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Blood Glucose Reference Personalization for Subjects with Type 2 Diabetes*

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***Abstract*— In this paper, we present two simple and novel methods for automatic personalization of target blood glucose concentration values for individuals with Type 2 Diabetes (T2D). The methods can be integrated with any insulin dosing algorithm, or used to provide an individualized reference BG concentration value for medical professionals to consider when determining long-acting insulin doses and other oral medications. The proposed methods were tested in three different simulation models, with different long-acting insulin dosing strategies, and were found to reduce instances of hypoglycemia.**

I. Introduction

Type 2 diabetes (T2D) is characterized by high blood glucose (BG) concentrations, or hyperglycemia, caused by an imbalance between insulin secretion and the ability of insulin to lower BG concentrations. If left untreated, high BG concentrations can lead to complications such as cardiovascular diseases and damage to eyesight. The first steps in the treatment of T2D typically involve lifestyle adjustments and the use of oral medications. However, if these methods are insufficient in lowering BG concentrations, individuals with T2D may need to use long-acting insulin, such as once-daily insulin pens, based on self-monitored blood glucose (SMBG) measurements or continuous glucose monitoring (CGM) devices. Strategies for automatically computing insulin doses for T2D subjects range from simple table-based strategies, as described in [1], to physiological model-based strategies, such as the one in [2], as well as model-free strategies, like the ones discussed in [3], [4]. The glucose target for these titration algorithms is fixed. However, for individuals with high variations in blood glucose concentrations, this fixed target may not be ideal as it can lead to increased instances of low BG concentrations (hypoglycemia) which can cause symptoms such as nausea, fainting, and in severe cases, death. To address this issue, we propose adapting the glucose target in real-time to reduce the occurrence of hypoglycemic events. The idea of adapting has been shown to be effective in closed-loop artificial pancreas systems for individuals with type 1 diabetes in combination with a model predictive controller [5]. In this paper, we propose new methods for automatic penalization of target BG for individuals with T2D utilizing CGM readings. The developed strategies can generally be connected with any insulin dosing algorithm or they can be directly recommending an individualized reference BG to the medical professionals who are deciding on the long-acing insulin dose and other medications. The contribution of this paper are as follows

- We propose a simple integral-derivative (ID) controller with a nonlinear error function to adapt a personalized target BG concentration for T2D subjects.
- We propose a different method which calculates a personalized BG target by taking a weighted average of the outputs from multiple ID controllers. The weights are adapted in an online fashion for each subject.
- We test the method with three different simulation models augmented with three different insulin dosing strategies: two standard of care dosing strategies, and a newly proposed modified version of one of them.

II. notations

The symbol $:=$ indicates *defined by*. All vectors are considered as column vectors, $\|\cdot\|_p$ denotes the p-norm, and $^{\mathrm{T}}$ denotes transpose. We use $\mathcal{N}(\mu, \Sigma)$ to denote the normal distribution with mean μ and covariance Σ, and $\mathcal{U}(a, b)$ for a continuous uniform distribution with bounds a and b. If the difference between two time instants t_k and t_{k+j} is such that $t_{k+j} - t_k = jT,\ j, k \in \mathbb{N}$ with $T \in \mathbb{R}$ being a constant, then variables that are indexed with time $x(t_k), x(t_{k+j})$ will be denoted by $x(k), x(k+j)$ for ease of notation. We let $[a, b]$ denote the closed interval from a to b, and $[a\ b]$ denote the row vector with coordinates a and b. For a diagonal matrix A with diagonal entries $a = [a^1 \cdots a^n]^{\mathrm{T}}$, the notation $A = \mathrm{diag}(a)$ is used. The symbol I_n is used to denote the $n \times n$ identity matrix and the symbol $\mathbf{1}_n$ is used to denote the n_{th} dimensional column vector of 1s. For an interval $\Theta = [x_\ell, x_u]$, we define the saturation function $\Pi_\Theta : \mathbb{R} \to \Theta$, $\Pi_\Theta(x) := \max\left(\min\left(x, x_u\right), x_\ell\right)$. For $w, v \in \triangle_n := \left\{ w \in \mathbb{R}^n_{\geq 0} \mid \|w\|_1 = 1 \right\}$, we write the Kullback–Leibler (KL) divergence (relative entropy) as $D_{KL}(w \ || \ v) = \sum_{i=1}^n w^i \ln\left(w^i / v^i\right)$. For a vector $x = [x_1, \ldots, x_N]^{\mathrm{T}} \in \mathbb{R}^N$, we define a vector of moving averages with a window $H \leq N$ as $\mu_H(x) := 1/H \left[\sum_{i=1}^H x_i, \ldots, \sum_{i=N-H+1}^N x_i\right]^{\mathrm{T}}$.

III. Description of the method

As discussed in the introduction, the adaptive BG target methods in this paper are designed to be used in connection with an insulin dosing strategy or as a recommendation to medical professionals, see figure III. We will first describe a nonlinear error function in III-A. Afterwards, we describe

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the simple ID method for BG target adaptation in III-B.1 and an adaptive weighted average version of it in III-B.2.

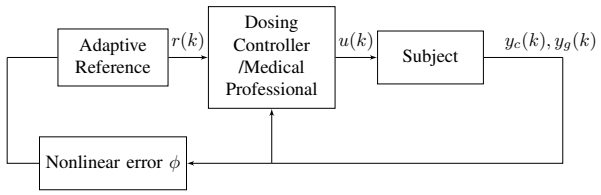

Fig. 1. Block diagram of the setup. The command $r(k)$ is a personalized average/fasting glucose target, $u(k)$ is a long-acting insulin dose, $y_c(k)$ is a vector of the available CGM measurements between the days $(k-1)T$ and kT, and $y_g(k)$ is an average/fasting BG measurement.

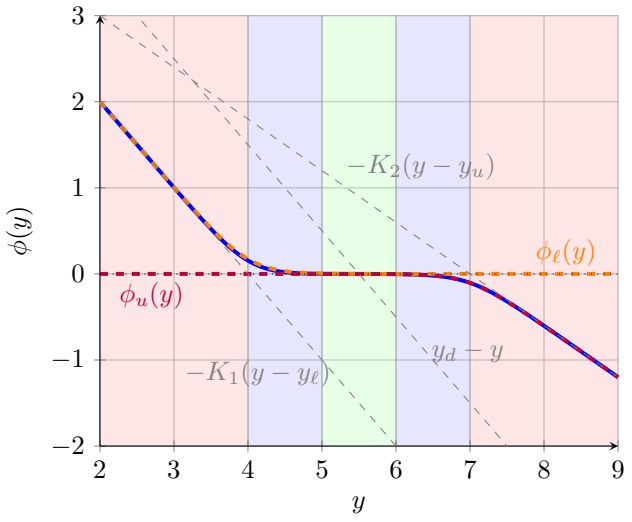

Fig. 2. A plot of $\phi(y)$ defined in (1c) with $K_1 = 1, K_2 = 0.6, a = b = 2, y_\ell = 4, y_u = 7$. The figure demonstrates the approximately linear error zones, the zero zone, and the transitioning zones. Note that $y > 0$ since it represents a BG concentration value

A. Nonlinear Error Functions

Let $k \in \mathbb{Z}_{\geq 0}$ represent the current iteration of our strategy at time $t_k := kT$ [day]. Similarly, let $m \in \mathbb{Z}_{\geq 0}$ represent the CGM sample at time $t_m := mT_m$ [day] with $T_m < T$. We define the vector $y_c(k) \in \mathbb{R}^q$ as the vector of the available q CGM measurements y from time t_{k-1} until t_k. In other words, $y_c(k) = \begin{bmatrix} y(m_{k_1}) & \dots & y(m_{k_q}) \end{bmatrix}^{\mathrm{T}}$ such that $T_m m_{k_i} \in \big[(k-1)T, kT\big]$ for $i \in \{1, \dots, q\}$. Before proceeding to the description of the strategies, we first define the functions $\phi_\ell, \phi_u, \phi : \mathbb{R} \to \mathbb{R}$

$$\phi_\ell(y) := K_1 s_a(-(y - y_\ell)) \tag{1a}$$
$$\phi_u(y) := -K_2 s_b(y - y_u) \tag{1b}$$
$$\phi(y) := \phi_u(y) + \phi_\ell(y) \tag{1c}$$

where $s_\alpha(x) := \frac{1}{\alpha}\log(1 + \mathrm{e}^{\alpha x})$, $K_1, K_2 \in \mathbb{R}_{>0}$ are gain constants, $a, b \in \mathbb{R}$ are shape parameters, and $y_\ell, y_u \in \mathbb{R}$ are lower and upper bounds respectively. Figure 2 shows an example of $\phi(y)$. The function $\phi(y)$ can be viewed as a modified version of the linear error $e(y) := y_d - y$ where y_d is taken as a "desired value". Unlike $e(y)$, the function $\phi(y)$ asymptotically converges to a linear error $-K_1(y - y_\ell)$ when $y \to -\infty$ and to another linear error $-K_2(y - y_u)$ when $y \to \infty$. In between, the function will be approximately zero. Additionally, observe that for $y_\ell = y_u = y_d$, and $K_1 = K_2 = 1$, we have $\phi(y)$ asymptotically converging to $e(y)$ when $a, b \to \infty$. Loosely put, the function $\phi(y)$ divides its domain "smoothly" into five different zones (see Figure 2): two zones with two different approximately linear error functions, one zone where the function is approximately zero, and two zones to transition from approximately zero to approximately linear error functions. On the other hand, the linear error function $e(y)$ is linear with the same gain for all $y \in \mathbb{R}$. The smoothing for the error function $\phi(y)$ between the approximately linear error zones and the zero zone helps with damping chattering effects when $\phi(y)$ is used as a feedback. The smooth transition is controlled by the parameters a and b. The parameters for ϕ for the rest of the paper are chosen as $K_1 = 1, K_2 = 0.6, a = b = 2, y_\ell = 4$, and $y_u = 7$. For the following subsections, we will present the two reference adapting approaches with the use of the function ϕ.

B. Reference Adaptation

We propose two approaches for adapting an average/fasting BG reference for each specific T2D individual based on $\phi(y)$ in (1c) and CGM measurements. The first approach is a single Integral-Derivative (ID) based controller and the second approach is an Adaptive Weighted Average method of multiple ID based controllers (AWAID).

1) Single ID Method: Consider an initial average/fasting BG reference $r(0) \geq 4$ [mmol/L]. At iteration k at time kT [day], we use the available CGM measurements $y_c(k)$ to compute a quantity related to the average error as

$$\bar{\phi}(y_c(k)) := \frac{1}{q}\sum_{i=1}^{q} \gamma_{y_\ell, y_u}(y(m_{k_i}))\phi(y(m_{k_i})), \tag{2}$$

where the cutoff function [1] γ_{y_ℓ, y_u} is defined as

$$\gamma(y)_{y_\ell, y_u} := \begin{cases} 0, & y \in [y_\ell + 1, y_u - 1] \\ 1, & \text{Otherwise.} \end{cases} \tag{3}$$

Afterwards, the suggested single point average/fasting BG reference is updated according to an ID type controller

$$\begin{aligned} r(k) = \Pi_\Omega\Big(&r(k-1) + TK_I\bar{\phi}\left(y_c(k)\right) \\ &+ K_D\left(\bar{\phi}\left(y_c(k)\right) - d_r(k-1)\right)\Big), \end{aligned} \tag{4a}$$
$$d_r(k) = (1-\beta)d_r(k-1) + \beta\bar{\phi}\left(y_c(k)\right), \; d_r(0) = 0. \tag{4b}$$

[1]The cutoff function is added to ensure that the error function ϕ is zero for $y \in [y_\ell + 1, y_u - 1]$ to avoid drift in the ID controller since $s(x)$ only asymptotically converges to zero for $x \to -\infty$. Although including the cutoff function affects the smoothness of the average error, the impact on chattering is negligible. This is because the cutoff function is applied within a region where the error is close to zero.

where $K_I > 0$ is the integral gain, $K_D \geq 0$ is the derivative gain, $0 < \beta \leq 1$, and $\Omega = [r_\ell, r_u]$ [2] The bounds r_ℓ and r_u are chosen to ensure that at any point, the reference $r(k)$ will always be safe. In this paper, we choose $r_\ell = 5$ [mmol/L] and $r_u = 10$ [mmol/L].

2) Adaptive Weighted Average ID (AWAID): For this method, we consider multiple ID based controllers of the form (4) and take the weighted average of their individual outputs as the suggested average/fasting BG reference. The method is made adaptive by updating the weights using an online multiplicative weight approach. Let $\theta := [K_I \ K_D \ \beta]^{\mathrm{T}}$ and consider $N \in \mathbb{Z}_{>0}$ different ID based controllers such that each individual controller is characterized by the parameters $\theta^i \in \Theta = \{\theta^1, \ldots, \theta^N\}$. To compute a reference $r(k)$ at time kT [day], we first compute the output of the N different ID controllers

$$r^i(k) = r(k-1) + TK_I^i \bar{\phi}\left(y_c(k)\right) + K_D^i\left(\bar{\phi}\left(y_c(k)\right) - d_r(k-1)\right), \tag{5a}$$

$$d_r^i(k) = (1-\beta^i)d_r^i(k-1) + \beta^i \bar{\phi}\left(y_c(k)\right), \ d_r(0) = 0. \tag{5b}$$

The output recommended reference is then computed as a weighted average with weights

$$w(k) = \left[w^1(k) \ \ldots \ w^N(k)\right]^{\mathrm{T}} \in \triangle_N,$$

as following

$$r_a(k) = \sum_{i=1}^{N} w^i(k) r^i(k), \tag{6a}$$

$$r(k) = \Pi_\Omega\left(r_a(k)\right). \tag{6b}$$

The weights $w(k)$ at step k are chosen such that $\phi(r_a(k))$ is close to zero to promote references on the interior of Ω which makes it safer for the subject. We achieve this with the following update step

$$\tilde{w}^i(k) = \frac{e^{-\eta(k)\phi^2\left(r^i(k)\right)}}{\sum_{i=1}^{N} e^{-\eta(k)\phi^2(r^i(k))} w^i(k-1)} w^i(k-1), \tag{7a}$$

$$w^i(k) = \zeta(k)\tilde{w}^i(k) + (1-\zeta(k))\frac{1}{N}\mathbf{1}_N, \tag{7b}$$

with $\eta(k) = \sqrt{\frac{\ln(N)}{50k}}$ (see Remark 3.2) and $\zeta(k) = \frac{\eta(k+1)}{\eta(k)} \in (0, 1]$. The update rule (7a) scales the weight for each individual reference output $r^i(k)$ based on how small the value of $\phi^2(r^i(k))$ is, meaning that reference outputs which are closer to the zero safe zone of the function ϕ will be scaled higher than other reference outputs. The update rule in (7) is the solution of the following optimization problem

$$\tilde{w}(k) = \underset{w \in \triangle_N}{\operatorname{argmin}} \ \sum_{i=1}^{N} \eta(k)\phi^2\left(r^i(k)\right) w^i + D_{KL}(w \,||\, w(k-1)), \tag{8}$$

[2] r_ℓ can be made time dependent with $r_\ell(k) = r_\ell(k-1) + T\alpha\left(\tilde{r}_\ell - r_\ell(k-1)\right)$ to give the option of the medical professionals to restrict how fast the BG reference should drop to minimum value of $\tilde{r}$ with a rate α $[day^{-1}]$ to prevent complications and pseudo-hypoglycemia symptoms [6].

and

$$\phi^2(r_a(k)) \leq \sum_{i=1}^{N} \phi^2\left(r^i(k)\right) w^i(k)$$

using Jensen's inequality since ϕ^2 is convex. In other words, minimizing $\sum_{i=1}^{N} \phi^2\left(r^i(k)\right) w^i(k)$ will minimize an upper bound on $\phi^2(r_a(k))$ to promote for a safer output reference $r_a(k)$. The regularization term $D_{KL}(w \,||\, w(k-1))$ is to ensure that the weights do not change arbitrary between different iterations in order to avoid sharp changes in $r(k)$. Additionally, the inclusion of the term $D_{KL}(w \,||\, w(k-1))$ pushes w away from the boundary of $\triangle_N$, and towards where $\sum_{i=1}^{N} \phi^2\left(r^i(k)\right) w^i(k)$ is minimized [7].

Remark 3.1: The step in equation (7b) performs interpolation between uniform weights ($\frac{1}{N}\mathbf{1}_N$) and the updated weights $\tilde{w}(k)$ at each iteration to account for the time-varying nature of the problem ($r^i(k)$ varies with k) by preventing the weights from quickly converging to one of the vertices of the simplex $\triangle_N$ and becoming fixed there.

Remark 3.2: Let $J_k(w) = \phi^2\left(\sum_{i=1}^{N} r^i(k) w^i\right)$, and define the average regret Ψ_K up until time step K between the weights computed according to (7) and the fixed weights $v = \underset{w \in \triangle_N}{\operatorname{argmin}} \sum_{k=1}^{K} J_k(w)$ as

$$\Psi_K := \frac{1}{K}\left(\sum_{k=1}^{K} J_k(w(k)) - \sum_{k=1}^{K} J_k(v)\right), \tag{9}$$

then using Corollary 10 in [8] and applying Jensen's inequality, we can bound the average regret with the update in (7) and $\zeta(k) = \frac{\eta(k+1)}{\eta(k)}$ with $w(1) = \frac{1}{N}\mathbf{1}_N$ as following

$$\Psi_K \leq \frac{1}{K}\sum_{k=1}^{K} \frac{\eta(k)\left\|g(k)\right\|_\infty^2}{2} + \frac{1}{K}\frac{\ln(N)}{\eta(K+1)}, \tag{10}$$

where $g(k) = \left[\phi^2\left(r^1(k)\right) \ldots \phi^2\left(r^N(k)\right)\right]^{\mathrm{T}}$.

Furthermore, due to the fact that the blood glucose concentration must have limits, and with parameters $\theta^i \in \Theta, \ i \in \{1, \ldots, N\}$ that ensures bounded input bounded output stability of the corresponding controllers, we can bound $\left\|g(k)\right\|_\infty^2 \leq G_\infty^2$. With this bound, if we choose $\eta(k) = \sqrt{\frac{2\ln(N)}{kG_\infty^2}}$, then the average regret becomes

$$\Psi_K \leq \frac{\sqrt{2\ln(N)}G_\infty}{K}\left(\frac{1}{2}\sum_{k=1}^{K}\frac{1}{\sqrt{k}} + \sqrt{K+1}\right) \leq \frac{2G_\infty\sqrt{2\ln(N)}}{\sqrt{K}}, \tag{11}$$

where we used $\sum_{k=1}^{K}\frac{1}{\sqrt{k}} \leq 2\sqrt{K} - 1$ (using the integral test) and $\sqrt{K+1} \leq \sqrt{K} + \frac{1}{2}$ for $K \geq 1$ (using the concavity and differentiability of the square root function). With $v = \underset{w \in \triangle_N}{\operatorname{argmin}} \sum_{k=1}^{K} J_k(w)$ being the best weights choice up until K, it means that the performance of the weights computed according to (7) compared to the case when we take the

best fixed weights v over the horizon K is bounded by a function in the order of $\frac{1}{\sqrt{K}}$. For the choice of G_∞, we used simulation results with the three different models in IV-B to obtain an estimate bound $\hat{G}^2_\infty = 100$ for G^2_∞ such that $G^2_\infty \leq \hat{G}^2_\infty$. Therefore, our choice for $\eta(k)$ is $\eta(k) = \sqrt{\frac{\ln(N)}{50k}}$.

IV. Simulation Setup

In this section, we intend to simulate and compare between insulin dosing strategies on T2D subjects with and without the adaptive reference scheme in (4). To do so, we first present our choice of insulin dosing strategies in IV-A. Afterwards, we present 3 different insulin-glucose simulation models in IV-B, Finally, we present and discuss the results of the simulations in V.

A. Simulated Dosing Strategies

In this section, we list the long-acing insulin dosing strategies which we will use for the simulations of individual with T2D. The first two strategies are the standard of care methods

$$\Delta u(k) = \begin{cases} 2, & y_g(k) > r(k) + 1 \\ 0, & y_g(k) \in [r(k) - 1, r(k) + 1] \\ -2, & y_g(k) < r(k) - 1 \end{cases} \tag{12a}$$

$$\text{Step} \quad \Delta u(k) = \begin{cases} 8, & \bar{y}_g(k) \geq r(k) + 4 \\ 6, & \bar{y}_g(k) \in [r(k) + 3, r(k) + 4) \\ 4, & \bar{y}_g(k) \in [r(k) + 2, r(k) + 3) \\ 2, & \bar{y}_g(k) \in [r(k) + 1, r(k) + 2) \\ 0, & \bar{y}_g(k) \in [r(k) - 1, r(k) + 1) \\ -2, & \bar{y}_g(k) \in [r(k) - 2, r(k) - 1) \\ -4, & \bar{y}_g(k) < r(k) - 2 \end{cases} \tag{12b}$$

$$u(k) = u(k-1) + \Delta u(k) \tag{12c}$$

where $u(k)$ is the prescribed insulin dose at $t = kT$ [day], $y_g(k)$ is a glucose value that can either be a glucose measurement obtained by finger pricking devices (SMBG) before breakfast, or a value calculated from CGM readings as $y_g(k) = \min\left(\mu_H\left(y_c(k)\right)\right)$ similar to [9], and $\bar{y}_g(k) := \frac{1}{3}\sum_{i=0}^{2} y_g(k-i)$ is an average value of $y_g(k)$ over the last three days. For the default standard of care strategies, $r(k)$ is constant and it is chosen to be 5 mmol/L. In addition to the standard of care strategies in (12), we consider a linear smooth (LS) version of Step defined as

$$\Delta u(k) = 2s_2(\bar{y}_g(k) - r(k) - 1) - 2s_2(r(k) - 1 - \bar{y}_g(k)) \tag{13a}$$

$$u(k) = u(k-1) + \Delta u(k) \tag{13b}$$

Note that the right-hand side of (13a) is $\phi(\bar{y}_g(k))$ in (1c) with $K_1 = K_2 = -2, a = b = 2, y_\ell = r(k) - 1$, and $y_u = r(k) + 1$. Figure 3 shows $\Delta u(k)$ versus $\bar{y}_g$ for both the Step and LS schemes. The parameters for the methods with AWAID are

$$\Theta = \{0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8\} \times \{0.8, 1, 1.2\} \times \{1, 0.8, 0.2\}$$

where $\theta^i = \left[K_I^i \; K_D^i \; \beta^i\right]^{\mathrm{T}}$ are the parameters for the i_{th} controller. For the methods with single ID, we choose after some simple tuning $\theta = [0.5 \; 1 \; 0.8]^{\mathrm{T}}$ (the median ID controller in Θ). The time constant T is chosen to be 7 days. Meaning that the reference and the insulin dose are updated every week.

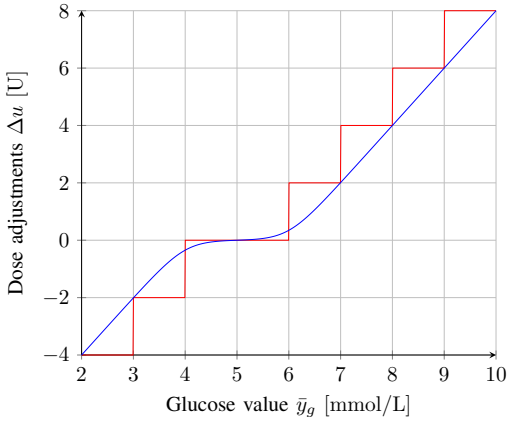

Fig. 3. The Step strategy (red) and its LS (blue) approximation with $r = 5$ mmol/L.

B. Glucose-Insulin Simulation Models

For the glucose-insulin dynamic simulations, we consider three different simulation models. For the first model, denoted "Model 1", we consider the jump diffusion model in [10]. The average meal rate in the jump part is chosen to be 3 meals/day between the hours 7:00 and 23:00 and 0.1 meals/day otherwise to take into account that individuals do not eat as frequently at night. As for the diffusion part, a constant diffusion is added to the BG concentration state. For the second model, denoted "Model 2", we consider the model presented in [11] augmented with a jump diffusion model for meals and disturbances matching "Model 1". Finally, the third model, denoted "Model 3", is the high fidelity model [12]. The meal times for Model 3 are drawn from uniform distributions as following: $\mathcal{U}(6, 8)$ [h] for breakfast meals, $\mathcal{U}(12, 14)$ [h] for lunch meals, and $\mathcal{U}(19, 20)$ [h] for dinner meals. The carbohydrate intake for each meal is also drawn uniformly according to $\mathcal{U}(10, 25)$ [g] for breakfast, $\mathcal{U}(20, 30)$ [g] for lunch, and $\mathcal{U}(25, 45)$ [g] for dinner. The choice of simulating the meals differently for Model 3 was to evaluate the insulin dosing strategies against a distinct type of stochastic disturbances. For the measurement errors, we consider an SMBG measurement error model [13] as the

following

$$y_g(k) = x_g(k) + \sigma_s\left(x_g(t_s)\right)\varepsilon_s(k), \tag{14a}$$

$$\sigma_s\left(x_g\right) = \frac{1}{\kappa}\sigma_2 \log\left(1 + \mathrm{e}^{\kappa\left(x_g - 4.2\right)}\right) + \sigma_1, \tag{14b}$$

with σ_1 and σ_2 chosen in accordance to the ISO standard [14] to be $\sigma_1 = 0.415$ [mmol/L] and $\sigma_2 = 0.1$, and $\kappa = 5$. Additionally, we consider a CGM measurement error model according to

$$y(m) = x_c(m) + \sigma_c x_c(m)\varepsilon_c(m), \tag{15}$$

with $\sigma_c = 0.42$ in accordance to a MARD of 10% [15] as done in [16]. The state x_c represents the glucose concentration in the blood for the models. Table I summarizes the models used for simulations in this paper.

TABLE I

GLUCOSE-INSULIN SIMULATION MODELS USED IN THE PAPER

Model 1	Based on [10]. Includes a measurement error model.
Model 2	Based on the model from [11]. Augmented with a jump diffusion model matching the one in [10] for meals. Includes measurement error models.
Model 3	Based on the model from [12]. The timing and size of meals are drawn from uniform distributions. Includes a measurement error model. A diffusion term matching the one in [10] is added to the state corresponding to BG concentration.

V. RESULTS AND DISCUSSION

This section describes a simulation involving 1500 individuals with T2D over the course of one year. The first 500 subjects were generated using Model 1, the next 500 using Model 2, and the final 500 using Model 3. Initial glucose and insulin concentrations, as well as parameters affecting insulin resistance and insulin secretion, and the time constant for injected long-acting insulin, were randomly chosen for each individual. Table III provides a summary of the parameters used for each T2D model.

We simulate the Step and LS strategies with different scenarios according to table II.

To compare the scenarios and the algorithms used in the simulations, we use the performance measures and their targets described in [17] for glucose managements. The measures are shown in table IV. In addition to the measures in table IV, we compute the mean long acting insulin dose. Table V shows computed mean and Standard deviation (Std) over the 1500 simulations for each strategy or scenario.

Figure 4 illustrates the outcomes of various methods: LS, LSAR, AvgLS, AvgLSAR, Step, StepAR, 202, and 202AR. Additionally, table V presents statistical data for all the methods discussed in table II. Among these methods, LSAR, AvgLSAR, and StepAR, which employ an adaptive BG reference, exhibit higher mean BG concentrations compared to LS, AvgLS, and Step. Consequently, there are lower BG values within the hypoglycemic range, as indicated by the BG histograms across all subjects.

This observation aligns with the table's results, demonstrating how adapting the reference can reduce instances of hypoglycemia. The table also reveals that the average glucose, TAR1, and TAR2 are higher when BG reference adaptation is utilized, which concurs with the findings in the figure. In summary, the adaptive BG reference strategies for Step and LS effectively elevate the BG reference, thus preventing hypoglycemic episodes in susceptible subjects. It is worth noting that methods employing an adaptive moving average of multiple ID controllers exhibit better performance

TABLE II

SUMMARY OF THE DIFFERENT SETUPS CONSIDERED FOR SIMULATIONS. IF CGM IS USED FOR y_g, THEN $H = 3$ [hour].

Name	y_g Value Based On	Adaptive Target	Insulin Dosing
Step	SMBG	none	Method (12b)
StepR	SMBG	Single ID (4)	Method (12b)
StepAR	SMBG	AWAID (6)	Method (12b)
202	SMBG	none	Method (12a)
202R	SMBG	Single ID (4)	Method (12a)
202AR	SMBG	AWAID (6)	Method (12a)
LS	SMBG	none	Method (13)
AvgLS	CGM	none	Method (13)
LSR	SMBG	Single ID (13)	Method (12b)
AvgLSR	CGM	Single ID (13)	Method (12b)
LSAR	SMBG	AWAID (6)	Method (13)
AvgLSAR	CGM	AWAID (6)	Method (13)

TABLE III

PARAMETERS FOR GENERATING SUBJECTS FROM MODEL 2, MODEL 3, AND MODEL 4. THE STATE x_G DENOTES THE BG CONCENTRATION STATE WHILE x_I DENOTE THE BLOOD INSULIN CONCENTRATION STATE.

Model 1	$x_G(0) \sim \mathcal{U}(15, 25)$ [mmol/L], $p_4 \sim \mathcal{U}(0.5, 2.5)$, $p_7 \sim \mathcal{U}(0.5, 2.5)$, $p_1 \sim \mathcal{U}(1.5, 2.5)$, p_6 and the initial conditions of the remaining states are calculated such that $x_G(0)$ is stationary. Diffusion term $\sigma_G \sim \mathcal{U}(0.1, 2)$.
Model 2	$x_G(0) \sim \mathcal{U}(15, 25)$, $x_I(0) \sim \mathcal{U}(20, 30)$ [pmol/L], $CL_{GI} \sim \mathcal{U}(0.71 \times 10^{-4}, 0.11 \times 10^{-2})$, $I_{PRG} \sim \mathcal{U}(0.05, 2)$, and the initial conditions of the remaining states are calculated such that $x_G(0)$ and $I_G(0)$ are stationary. Diffusion term $\sigma_G \sim \mathcal{U}(0.1, 2)$.
Model 3	$x_G(0) \sim \mathcal{U}(15, 25)$ [mmol/L], $x_I(0) \sim \mathcal{U}(0.5, 2)$ [mU/L], $c_1 \sim \mathcal{U}(0.04, 0.09)$, $c_2 \sim \mathcal{U}(2.3, 0.95)$, $c_4 \sim \mathcal{U}(1, 2.4)$, and the initial conditions of the remaining states are calculated such that $x_G(0)$ and $I_G(0)$ are stationary. Diffusion term $\sigma_G \sim \mathcal{U}(0.1, 2)$.

TABLE IV

GLUCOSE MANAGEMENT MEASURES FROM [17]. THE UNIT FOR THE RANGES AND GLUCOSE VALUES IS [mmol/L].

Measure	% of time for BG in	Target
Time in Range (TIR)	$[3.9, 10)$	$> 70\%$
Time Above Range 1 (TAR1)	$[10, 13.9)$	$< 25\%$
Time Above Range 2 (TAR2)	$[13.9, \infty)$	$< 5\%$
Time Below Range 1 (TBR1)	$[3, 3.9)$	$< 4\%$
Time Below Range 2 (TBR2)	$[0, 3)$	$< 1\%$
Average Glucose (AG)		< 8.6
Glucose Variability (GV)		36%
Glucose Management Index (GMI)		7%

in reducing incidents of hypoglycemia with slightly lower average BG concentration compared to those using a single ID controller. Although it may be possible to fine-tune the parameters of a single ID controller for improved results, this process can be challenging, particularly when dealing with different groups of T2D subjects. On the other hand, the AWAID strategy offers a more flexible approach, as it only requires specifying the parameters of multiple ID controllers. The method then adapts the weights in an online manner to enhance performance. However, in the case of the 202 strategies, the results shown in the figure do not demonstrate good performance, which is consistent with the TIR, TAR1, and TAR2 statistics presented in table V. Even when an adaptive BG reference is employed, these statistics do not change significantly. In fact, the adaptive reference strategies worsen TIR, TAR1, and TAR2 in exchange for a slightly lower TBR1.

This occurs because the 202 strategy is slow in bringing BG levels within the safe range (indicated by the mean insulin dose being lower than other methods). The adaptive references cannot decrease the BG reference below $r_\ell = 5\ [\mathrm{mmol/L}]$ to ensure a safe range according to (12a). Consequently, they are unable to expedite the titration process more than the default strategy with $r = 5\ [\mathrm{mmol/L}]$. As a result, the adaptive reference methods can solely increase the reference r to reduce instances of hypoglycemia. Moreover, due to the strategy's slowness, it takes a relatively long time for BG concentration to reach the elevated glucose reference.

This suggests that when the default strategy is not fast enough, employing the adaptive reference strategy does not offer significant improvements.

VI. Conclusion and Future Work

In this paper, we presented two simple methods for adapting the BG target for subjects with T2D based on CGM measurements. Simulation results with three different models showed that these methods, when combined with insulin titration strategies, managed to reduce instances of hypoglycemia when compared to using the insulin titration methods alone. Future research will involve conducting a more thorough analysis of the proposed methods under various simulation scenarios and in combination with different insulin titration strategies, as well as testing them in different models of T2D.

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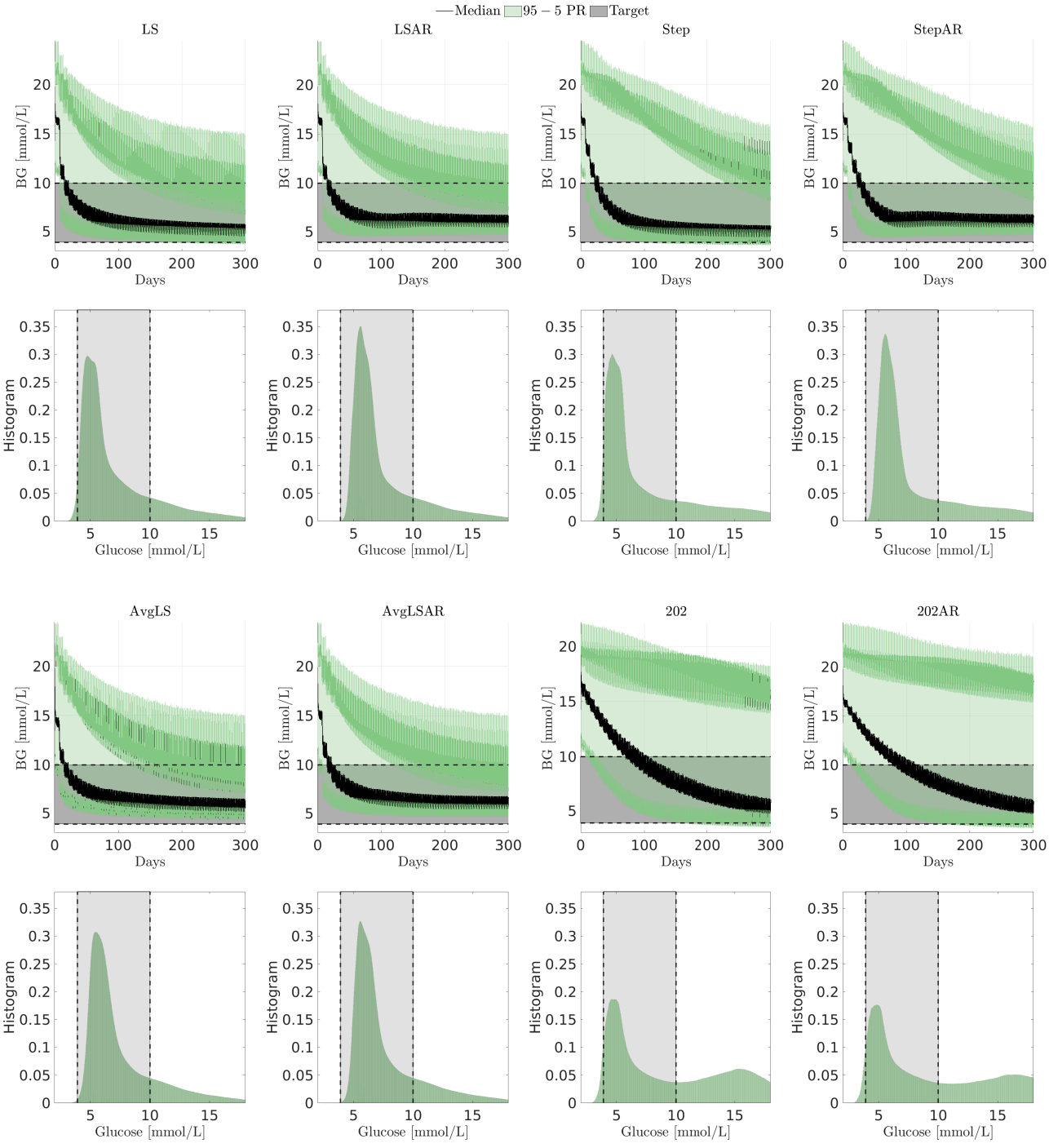

Fig. 4. Simulation results for LS, LSAR, AvgLS, AvgLSAR, Step, StepAR, 202, 202AR with Model 1, Model 2, and Model 3. The plots on the second row are normalized histograms for all the glucose readings with $T_m = 5$ [min] among the 1500 simulated subjects.

TABLE V

STATISTICS FOR DIFFERENT SCENARIOS AND ALGORITHMS. STD. IS SHORT FOR STANDARD DEVIATION.

	Mean TIR	Std. TIR	Mean TBR1	Std. TBR1	Mean TBR2	Std. TBR2	Mean AG	Std. AG
Target [17]	$> 70\%$		$< 4\%$		$< 1\%$		< 8.6 [mmol/L]	
LS	93%	5.55%	1.8%	0.5%	0%	0%	6.26	1.08
LSR	93.4%	5.52%	0.9%	0.5%	0%	0%	6.4	1.1
LSAR	94.2%	5.02%	0%	0.03%	0%	0%	6.52	1.2
AvgLS	92.7%	0.5%	0.1%	0%	0%	0%	7.3	0.8
AvgLSR	92.7%	0.5%	0.1%	0%	0%	0%	7.3	0.8
AvgLSAR	94.4%	0.48%	0%	0%	0%	0%	7.38	2.12
Step	91.27%	5.3%	1.2%	2.92%	0%	0%	6.46	1.05
StepR	92%	5%	0.9%	2.9%	0%	0%	6.61	0.92
StepAR	93.1%	5%	0.01%	0.06%	0%	0%	6.8	0.74
202	77.67%	14%	0.9%	3%	0%	0%	7.8	1.6
202R	76.5%	13.4%	0.87%	2.4%	0%	0%	7.9	1.63
202AR	76.5%	13.4%	0.87%	2.4%	0%	0%	7.9	1.63

	Mean TAR1	Std. TAR1	Mean TAR2	Std. TAR2	Mean Insulin	Mean GV	Std. GV	Mean GMI	Std. GMI
Target [17]	$< 25\%$		$< 5\%$			$< 36\%$		$< 7\%$	
LS	4.02%	4.24%	1.18%	0.8%	75.8 [U]	27.7%	6.7%	6.04%	0.45%
LSR	5.2%	4%	1.3%	0.73%	80.1 [U]	25%	5.4%	6.81%	1.2%
LSAR	5.5%	1.23%	1.02%	0.4%	109.67 [U]	28%	5.88%	6.98%	1.5%
AvgLS	6.35%	5%	0.9%	0.9%	58.9 [U]	19.77%	3.44%	6.46%	0.38%
AvgLSR	6.4%	5.1%	0.87%	0.9%	61 [U]	20.02%	3.53%	6.5%	0.5%
AvgLSAR	6.38%	5%	0.87%	0.9%	64.9 [U]	19.85%	3.45%	6.48%	0.38%
Step	5.91%	4.81%	1.63%	1.64%	74.7 [U]	29.47%	7.8%	6.12%	0.46%
StepR	5.7%	4.5%	1.6%	1.6%	72.04 [U]	28.2%	7.8%	6.2%	0.4%
StepAR	5.71%	4.5%	1.6%	1.6%	68.04 [U]	26.01%	6%	6.27%	0.32%
202	17.3%	11.5%	4.1%	5.2%	47.77 [U]	30.6%	8%	6.7%	0.7%
202R	18%	11%	4.3%	5%	47.8 [U]	30.65%	8%	6.7%	0.71%
202AR	18%	11%	4.3%	5%	47.8 [U]	30.65%	8%	6.7%	0.71%