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A Mathematical Formula to Determine the Minimum Continuous Glucose Monitoring Duration to Assess Time-in-ranges: Sensitivity Analysis Over the Parameters

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***Abstract*— In diabetes management, the fraction of time spent with glucose concentration within the physiological range of $[70-180]$ mg/dL, namely time in range (TIR) is often computed by clinicians to assess glycemic control using a continuous glucose monitoring sensor. However, a sufficiently long monitoring period is required to reliably estimate this index. A mathematical equation derived by our group provides the minimum trial duration granting a desired uncertainty around the estimated TIR. The equation involves two parameters, p_r and α, related to the population under analysis, which should be set based on the clinician's experience. In this work, we evaluated the sensitivity of the formula to the parameters.**

Considering two independent datasets, we predicted the uncertainty of TIR estimate for a population, using the parameters of the formula estimated for a different population. We also stressed the robustness of the formula by testing wider ranges of parameters, thus assessing the impact of large errors in the parameters' estimates.

Plausible errors on the α estimate impact very slightly on the prediction (relative discrepancy $< 5\%$), thus we suggest using a fixed value for α independently on the population being analyzed. Instead, p_r should be adjusted to the TIR expected in the population, considering that errors around 20% result in a relative discrepancy of $\sim 10\%$.

In conclusion, the proposed formula is sufficiently robust to parameters setting and can be used by investigators to determine a suitable duration of the study.

I. INTRODUCTION

Diabetes is a chronic metabolic disease that causes undesirable excursions of blood glucose (BG) concentration outside the physiological range of $[70-180]$ mg/dL. Increasing the time spent in this range, namely time in range (TIR), allows limiting the risk of complications [1]. Therefore, BG monitoring is an essential component of diabetes management. The most modern approach to track BG excursions relies on Continuous Glucose Monitoring (CGM) sensors, which produce readings almost continuously (e.g., every 5 min) for several consecutive days/weeks [2]. CGM sensors are currently used in numerous clinical trials having time-in-ranges as endpoints [3], but the duration of these trials is crucial for a precise estimation of the outcome metrics: too short monitoring periods provide a poor estimation, affected by weekly fluctuations, while long trials result in excessive costs, not justified by real benefits. Thus, determining a suitable duration of CGM recordings providing a reliable estimation of time-in-ranges represents an open issue.

Although different studies approached this problem [4], [5], their suggestions are only empirical and the generalization to different populations poses some issues [6]. In a recent work, [7] we proposed a new analytical approach to address this issue, deriving a mathematical formula predicting the uncertainty of time-in-ranges estimates based on the number of CGM days. This formula could be used by an investigator who is designing a clinical trial, to identify the minimum trial duration required to achieve a desired level of uncertainty around the final time-in-ranges.

The formula involves two parameters: p_r, related to the population to be monitored, and α, linked to the glycemic range under analysis. When designing a clinical trial, the values of these parameters are not exactly known a priori and they can be only hypothesized (e.g., based on clinical experience or previous pilot studies). Understanding how much sensitive the formula is to parameters setting is important to assess the robustness of this new approach.

In this work, we evaluate the impact of sub-optimal parameters p_r and α on the predicted uncertainty, focusing on TIR.

II. METHODS

A. Mathematical formulation of the problem

Glucose concentration can be modelled as a continuous random variable, which assumes values in the range $[0, +\infty]$ mg/dL. CGM measurements can be modelled as non-independent realizations $g_1, g_2, \ldots, g_N$ of a random process g_k, collected at time $t = kT$, where T is the CGM sampling period. When considering a generic glycemic range $\mathbf{R} \subset \mathbb{R}$ (e.g., $\mathbf{R} = [70 - 180]$ mg/dL), the time-in-range to be estimated is $p_r = \mathbb{P}[g_k \in \mathbf{R}]$.

Let us now introduce h_k, a random process made of binary random variables, obtained as dichotomization of the process g_k to model samples within the range $\mathbf{R}$ (i.e., $h_k = 1$ if $g_k \in \mathbf{R}$, $h_k = 0$ otherwise). By construction, h_k is a Bernoulli random variable of parameter p_r, hence mean and standard deviation of h_k are $\mu = p_r$ and $\sigma = \sqrt{p_r(1-p_r)}$.

In this framework, the time-in-ranges usually computed in

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clinical practice can be seen as the (unbiased and asymptotically consistent) estimators of p_r: $t(n) = \frac{1}{n}\sum_{k=1}^{n} h_k$.

Let us assume an autoregressive structure of order 1 for h_k (hypothesis already validated in [8]). This means that two samples k, ℓ, with $k \leq \ell$, have the following autocorrelation function: $R_h(\tau) = \alpha^{\ell-k}$.

Finally, let us define the estimation error as: $e(n) = t(n) - p_r$, distributed around 0 with a certain standard deviation $sd[e(n)]$.

Under the previous assumptions, the following equation:

$$sd[e(n)] = \sqrt{\frac{p_r(1-p_r)}{n}\left(1 + \frac{2\alpha}{1-\alpha} + \frac{2\alpha}{n}\frac{(\alpha^n - 1)}{(1-\alpha)^2}\right)} \quad (1)$$

describes how fast the uncertainty around time-in-range $sd[e(n)]$ decreases as the number of CGM samples n increases. Proof in [8].

In Camerlingo et al. [7], we validated the previous assumptions and we showed that the uncertainty predicted by (1) well matches the variability observed on clinical data.

Equation (1) involves two parameters: i) p_r is the probability of a CGM sample to be in the glycemic range $\mathbf{R}$ (i.e., it is the "true" time-in-range), which depends both on $\mathbf{R}$ and on the population under analysis; ii) α represents the correlation between consecutive samples of the dichotomized process h_k. This correlation parameter is expected to be mainly related to $\mathbf{R}$, rather than to the population under analysis. In the following, we evaluate how sub-optimal values of p_r and α impact on $sd[e(n)]$.

B. Dataset

The analysis is performed using CGM data collected in the REPLACE-BG study: a randomized trial comparing two independent populations with different diabetes management approaches [9]. Group A involves 149 subjects (71 women) aged 44 ± 14 y.o., with glycated hemoglobin (HbA1c) of $7.1 \pm 0.7\%$ and baseline TIR of $63 \pm 13\%$ (mean$\pm$sd). Group B involves 77 subjects (41 women) aged 45 ± 13 y.o., with HbA1c of $7.0 \pm 0.7\%$ and baseline TIR of $65 \pm 11\%$, (mean$\pm$sd). Both the groups wore the Dexcom G4 Platinum CGM sensor (Dexcom, Inc.) for 182 ± 6 days.

C. Design of the analysis

Focusing on TIR, we use (1) to obtain the theoretical uncertainty $sd[e(n)]$. The parameters of the formula p_r, α are computed using, separately, data of Group A (i.e., p_{rA}, α_A), and data of Group B (i.e., p_{rB}, α_B). To illustrate the effectiveness of the proposed formula, the predicted uncertainty $sd[e(n)]$ is compared against the sample uncertainty $SD_A[e(n)]$, computed retrospectively by CGM data of Group A, as explained in the following.

For each participant of Group A, the most accurate estimate of TIR, i.e., $TIR(N)$, is evaluated over the whole trial duration N. Then, shorter trials are simulated extracting several shorter windows of fixed durations n, ranging from 1 to 30 days. For each window j, $TIR(n, j)$ is computed and the estimation error is obtained as: $e(n, j) = TIR(n, j) - TIR(N), \quad j \in 1, 2, \ldots, M_p$, where M_p is the number of different windows available for each participant, obtained by considering different starting points (with a window shift of 1 day), as proposed in [8].

Repeating this procedure for all the participants, a total of M values of estimation error are obtained for each duration n. Finally, the standard deviation of the estimation error is computed as:

$$SD_A[e(n)] = \sqrt{\left(\frac{1}{M-1}\sum_{j=1}^{M} e(n, j)\right)^2}$$

The comparison between the sample uncertainty and the theoretical uncertainty is performed in 4 different scenarios:

- In Scenario 1, the ideal case in which the most suitable values of the parameters are available is analyzed. The sample $SD_A[e(n)]$ is compared against the theoretical $sd[e(n)]$, obtained using p_{rA} and α_A, both computed by data of Group A.
- In Scenario 2, to simulate an error in setting p_r, the theoretical $sd[e(n)]$ is obtained using p_{rB}, computed by data of Group B, and α_A, computed by data of Group A.
- In Scenario 3, to simulate an error in setting α, the theoretical $sd[e(n)]$ is obtained using p_{rA}, computed by data of Group A, and α_A, computed by data of Group B.
- In Scenario 4, the real-world case in which the true values of the parameters are unknown is analyzed. To simulate a suboptimal setting, the theoretical $sd[e(n)]$ is obtained using p_{rB}, α_B, both computed by data of Group B.

Furthermore, we test the sensitivity of the formula over wider ranges of parameters values. Specifically, let us define $\Delta\alpha = |\alpha_A - \alpha_B|$ and $\Delta p_r = |p_{rA} - p_{rB}|$; we compare the theoretical $sd[e(n)]$ obtained in Scenario 1 against the $sd[e(n)]$ obtained first using α_A and p_r ranging in $[p_{rA} - 5\Delta p_r, p_{rA} + 5\Delta p_r]$, and then using p_{rA} and α ranging in $[\alpha_A - 5 * \Delta\alpha, \alpha_A + 5 * \Delta\alpha]$. Finally, we vary simultaneously both the parameters, among the previously defined ranges.

D. Metrics of comparison

To evaluate the error related to suboptimal parameters setting, the sample and the theoretical uncertainties are compared within $[1, 30]$ days of monitoring in the four scenarios. Their difference is then quantified by the absolute relative discrepancy (RD) computed for a different amount of collected samples n, corresponding to trial durations of 7, 14 and 30 days:

$$RD(n) = 100 \times \left|\frac{SD[e(n) - sd[e(n)]}{SD[e(n)]}\right|$$

III. RESULTS

The parameters p_r and α are computed following the pipeline described in [8]. Table I reports the values of the parameters for Group A (second row) and Group B (third

row). The relative difference in p_r is 3.65%: this is a realistic value to represent a limited error that could be committed when setting p_r before the clinical trial. As expected, the difference in α is much lower, because it depends mainly on the considered glycemic range and little on the population under analysis.

TABLE I

FORMULA'S PARAMETERS p_r AND α FOR THE TWO POPULATIONS UNDER STUDY

Dataset	p_r	α
Group A	0.6266	0.9616
Group B	0.6495	0.9599

In Figure 1, we compare the sample $SD_A[e(n)]$, computed using data of Group A (solid red), against the uncertainty predicted by the proposed formula, in the four scenarios, from day 1 to day 30.

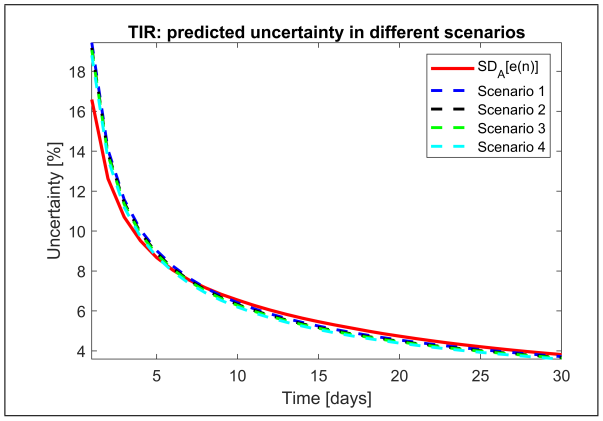

Fig. 1. Sample uncertainty $SD_A[e(n)]$ computed by data of group A (solid red) vs predicted uncertainty $sd[e(n)]$, for Scenario 1 (dashed blue), 2 (dashed black), 3 (dashed green), and 4 (dashed cyan).

As expected, in Scenario 1 the predicted uncertainty is the closest to the sample uncertainty for most of time, while in Scenario 4 the two curves are the most distant. The uncertainty obtained in Scenario 3 exhibits a higher discrepancy than in Scenario 2.

Although using optimal parameters grants the best prediction of the sample uncertainty, it is important to note that the curves obtained with suboptimal parameters are very close to each other and very close to the curve with optimal parameters.

Table II reports the values of RD between the sample and the theoretical uncertainties at day 7, day 14 and day 30, for the four scenarios under analysis.

In Scenario 4, the maximum RD is reached at day 30 and it is equal to 10.71%. Since $SD[e(n)] = 4.01\%$ at day 30, even when both the parameters are suboptimal, the proposed equation commits a very limited error of 0.43%. Therefore, limited (but plausible) errors in setting the formula's parameters are not crucial for the prediction of the sample uncertainty.

TABLE II

ABSOLUTE RELATIVE DISCREPANCY BETWEEN $SD_A[e(n)]$ AND $sd[e(n)]$, IN THE FOUR DIFFERENT SCENARIOS

Scenario	Absolute Relative Discrepancy [%]		
	7 days	14 days	30 days
Scenario 1	1.35	7.04	7.53
Scenario 2	2.69	8.30	8.79
Scenario 3	3.41	8.99	9.48
Scenario 4	4.72	10.23	10.71

To evaluate the sensitivity of (1) to p_r, panel a of Figure 2 reports the mean curve and the [min-max] interval of the predicted uncertainty obtained using $\alpha_A = 0.9616$ and p_r ranging in $[p_{rA} - 5\Delta p_r, p_{rA} + 5\Delta p_r] = [0.5123, 0.7410]$, for trial durations of $[1 - 30]$ days. Panel b shows the RD computed between the $sd[e(n)]$ curves obtained for the different p_r values and $sd[e(n)]$ obtained using p_{rA}, at day 7, 14 and 30. Similarly, in panel c, the predicted uncertainty is computed using $p_{rA} = 0.6266$ and α ranging in $[\alpha_A - 5\Delta\alpha, \alpha_A + 5\Delta\alpha] = [0.9533, 0.9698]$, while panel d reports the RD between each curve and $sd[e(n)]$, obtained using α_A, after 7, 14 and 30 days.

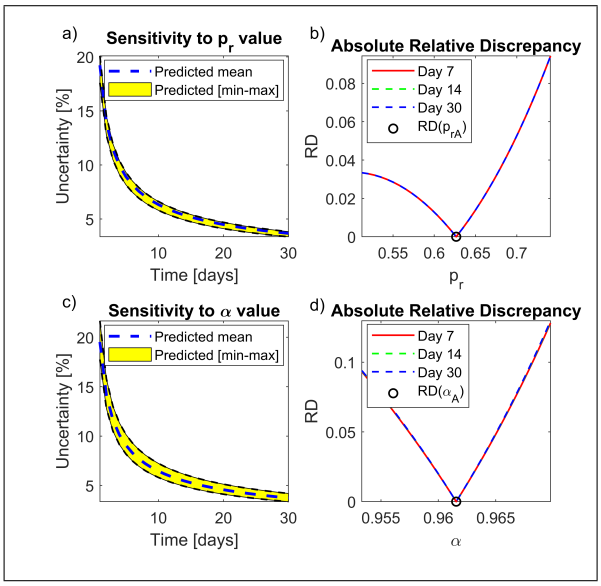

Fig. 2. Sensitivity of the proposed formula to the parameters p_r and α. Left: mean curve (dashed blue) and [min-max] range (yellow area) for different p_r values (panel a) and for different α values (panel c). Right: RD between the $sd[e(n)]$ obtained using p_{rA}, α_A and the $sd[e(n)]$ obtained simulating an error in setting p_r (panel b) or α (panel d), evaluated at day 7 (solid red), 14 (dashed green) and 30 (dashed blue). The black circle indicates the RD computed using p_{rA} and α_A.

The proposed formula results more sensitive to α than to p_r. The RD is equal to 9.43% for the highest p_r value tested (18% of relative error added to the p_{rA}), while it is equal to 3.33% for the lowest one, showing an asymmetric variation, with an exponential shape. Therefore, the overestimation of p_r yields a greater discrepancy than its underestimation.

Variations of α induce RD values, up to 12.96% for $\alpha = 0.968$. Also in this case, RD varies in a non-symmetric way, reaching 9.39% for $\alpha = 0.9533$.

For both the analyses, the RD profiles at day 7, 14 and 30 are almost perfectly overlapped, pointing out that variations in p_r or α provide a homogeneous shift of the $sd[e(n)]$ curve.

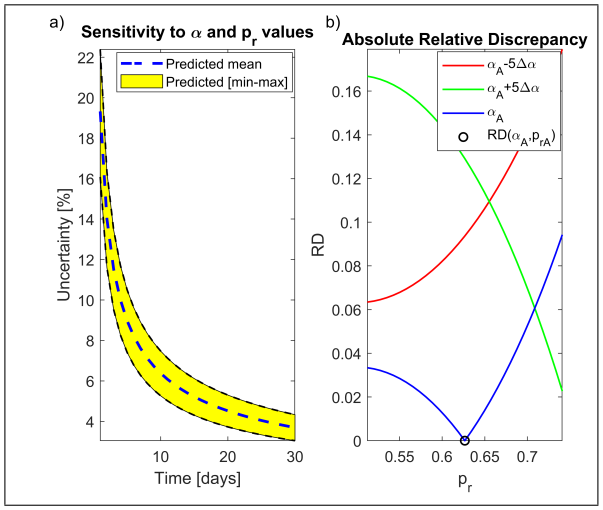

Fig. 3. Sensitivity of the proposed formula to the parameters p_r and α. Panel a: mean curve (dashed blue) and [min-max] range (yellow area) for simultaneous variations of p_r and α. Panel b: RD between $sd[e(n)]$ obtained using p_{rA}, α_A and $sd[e(n)]$ obtained using different p_r values and three different α: 0.9533 (red), 0.9698 (green) and α_A (blue), evaluated at day 14. The black circle indicates the RD computed using p_{rA} and α_A.

Panel a of figure 3 shows the mean curve and the [min-max] interval of the predicted uncertainty obtained using all the possible combinations of p_r ranging in $[p_{rA} - 5\Delta p_r, p_{rA} + 5\Delta p_r] = [0.5123, 0.7410]$ and α ranging in $\alpha_A - 5\Delta\alpha, \alpha_A + 5\Delta\alpha] = [0.9533, 0.9698]$, for trial durations of $[1 - 30]$ days. As expected, the uncertainty interval is wider than in panels a, b of figure 2. Furthermore, panel b of figure 3 reports the RD computed, at day 14, between $sd[e(n)]$ obtained using p_{rA}, α_A and the $sd[e(n)]$ curves obtained using different p_r values and three different values of α among those tested: the minimum, the maximum, and α_A. The worst cases, with maximum discrepancy, are represented by the pairs $(p_{r_A} + 5\Delta p, \alpha_A - 5\Delta\alpha)$, providing $RD = 17.91\%$, and $(p_{r_A} - 5\Delta p, \alpha_A + 5\Delta\alpha)$, providing $RD = 16.68\%$. Finally, overestimating both α and p_r seems to be not so crucial, with a discrepancy of only 2.27%.

IV. DISCUSSION AND CONCLUSIONS

In clinical trials involving patients with diabetes, the fraction of time spent with CGM sensors within the physiological range (namely TIR) is often computed as an index of glycemic control. However, a sufficiently long monitoring period is required to reliably estimate this index.

A mathematical equation derived by our group can be used to set a suitable trial duration, since it predicts the uncertainty around the estimated TIR (or other time-in-ranges), based on the length of the monitoring period. The equation involves two parameters, p_r and α, which should be set before the clinical trial based on the clinician's experience.

In this work, we evaluated how errors on the parameters impact on the predicted uncertainty. Specifically, we first predicted the uncertainty around TIR, computed retrospectively from CGM data, using the parameters computed from an independent population. Then, we stressed the robustness of the formula by testing wider ranges of parameters, thus assessing the impact of higher errors. Since realistic variations of α are very limited, we suggest using fixed values of α (e.g., for the TIR, α_A can be used), thus accepting a limited error on the uncertainty. Regarding p_r, it should be adjusted to the TIR expected in the population. When a reasonable guess is not available, errors around 20% result in a higher discrepancy than errors around -20%.

In conclusion, since the proposed formula is robust to parameters setting, clinical investigators could use it to determine a suitable duration of studies involving CGM. Future works include a sensitivity analysis on the other time-in-ranges and to investigate variations of α in populations with different characteristics (e.g., type 2 diabetes, pregnant, pediatrics, etc.).

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