioral factors on TBR (time spent under 70 mg/dl). For each factor, the sensitivity index (second column) and its 95% confidence interval (third column) are reported. Sensitivity indices in bold are the ones whose confidence interval does not contain zero. The factors are ordered from the most impactful to the least impactful, based on the absolute value of the sensitivity indices.

Behavioral factors	Sensitivity index α	95% confidence interval	Position in the ranking
Systematic carb-counting error [%]	**2.05%**	[2.02%, 2.07%]	1
Random carb-counting error [%]	**1.35%**	[1.32%, 1.37%]	2
Hypotreatment dose [g]	**-1.21%**	[-1.24%, -1.18%]	3
Insulin bolus time w.r.t. mealtime [min]	**1.09%**	[1.06%, 1.12%]	4
Low CGM alert threshold [mg/dl]	**-0.90%**	[-0.93%, -0.87%]	5
Delay in responding to CGM hypo-alerts [min]	**0.89%**	[0.87%, 0.91%]	6
High CGM alert threshold [mg/dl]	**0.35%**	[0.32%, 0.37%]	7
Recheck time after hypotreatment [min]	**0.25%**	[0.22%, 0.28%]	8
Time between main meals [h]	**0.16%**	[0.12%, 0.19%]	9
Delay in responding to CGM hyper-alerts [min]	0.02%	[-0.01%, 0.05%]	10
Fake factor [h]	0.003%	[-0.02%, 0.03%]	11

- In the One-at-a-time (OAT) simulation set we varied a single factor at a time, while keeping the other factors fixed to their nominal values. All the factors were considered, except for the fake factor, resulting in 10 factors explored. For each factor, all the possible factor values presented in Table 1 were considered. This is a standard approach in literature [24] employed in different applications to investigate the local sensitivity to different model parameters of a given outcome [25,26].
- In the Two-at-a-time (TAT) simulation set we varied two factors simultaneously, while the other factors were kept at their nominal value. All the possible pairs of factors (except for the fake factor) were considered, resulting in $10 \times 9/2 = 45$ pairs of factors explored. Each of these 45 two-dimensional spaces was investigating considering the grid of all combinations of possible values that each of the two factors can take, i.e. considering all the pairs of values reported in Table 1. Instead of exploring the grid systematically, a point in the two-dimensional grid was randomly extracted every time, with uniform probability. If a previously considered combination was obtained through the sampling, the combination was discarded and a new combination extracted. The same resampling procedure was used if a combination considered in OAT was extracted.
- In the Multiple-at-a-time (MAT) simulation set we varied all the factors simultaneously by randomly assigning to each of the factors one of its possible values listed in Table 1. All values were equally probable. If the obtained combination of perturbations was previously considered or was already considered in the OAT and TAT dataset, the combination is discarded and a new combination is extracted.

As anticipate, in the OAT set all the values reported in Table 1 for each behavioral factor were explored, resulting 64 1-factor perturbations tested on the population of 100 virtual patients (6400 simulations)). In the TAT set, we stopped after exploring the impact of 1500 perturbations of two factors on the population of 100 virtual patients. Finally, MAT was stopped after exploring 2000 perturbations on the population of virtual subjects.

The final dataset employed for the sensitivity analysis was built by merging all the three simulations sets performed as described above. Overall, it contains a total of about 3600 unique observations of the factors perturbation the associated 3600 average TBR observed in the population.

3.4. Local linear approximation fitting and validation for sensitivity analysis

The simulated data are used to fit the local linear approximation of eq. (5) via multiple linear regression. The model inputs, $\frac{\Delta x_i}{\Delta I_i}$, are the normalized variations of the 11 behavioral factors described in Section 3.2 compared to their nominal values. For each combination of factors' values, the output of the model, Δy, is the variation of the average TBR over the entire virtual population compared to the average TBR obtained with all factors fixed to nominal values.

First, we verify the assumption of local linearity of the input-output function f. To do that, we compute the coefficient of determination R^2 of the multiple linear regression model, which measures the proportion of variability in the output that can be explained using the inputs [27]. An R^2 close to 1 means that the regression model is able to represent a large part of the output variance, and therefore the input-output relationship is approximately linear [27]. After verifying the linearity assumption, we calculate the comparable sensitivity index, α_i, for each factor included in the analysis and perform a ranking of the factor importance based on the absolute value of the sensitivity indices.

Moreover, to further test the linearity assumption, we also fitted on the data a non-linear model containing the interaction among the factors:

$$\Delta y = \sum_{i=1}^{k} m_i \Delta x_i + \sum_{\substack{i,j=1 \\ i \neq j}}^{k} m_{ij} \Delta x_i \Delta x_j \tag{9}$$

where m_{ij} is the regression coefficient related to the interaction term between factors i and j. The R^2 of this non-linear model is then compared with the R^2 achieved by the simpler linear model to assess whether adding interaction terms in the regression model significantly increases the variance of the model output explained by the inputs.

To further assess the quality of the fit of the linear approximation, Root Mean Squared Error (RSME), Mean Absolute Error (MAE) and Mean Absolute Relative Error (MARE) are also reported.

4. Results

4.1. Outcomes of the sensitivity analysis

The linear model provided an $R^2 = 0.94$, confirming that the linearity assumption is suitable to the problem under analysis. Similar considerations hold for the other fit metrics: MARE resulted MARE = 7.1%, thus showing a limited relative error, on average smaller than 10%; both MAE and RMSE showed a limited deviation with respect to the average TBR in the population (2.0%), thus being MAE = 0.16% and RMSE = 0.22%. The sensitivity indices for each behavioral factor are reported in Table 2. The ranking of the behavioral factors based on their impact on TBR is obtained by considering the absolute value of the sensitivity indices, i.e., according to the absolute impact of the factor in both increasing or decreasing TBR. Such ranking is reported in the last column of Table 2 (for sake of readability, rows of Table 2 are ordered according to the position of the factor in the ranking). In addition, a graphical representation of the ranking is reported in Fig. 1.

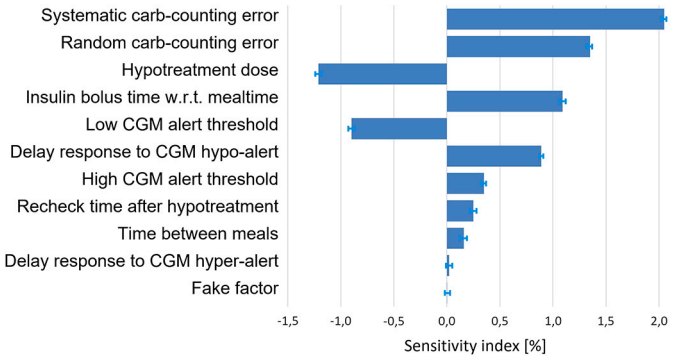

Fig. 1. Graphical representation of the outcome of the sensitivity analysis. The sensitivity indices are on the x-axis, while the behavioral factors are on the y-axis. The factors are ordered from the most impactful to the least impactful, based on the absolute value of the sensitivity indices. Blue bars are proportional to the sensitivity indices value, while lightblue lines indicate their 95% confidence intervals. A positive index means that an increase in the factor corresponds to an increase in the TBR; conversely, when the index is negative, an increase in the factor corresponds to a decrease in TBR.

Notably, the systematic carb-counting error results to be the most impactful factor. In the factors' ranking from the most impactful to the least impactful, the systematic carb-counting error is followed, in order, by the random carb-counting error, the hypotreatment dose, the meal insulin bolus time compared to mealtime, the setting of low alert threshold, the delay in responding to CGM hypo-alerts, the high alert threshold, the recheck time after a hypotreatment, and the time between main meals. Finally, the least impactful behavioral factors are the delay in responding to CGM hyper-alerts and the fake factor, for which the 95% confidence interval of the sensitivity index contains the zero value, meaning that these factors have a non-significant impact on TBR.

Considering the factors that present a significant impact on TBR, a positive sensitivity index results for the systematic and random carb-counting error, the insulin bolus time compared to mealtime, the delay in responding to CGM hypo-alerts, the setting of CGM high alert threshold, the recheck time after a hypotreatment and the time between main meals, thus meaning that an increase in such factors increases the TBR. Conversely, for the hypotreatment dose and the setting of low CGM alert threshold, an increase in the factor results, on average, in a decrease of the TBR, as demonstrated by the negative sign of their sensitivity indices.

Finally, the non-linear model considering interactions among terms showed an $R^2 = 0.98$, thus only marginally improving the model fit to the data.

4.2. Interpretation

Since we obtained a R^2 coefficient of the linear model very close to 1 ($R^2 = 0.94$), we can affirm that the input-output relationship can be approximated as linear in our working conditions. Moreover, we found that the R^2 parameter of the linear model is also very close to the one of the model which includes interaction terms among the behavioral factors ($R^2 = 0.98$). Therefore, since the variance of the output explained by the linear and the interaction terms is just slightly higher than that explained by the only linear terms, we can conclude that the addition of interaction terms in the model does not lead to a strong improvement of the model. Such conclusions corroborate the assumptions on which is based our methodology, thus confirming the validity of the use of linear regression with only linear terms to model the function f linking the considered behavioral factors with TBR.

Then, the ranking of the behavioral factors reported in Table 2 evidenced the (expected) crucial role that accurate carb-counting has on hypoglycemia occurrence. Indeed, the most impactful factor was the systematic carb-counting error ($\alpha = 2.05\%$), followed by the random carb-counting error ($\alpha = 1.35\%$). Nevertheless, a systematic carb-counting error can be easily compensated by adjusting the patient's carbohydrate-to-insulin ratio (a parameter used in the meal bolus computation).

Looking at the ranking of the other factors, two different groups of factors can be identified based on a similar magnitude of their impact on TBR. A first group is composed by factors with relatively high impact: the hypotreatment dose ($\alpha = -1.21\%$), the meal insulin bolus time compared to mealtime ($\alpha = 1.09\%$), the setting of low alert threshold ($\alpha = -0.90\%$), and the delay in responding to CGM hypo-alerts ($\alpha = 0.89\%$). Except for the meal insulin bolus time, all the other factors present in this group are related to the treatment of hypoglycemic episodes, thus, as expected, they directly impact the TBR. The second group is instead composed by factors with relatively low impact, i.e. the setting of high alert threshold ($\alpha = 0.35\%$), the recheck time after a hypotreatment ($\alpha = 0.25\%$), and the time between main meals ($\alpha = 0.16\%$). Finally, the delay in responding to CGM hyper-alerts ($\alpha = 0.02\%$) results to have a non-statistically significant impact on TBR.

The reliability of the methodology used was corroborated by the inclusion in the analysis of a "fake" factor, i.e. a factor not related to diabetes. Our methodology correctly placed the fake factor at the end of the ranking with a non-statistically significant impact on TBR ($\alpha = 0.003\%$), thus confirming the ability of our methodology to discriminate the importance of the factors.

On the other hand, several, rather straightforward, clinical interpretations can be given to the sign of the sensitivity index of certain factors. For example, the positive sign of the sensitivity index related to the systematic carb-counting error indicates that an overestimation of the meal CHO amount leads, on average, to an higher TBR. This happens because the overestimation of the meal CHO amount is associated to an overestimated insulin dose that, in turn, may lead the BG towards the hypoglycemic range. Moreover, also the random carb-counting error has a positive sensitivity index: increasing the magnitude of the random carb-counting errors means an increase in episodes characterized by both overestimation or underestimation of meal CHO amount; meal CHO overestimations, as explained above, may lead to more time in hypoglycemia. A similar scenario happens for the meal insulin bolus time: a positive time means that the insulin bolus is given after the start of the meal, and this behavior can induce a post-prandial hypoglycemia, with consequent increase of time in hypoglycemia. Similarly, for the delay in responding to CGM hypo-alerts, the longer the subject takes to respond to a hypo-alert, the more the consequent time he/she spends in hypoglycemia. Conversely, a negative sensitivity index results for the hypotreatment dose and the setting of low CGM alert threshold. Indeed, the more the grams of fast-acting CHO that the subject assumes when a hypoglycemic episode occurs, the less the time in the hypoglycemic range spent by the subject. Similarly, the higher the BG level set as hypo-alert threshold (i.e., above 70 mg/dl), the more the subject anticipates a possible hypoglycemic episode by taking, e.g., a hypotreatment, thus reducing the time spent in the hypoglycemic range.

In this paper we focused on the impact of the behavioral factors on hypoglycemia. However, a parallel sensitivity analysis on hyperglycemia was performed to have a broader picture of the factors impact on glycemic control. For sake of brevity, the ranking of factors based on their impact on Time Above Range (TAR), the percent of time with BG > 180 mg/dL, is reported in Appendix B. As we can see in Table B.4, most impactful factors for TAR are the same as the ones found for TBR, i.e. the first four positions of the TAR ranking are held by systematic and random carb-counting error, insulin bolus time and hypotreatment dose. The sign of some SIs changed, reflecting the opposite direction of the impact of some factors on TAR compared to TBR. For example, a negative sign of the SI has been found for the systematic carb-counting error, meaning that an overestimation of the meal CHO amount leads, on average, to a lower TAR, as expected. SI related to the hypotreatment dose has instead a positive sign, representing the high time the

subject spends in the hyperglycemic range when he/she assumes more grams of fast-acting CHO. Moreover, interestingly, the positions of factors related to high and low CGM alert threshold in the TAR ranking (positions 5 and 9, respectively) have been reversed compared to the TBR ranking (where they occupied positions 7 and 5, respectively), correctly representing the different impact of these two factors on hyper- and hypoglycemia.

As a further sub-analysis we performed the factors ranking on different groups of patients stratified based on their HbA1c level. Considering groups of patients with different glycemic control slightly affects the ranking compared to the one obtained over the entire population. However, each factor changes only for a few positions in the ranking, at most exchanges with the closest factors with similar sensitivity indices. More details on such analysis are reported in Appendix A.

5. Conclusion

In this work we investigated a clinical question "what behavioral factors impact the most on hypoglycemia?". To quantitatively address the above question, we reformulated this clinical problem as sensitivity analysis problem. Specifically, we considered the average TBR in a population with T1D as a function of a multidimensional parameters vector containing eleven behavioral factors related to the T1D therapy management, including meal habits, meal insulin dose computation, the use of CGM alerts and the treatment of hypoglycemia. A local sensitivity analysis, based on linear approximation of the TBR as a function of the parameters, was then performed to obtain comparable sensitivity indices, which allow to rank factors with different range of variation and measurement unit based on their impact on TBR.

A factor that did not influence the simulation in any way, called "fake" factor, was introduced in the procedure with the sole purpose of debugging and was correctly placed at the end of the ranking, confirming the soundness of the approach. Similarly, it can be noticed that the first positions of the ranking are occupied by factors that are clearly understood to have a strong impact on hypoglycemia: carb-counting errors, hypotreatment dose first and foremost, but also mean bolus timing and habits associated to the CGM low alerts. This expected result corroborates the clinical soundness of the proposed approach.

While some factors were expected to appear in highest position of the ranking, the final order seems much less trivial. The obtained ranking and the quantitative information carried by the SIs can be used to shed light on issues such as "is prompt response to hypo alarm more or less impactful on hypoglycemia than the hypotreatment dose chosen?", whose answer seems far from trivial.

The understanding offered by this analysis could then guide clinician during patient training, prioritizing impactful factors over to moderately impacting ones.

An intrinsic limitation of the proposed sensitivity analysis is that it is seems to be implementable only *in silico*. In fact, it involves testing several different combined perturbations of a subset of the behavioral factors, while all other factors and possible confounders were kept perfectly under control. Moreover, the number of combinations tested is extremely high, making implementation on real patients hard to imagine.

The simplifications, unavoidably introduced in any simulator describing T1D treatment, impact on the final ranking. To limit their impact, we resorted to one of the most widely used T1D simulators, accepted by the American FDA. The simulator was updated and integrated using recently published modules. Known residual limitations include the fact that the proposed meal timing model prescribes three main meals per day (plus a variable number of snacks) and that a fixed breakfast-lunch and lunch-dinner distance was enforced between. While introduced to avoid unlikely meal patterns, these assumptions prevent skipped main meals to occur and the minimum distance between main meals considered in our analysis was 5 h. To overcome these limitations one might resort to a recent model proposed in [28] or replicating meal schedule as they appear in real data. Another limitation is that a certain level of correlation is expected between the source of randomness introduced in our simulations, while they are simulated as independent. Nevertheless, to the best of our knowledge, no validated model capturing these correlations exist and even guessing their magnitude is difficult.

Finally, it is important to remark that in this sensitivity analysis we performed the linear approximation of the function f (see Section 2) around a working point x_0 (i.e. the nominal behavior). The choice of the working point is arbitrary and the proposed methodology can promptly be adapted, repeating the simulations, to allow performing the sensitivity analysis around any other working point of interest. Clearly, being a local sensitivity analysis, the change of the considered working point could change the results. This limit could be overcome with a global sensitivity analysis. Moreover, the whole methodology for the multifactor sensitivity analysis is general, and thus it can be extended to other applications in which a linear model is suitable to represent the input-output relationship.

To conclude, to the best of our knowledge, this is the first study in which the impact of different behavioral factors on hypoglycemia has been compared. The obtained results are important to provide healthcare providers and educators a deeper knowledge regarding the major causes of hypoglycemia, and thus helpful to optimize the daily management of T1D. Future works include the evaluation of the impact of different behavioral factors on other glucose metrics, e.g. other time-in-ranges.

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Declaration of competing interest

None.

Appendix A. Factors ranking for different groups of patients based on the estimated HbA1c level

As a sub-analysis we performed the factor ranking on different groups of patients. The stratification was based on different HbA1c levels. To perform such analysis, we estimated the HbA1c level for each of

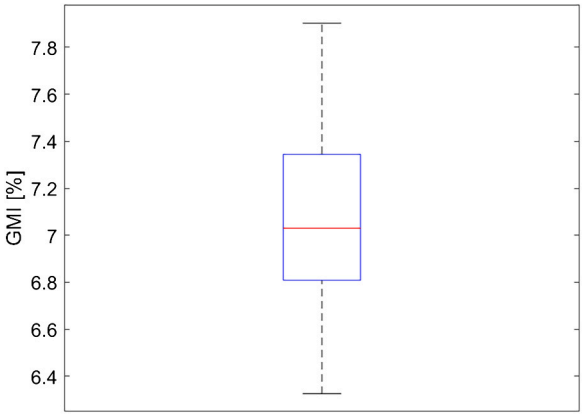

Fig. A.1. Distribution of the Glucose Management Indicator (GMI) [%] of the 100 virtual subjects under nominal conditions of the behavioral factors.

Table A.1
Impact of the behavioral factors on TBR for the group of subjects with $GMI \leq 6.81\%$ (i.e. GMI below the $25th$ percentile of the GMI distribution over the entire virtual population). For each factor, the sensitivity index (2nd column) and its 95% confidence interval (3rd column) are reported. Factors are ordered from the most to the least impactful based on the magnitude of the sensitivity index. For comparison, the ranking obtained over the entire virtual population is reported in the last column.

Behavioral factors	Sensitivity index α	95% confidence interval	Position in the ranking	Entire population ranking
Systematic carb-counting error [%]	**2.62%**	[2.59%, 2.66%]	1	1
Hypotreatment dose [g]	**-1.59%**	[-1.62%, -1.56%]	2	3
Insulin bolus time w.r.t. mealtime [min]	**1.47%**	[1.43%, 1.51%]	3	4
Random carb-counting error [%]	**1.46%**	[1.43%, 1.49%]	4	2
Low CGM alert threshold [mg/dl]	**-1.09%**	[-1.13%, -1.06%]	5	5
Delay in responding to CGM hypo-alerts [min]	**1.03%**	[1.00%, 1.06%]	6	6
High CGM alert threshold [mg/dl]	**0.55%**	[0.52%, 0.58%]	7	7
Recheck time after hypotreatment [min]	**0.34%**	[0.30%, 0.38%]	8	8
Time between main meals [h]	**0.25%**	[0.21%, 0.30%]	9	9
Delay in responding to CGM hyper-alerts [min]	0.02%	[-0.01%, 0.06%]	10	10
Fake factor [h]	-0.002%	[-0.03%, 0.03%]	11	11

Table A.2
Impact of the behavioral factors on TBR for the group of subjects with $6.81\% < GMI \leq 7.34\%$ (i.e. GMI between the 25^{th} and 75^{th} percentiles of the GMI distribution over the entire virtual population). For each factor, the sensitivity index (2nd column) and its 95% confidence interval (3rd column) are reported. Factors are ordered from the most to the least impactful based on the magnitude of the sensitivity index. For comparison, the ranking obtained over the entire virtual population is reported in the last column.

Behavioral factors	Sensitivity index α	95% confidence interval	Position in the ranking	Entire population ranking
Systematic carb-counting error [%]	**2.03%**	[2.00%, 2.06%]	1	1
Random carb-counting error [%]	**1.42%**	[1.39%, 1.45%]	2	2
Insulin bolus time w.r.t. mealtime [min]	**1.19%**	[1.16%, 1.22%]	3	4
Hypotreatment dose [g]	**-1.16%**	[-1.19%, -1.13%]	4	3
Low CGM alert threshold [mg/dl]	**-0.90%**	[-0.93%, -0.87%]	5	5
Delay in responding to CGM hypo-alerts [min]	**0.89%**	[0.87%, 0.91%]	6	6
High CGM alert threshold [mg/dl]	**0.38%**	[0.36%, 0.41%]	7	7
Recheck time after hypotreatment [min]	**0.26%**	[0.23%, 0.30%]	8	8
Time between main meals [h]	**0.19%**	[0.15%, 0.22%]	9	9
Delay in responding to CGM hyper-alerts [min]	0.01%	[-0.02%, 0.04%]	10	10
Fake factor [h]	-0.003%	[-0.02%, 0.03%]	11	11

Table A.3
Impact of the behavioral factors on TBR for the group of subjects with $GMI > 7.34\%$ (i.e. GMI above the 75^{th} percentile of the GMI distribution over the entire virtual population). For each factor, the sensitivity index (2nd column) and its 95% confidence interval (3rd column) are reported. Factors are ordered from the most to the least impactful based on the magnitude of the sensitivity index. For comparison, the ranking obtained over the entire virtual population is reported in the last column.

Behavioral factors	Sensitivity index α	95% confidence interval	Position in the ranking	Entire population ranking
Systematic carb-counting error [%]	**1.51%**	[1.49%, 1.53%]	1	1
Random carb-counting error [%]	**1.08%**	[1.06%, 1.11%]	2	2
Hypotreatment dose [g]	**-0.93%**	[-0.95%, -0.90%]	3	3
Delay in responding to CGM hypo-alerts [min]	**0.76%**	[0.74%, 0.77%]	4	6
Low CGM alert threshold [mg/dl]	**-0.69%**	[-0.72%, -0.67%]	5	5
Insulin bolus time w.r.t. mealtime [min]	**0.50%**	[0.48%, 0.53%]	6	4
Recheck time after hypotreatment [min]	**0.14%**	[0.12%, 0.17%]	7	8
High CGM alert threshold [mg/dl]	**0.08%**	[0.06%, 0.10%]	8	7
Delay in responding to CGM hyper-alerts [min]	0.02%	[-0.008%, 0.04%]	9	10
Fake factor [h]	0.009%	[-0.01%, 0.03%]	10	11
Time between main meals [h]	0.002%	[-0.028%, 0.032%]	11	9

virtual subject from the average glucose of 14 days extracted from the nominal simulation (i.e. when the behavioral factors are all set to their nominal values), thus computing the so-called Glucose Management Indicator (GMI) [29] as follows:

$$GMI\ (\%) = 3.31 + 0.2392 * [mean\ glucose\ in\ mg/dL] \quad \text{(A.1)}$$

Such formula is derived from the regression line computed from a plot of mean glucose concentration points on the x-axis and contemporaneously measured A1C values on the y-axis, combining data from four randomized trials using the Dexcom G4 sensor [29]. The distribution of the obtained GMI values over the virtual population under nominal conditions is shown in Fig. A.1 through a boxplot representation.

By considering the 25^{th} (i.e. 6.81%) and 75^{th} (i.e. 7.34%) percentiles of the obtained GMI distribution, we can divide the subjects in 3 different groups: the first composed by subjects with $GMI \leq 6.81\%$; the second one with $6.81\% < GMI \leq 7.34\%$; and the third one with $GMI > 7.34\%$.

The ranking was then repeated, with the same strategy reported in Section 3 of the manuscript, for the 3 groups of subjects, separately. The obtained results are reported in Table A.1, Table A.2 and Table A.3, respectively.

Compared to the factors ranking obtained over the entire population, only small changes can be detected when considering subjects belonging to group 1 ($GMI \leq 6.81\%$) and group 2 ($6.81\% < GMI \leq 7.34\%$) separately. More variations in the ranking position can instead be observed in the ranking of the group 3. In any case, it is important to underline that each factor changes only for a few positions in the ranking, at most exchanges with the closest factors with similar sensitivity indices.

Table B.4
Impact of behavioral factors on TAR (time spent above 180 mg/dl). For each factor, the sensitivity index (second column) and its 95% confidence interval (third column) are reported. Sensitivity indices in bold are the ones whose confidence interval does not contain zero. The factors are ordered from the most impactful to the least impactful, based on the absolute value of the sensitivity indices. For comparison, the ranking obtained based on the impact on TBR is reported in the last column.

Behavioral factors	Sensitivity index α	95% confidence interval	Position in the TAR ranking	Position in the TBR ranking
Systematic carb-counting error [%]	**-8.69%**	[-8.77%, -8.61%]	1	1
Random carb-counting error [%]	**4.73%**	[4.65%, 4.80%]	2	2
Insulin bolus time w.r.t. mealtime [min]	**3.70%**	[3.62%, 3.79%]	3	4
Hypotreatment dose [g]	**3.22%**	[3.14%, 3.29%]	4	3
High CGM alert threshold [mg/dl]	**1.97%**	[1.90%, 2.04%]	5	7
Delay in responding to CGM hypo-alerts [min]	**0.55%**	[0.49%, 0.61%]	6	6
Time between main meals [h]	**-0.52%**	[-0.62%, -0.41%]	7	9
Recheck time after hypotreatment [min]	**-0.29%**	[-0.38%, -0.20%]	8	8
Low CGM alert threshold [mg/dl]	**0.23%**	[0.14%, 0.31%]	9	5
Delay in responding to CGM hyper-alerts [min]	-0.07%	[-0.16%, 0.01%]	10	10
Fake factor [h]	-0.01%	[-0.08%, 0.06%]	11	11

Appendix B. Factors ranking based on the impact on time above range

Table B.4 reports the ranking of the behavioral factors based on their impact on TAR. As for TBR, for each subject, TAR was computed as the percentage of time spent with BG above 180 mg/dl over the entire length of each simulation (i.e. 14 days).

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