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Extremum Seeking Control for Personalized Zone Adaptation in Model Predictive Control for Type 1 Diabetes

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Abstract

Zone model predictive control has proven to be an effective closed-loop method to regulate blood glucose for people with type 1 diabetes (T1D). In this paper, we present a universal model-free optimization scheme for adapting the zone for T1D patients individually. The adaptation is based on a clinical glycemic risk index named relative regularized glycemic penalty index (rrGPI), which is calculated from glucose measurements by a continuous glucose monitor. The scheme's objective is to minimize rrGPI by simultaneously modulating a controller's blood glucose target zone's upper bound and lower bound. The adaptation mechanism is based on extremum seeking control, in which the zone boundaries are driven by gradient estimation obtained by continuously sinusoidally modulating and demodulating the rrGPI readings. To improve the adaptation method's robustness against uncertainties, a decaying feedback gain and a vanishing dither signal are employed. In-silico trials suggested that the personalized optimized zone can be reached within a week of adaptation. Both for announced and unannounced meals, the proposed method outperforms the fixed zone [80,140] mg/dL, which has been employed in the authors' clinical trials. It is also shown that the developed method has strong robustness against real-life uncertainties.

Keywords

Extremum seeking control; personalization; type 1 diabetes; zone model predictive control; zone adaptation

I. INTRODUCTION

A. Motivation

Type 1 diabetes (T1D) is a metabolic disease where the β -cells in the pancreas are destroyed by the body's immune system, and then fail to secrete sufficient insulin to maintain blood glucose homeostasis. If treated improperly, T1D patients suffer chronic hyperglycemia and may have a higher risk for severe complications, including heart disease, stroke, kidney failure, blindness [1]. There are approximately 1.25 million people with T1D in the United States [2]. This number has an increasing trend. People with T1D fully rely on the appropriate delivery of exogenous insulin, and regulating their glucose level within a healthy range is a challenging task.

Generally, there are two kinds of approaches to deliver insulin: *multiple daily injections* (MDI) and *continuous subcutaneous insulin infusion* (CSII). A large amount of clinical evidence indicates that CSII use yields significant improvements in glycemic regulation [3]. However, even with CSII pump use, the burden of programming the pump, i.e., making decisions about insulin dosing, lies with the patient. Research into an *artificial pancreas* (AP), a device that performs algorithmic insulin dosing based in glucose feedback, has become a very active research field [4]. With the significant improvement of sensor technology over the past several decades, numerous sophisticated closed-loop controllers became feasible and have been designed for blood glucose regulation, including *model predictive control* (MPC) [5], [6], PID [7]—[9], H_∞ [10]. Among these control strategies, zone-MPC has received increasing attention in the authors' group [11]—[13]. In zone-MPC the controller penalizes the excursion of blood glucose predictions from a zone with two degrees-of-freedom (upper bound and lower bound), rather than the deviation from a set point with only one degree-of-freedom. The zone concept renders the controller more robust against plant-model mismatch and *continuous glucose monitor* (CGM) error. The zone-MPC controller has been reported effective in outpatient clinical trials [12]—[17]. However, the zones in the state-of-the-art zone-MPC literature were uniformly chosen based on clinical rule of thumb. Therefore, it is natural to ask the following questions:

- Can the zone be personalized by minimizing the risk for hypo- and hyperglycemia using a risk function?
- Is there any adaptation method that can accommodate real-life uncertainties?

The contribution of this paper is to answer these two questions by presenting a systematic scheme to find the optimal zone for T1D patients individually. The scheme is based on the *extremum seeking control* (ESC) method, a model-free optimization approach. Preliminary results were presented in [18].

B. Summary of Related Literature

Extremum seeking control is a real-time model-free optimization method that has a well understood theory and has widely been applied in numerous industrial fields. On the theoretical side, the local and semi-global convergence proofs were presented in [19]—[23]; Newton-type approaches were developed in [24], [25]; the method's robustness against measurement noise was investigated in [26], [27]. On the side of industrial applications, numerous successful trials have been reported in various fields, e.g., combustion control [19] and injection molding [28].

The proposed method also falls into the category of *run-to-run* methods, which have been employed in the AP context previously. For example, Ref. [29] developed a proportional-type run-to-run approach to adjust the bolus injection time and amount; the approach was also used to adapt four-segment basal profiles [30]; in [31], [32], this approach was tested in clinical trials; a robustness analysis was presented in [33]; a refined version was proposed based on a nonlinear glycemic performance measure [34]. These references have one common point - employing sparse blood glucose measurements to adapt the basal rates or bolus dosage based on an established insulin-sensitivity model. A similar method to adapt MPC controller parameters was discussed in [35]; recently, an event-based run-to-run

strategy was developed to adjust basal rates according to a clinical risk index (time-in-range) instead of glycemic measurements [36]. Nevertheless, the methods mentioned above share three drawbacks. First, they depend on the knowledge of insulin-sensitivity, which is difficult to estimate. For example, in [29], a grid of 972 points was required to identify the sensitivity of one patient. Second, there inevitably exists a plant-model mismatch. The insulin-sensitivity is time-varying. It changes based on the time of day according to a diurnal profile, and, furthermore, the profile changes as time goes by, e.g., because of age, sickness, menstrual cycle, etc. Third, the methods are able to converge to a limit point, but it is not possible to make theoretically justified statements with regard to the limit point, such as optimality. To resolve these problems, in this paper we propose to incorporate the ESC mechanism into the zone-MPC strategy. ESC continuously perturbs the control input, in a sinusoidal manner, in order to minimize an objective function in a model-free way. The objective function is of CGM measurements of blood glucose values, thus the proposed strategy circumnavigates the trouble of modelling.

C. Results

In this paper, we present a universal online optimization method to personalize the zone definition by minimizing a certain clinical risk index. From the perspective of control and optimization theory this is a very difficult problem, because 1) the method should be sufficiently robust against the dynamics variations, e.g., insulin sensitivity; 2) it needs strong robustness to disturbances, e.g., meal time and amount variations; and 3) the corresponding convergence should be fast enough, for example, an algorithm that cannot converge within 30 days may be deemed useless. In our scheme, the ESC method uses the gradient estimated by continuously modulating and de-modulating the clinical risk index calculated from CGM measurements, to steer the zone towards the optimum. The clinical risk index is a combination of glycemic penalty index, which assigns the daily blood glucose excursions with different risk penalties, together with zone boundary regularizers to shape intermediate points. A relative clinical risk index is developed to enhance the proposed method's applicability to accommodate large variations between T1D patients. To improve the robustness against real-life uncertainties, the feedback gain and the magnitude of the dither signal (sinusoidal perturbation) are carefully designed in a decay form. In-silico trials illustrate the proposed method's excellent performance and robustness, and show the superiority over the constant fixed zone of [80,140] mg/dL.

D. Organization

In Section II a concise overview of the applied zone-MPC controller and clinical glycemic risk index is provided. In Section III we give a brief introduction to the theory of extremum seeking control. Section IV presents the zone adaptation strategy for the AP system with zone-MPC controller. In Section V we present the in-silico trial results. A summary is given in Section VI.

II. PRELIMINARY SETUP

This section comprises two parts: the first part is to briefly introduce the zone-MPC controller used; the second part is to discuss the clinical risk index - *relative regularized glycemic penalty index* (rrGPI).

A. Zone-MPC

The zone-MPC controller minimizes the cost of the predicted blood glucose excursion from the blood glucose target zone over a finite horizon, and implements the first element of the optimal solution. The controller used is based on reference [13] with simplifications (not using periodic zone) to focus on the effect of zone selections. At every time t , the controller solves

$$\min_{u_0, u_1, \dots, u_{N_u-1}} J_{\text{MPC}}(\hat{x}_t, \{u_0, \dots, u_{N_u-1}\})$$

with the cost function

$$J_{\text{MPC}}(\cdot, \cdot) = \sum_{j=1}^{N_y} z_j^2 + \sum_{j=0}^{N_u-1} \left[\hat{R}_{\max}\{u_j, 0\}^2 + \check{R}_{\min}\{u_j, 0\}^2 \right]$$

and subject to

$$x_{j+1} = f(x_j, u_j) \text{ with } x_0 = \hat{x}_t \quad 1a$$

$$y_j = h(x_j) \quad 1b$$

$$z_j = \begin{cases} y_j - \bar{b}_k & y_j > \bar{b}_k \\ \underline{b}_k - y_j & y_j < \underline{b}_k \\ 0 & \text{otherwise} . \end{cases} \quad 1c$$

$$0 \leq u_j + u_{\text{BASAL},j} T \leq u_{\max} \quad 1d$$

$$u_j \leq \bar{u}_{\text{IOB}} \quad 1e$$

Here (1a) and (1b) represent the model of insulin-glucose dynamics with sample-period of 5 min. $\hat{x}_t$ is the model state estimated from the most recent CGM measurements. uj is the predicted insulin deviation from basal every sample-period $T=5$ min. yj is the deviation of glucose from the blood glucose steady-state of 110 mg/dL, and zj is the corresponding excursion from the zone defined by $\bar{b}_k$ and $\underline{b}_k$, where the subscript k denotes the k -th day. N_y and N_u are the prediction horizon and control horizon, respectively. $\hat{R}$ and $\check{R}$ are weights imposed on the control input to tune the controller's responses to hyperglycemia and hypoglycemia. In (1d), u_{BASAL} [U/h] is the basal delivery rate, and u_{max} is the maximum bolus size CSII is allowed to deliver. The *insulin on board* (IOB) constraint is implemented via (1e). The IOB constraint is based on insulin delivery history, and is introduced to prevent insulin over-delivery. For the details of the model functions f , h in (1a), (1b), IOB constraints and parameters selection, the reader is referred to [13]. At each step, only the first entry u_0 is actuated by the pump.

B. Cost function

In this work we employ the *glycemic penalty index* (GPI) [37] (details later) as a metric for the extremum seeking algorithm to optimize against. The GPI [37] has proven useful for quantifying glycemic control performance, and captures the “quality” of a glucose trajectory in a scalar, i.e., a metric that is straightforward to interpret algorithmically ($A < B$ implies A is better than B). However, there exist numerous alternative methods to quantify the performance of glucose control, or to quantify the risk of a glucose trajectory. *Hemoglobin A1c* (HbA1c) is a common indicator of glucose risk in clinical practice. However, HbA1c is an indicator of average glucose levels over roughly 3-month timescales [38]. Thus, HbA1c fails to capture glucose risk and control performance over time-scales of interest, which in this work are days and weeks. The times in glucose ranges (e.g., the range [70,180] mg/dL, < 60 mg/dL, > 300 mg/dL) are another method popular in clinical care. However, to be insightful time in range analyses yield not one metric but a collection of numbers that typically require further analysis by clinicians to yield actionable conclusions, and are thus deemed unsuitable for use in an extremum seeking algorithm. The *high blood glucose index* (HBGI) and *low blood glucose index* (LBGI) [39] are useful, but these are two metrics to separately quantify hyperglycemia and hypoglycemia risk. The *average daily risk range* (ADRR) [40] was proposed for sparse measurements, and is not appropriate for the rich glucose data that the method sought after in this paper is expected to operate on. The *blood glucose risk index* (BGRI) [41] is often used for post hoc controller performance evaluation and could potentially be used as an alternative metric to the GPI. However, the BGRI employs a transform from the glucose space to risk space that is more complicated than the GPI, so for the purposes of this initial investigation into the use of extremum seeking control for algorithmic adaptation of the zone definitions in zone-MPC the authors focused on the GPI.

The GPI employs a penalty function in the form of $\phi(\chi) = a(\chi - \beta)^\gamma$. One needs to find 6 critical points to define the two branches of the GPI penalty function - penalties for hyperglycemia and hypoglycemia (see Fig. 1). Clinically, the range [80,140] mg/dL is deemed the highly desirable zone. The range [70,180] mg/dL is the safe zone with a GPI

penalty equal to 23 ([37] treated blood glucose with GPI less than 23 as safe). The range below 50 mg/dL or above 300 mg/dL is high risk. Then, the mapping from measured glucose g_M to GPI penalty $\varphi(g_M)$ is

$$\varphi(g_M) = \begin{cases} 1.0567(80 - g_M)^{1.3378} & g_M \in [50, 80] \\ 0 & g_M \in (80, 140] \\ 0.4607(g_M - 140)^{1.0601} & g_M \in (140, 300] \\ 100 & \text{otherwise} \end{cases}$$

Fig. 1 depicts the penalty functions of GPI and BGRI. Given a sequence of n glucose measurements $\{g_{M1}, g_{M2}, \dots, g_{Mn}\}$, the GPI glycemic risk index is defined as

$$\text{GPI} = \frac{1}{n} \sum_{i=1}^n \varphi(g_{M,i}).$$

In this work the GPI is calculated daily and the GPI of the k -th day is denoted $\text{GPI}(k)$. Recalling that $\bar{b}_k$ and $\underline{b}_k$ are the upper bound and lower bound of the k -th day, the *regularized GPI* (rGPI) for the k -th day is defined as

$$\text{rGPI}(k) = \frac{\text{GPI}(k)}{100} + \underbrace{\lambda_u \frac{(\bar{b}_k - 180)^2}{120^2} + \lambda_l \frac{(\underline{b}_k - 110)^2}{50^2}}_{\text{regularizer}},$$

where the last two terms are called regularizers, which are introduced to reduce the number of local minima [42]. For instance, given a sufficiently large λ_u , the cost function is locally dominated by $(\bar{b}_k - 180)^2$, which is a convex function. The regularizers are also utilized to prevent $\bar{b}_k$ and $\underline{b}_k$ reaching a clinically meaningless value, which may result in

hypoglycemia. The regularizer method is simpler than confining the yielded boundaries into a pre-determined interval whose tuning has a larger effect on the final solution and needs more empirical insights. $\bar{b}_k$ is upper bounded by 180 mg/dL, which is the upper limit of the safe range, and lower bounded by 60 mg/dL, which is usually considered to be hypoglycemia. Thus, this gives an estimate of the allowed range for $\bar{b}_k$, whose width is $180 - 60 = 120$ mg/dL. $\underline{b}_k$ is upper bounded by 110 mg/dL, which is typically considered to be a very desirable blood glucose value. The lower bound 60 mg/dL is also shared by $\underline{b}_k$.

Similarly, the estimate for $\underline{b}_k$'s range width is 50 mg/dL. The regularizers are normalized by their own allowed range. The weights $\lambda_u \in [0, 1)$ and $\lambda_l \in [0, 1)$ facilitate personalization of the ESC algorithm to the patient. However, for simplicity, in this paper, we use $\lambda_u = 0$ and $\lambda_l = 0.1$.

Even with the same zone, the corresponding GPI and rGPI vary from person to person. So does the initial value for ESC - rGPI(1). A large initial value may make the adaptation

process so aggressive that an undesirable zone results, which may lead to severe clinical consequences. A possible approach to resolve this issue is to personalize the ESC loop by individually tailoring the gains to the patients. This approach is cumbersome and inefficient. Thus, we define its relative version rrGPI as

$$\text{rrGPI}(k) = \frac{\text{rGPI}(k)}{\text{rGPI}(1)}.$$

It is introduced to improve our method's applicability to accommodate large variabilities within T1D population, by making the ESC index agnostic to the properties of the patient's initial glucose outcomes. Consequently, the ESC method starts with the same initial value (of unity) for every patient.

III. EXTREMUM SEEKING CONTROL

To the best of the authors' knowledge, this is the first time ESC is applied to control of artificial pancreas. Therefore, this section gives a brief introduction to the ESC's elements.

Fig. 2 illustrates the ESC's basic mechanism. In subplot (a), the variable to be optimized is θ ($\theta(k) = [\bar{b}_k, b_k]^\top$ in this study), $J(\theta)$ is a static mapping of θ , and $\frac{z-1}{z+h}$ is a high-pass filter. Using a Taylor expansion, $J(\theta)$ can be rewritten as

$$J[\theta(k)] = J[\bar{\theta}(k) + \sin(\omega k)] \approx J[\bar{\theta}(k)] + \nabla J|_{\bar{\theta}} \sin(\omega k).$$

Thus, the signal after high-pass filter denoted as a is

$$\sigma \approx \nabla J|_{\bar{\theta}(k)} \sin(\omega k).$$

It follows that the signal after de-modulation is

$$\alpha \nabla J \sin^2(\omega k) = \frac{\alpha}{2} \nabla J|_{\bar{\theta}(k)} [1 - \cos(2\omega k)].$$

Now the quantitative relation can be constructed as

$$\bar{\theta}(k+1) = \bar{\theta}(k) + \frac{\alpha}{2} \nabla J|_{\bar{\theta}(k)} [1 - \cos(2\omega k)]. \quad 2$$

By using the averaging technique in nonlinear system analysis [44], the obtained highly oscillatory system (2) can be understood by

$$\bar{\theta}(k+1) = \bar{\theta}(k) + \frac{\alpha}{2} \nabla J|_{\bar{\theta}}. \quad 3$$

This demonstrates that ESC is essentially a gradient descent optimization method. Fig. 2 depicts ESC in a graphical manner. We perturb θ in the neighborhood of the minimizer θ^* of an unknown cost function $J(\theta)$. If the input $\theta_I(k)$ is perturbed in the left branch, the output $J(\theta_I(k))$ and $\theta_I(k)$ are out of phase, the average of their product is negative. Contrarily, if the perturbation is carried out in the right branch, $J(\theta_2(k))$ and $\theta_2(k)$ are in phase, with a positive average of their product. The ESC method thereby drives the manipulated variable θ towards the minimum θ^* [23], [43].

IV. Zone adaption for closed-loop AP

The updating law of the zone adaptation used in this paper is as follows:

$$\zeta(k) = -h\zeta(k-1) + J(\theta(k-1)) \quad 4a$$

$$\hat{\theta}_i(k+1) = \hat{\theta}_i(k) - \gamma_i(k)\alpha_i(k)\sin(\omega_i k + \phi_i) \times [J(\theta(k)) - (1+h)\zeta(k)] \quad 4b$$

$$\bar{\theta}_i(k+1) = \hat{\theta}_i(k+1) + \alpha_i(k)\sin(\omega_i(k+1) + \phi_i) \quad 4c$$

$$\theta(k+1) = \mathbb{P}[\bar{\theta}(k+1)] \quad 4d$$

Here the scalar $\zeta(k)$ corresponds to an intermediate variable of the high-pass filter in Fig. 3. The subscript i denotes a vector's i -th component. When $i=1$, the component is related to the upper bound, particularly $\theta_1(k)$ is the upper bound of the k -th day. Note from Fig. 3 that the proposed ESC scheme operates daily, at a slower update rate than that of the control actions. Fast physiological variations are handled by the MPC strategy rather than the zone adaptation, and their effects on bounds are averaged out in the calculation of rrGPI. Slow variations would be picked up by the ESC mechanism. The proposed scheme is also amendable to account for the diurnal variability, possibly by parametrizing the zone as a time-varying function described by a few parameters, e.g., piecewise linear function in time. However, it is beyond the scope of this paper. Similarly, $i=2$ relates to the lower bound. The operator $\mathbb{P}$ in (4d) is to ensure the physical feasibility that the upper bound ($\bar{\theta}_1 = \bar{b}_k$ in (1c)) is greater than the lower bound ($\bar{\theta}_2 = \underline{b}_k$ in (1c)). The operator is defined as

$$\mathbb{P}[\bar{\theta}] = \begin{cases} [\bar{\theta}_2, \bar{\theta}_1]^T & \bar{\theta}_1 < \bar{\theta}_2, \\ \bar{\theta} & \text{otherwise,} \end{cases}$$

and enforces that the upper bound $\theta_1(k)$ is greater than the lower bound $\theta_2(k)$. The modulation frequency ω_i is usually chosen to lie between 0 and π in the ESC literature, e.g.,

[45]. In our problem, $\omega_1 = 0.64\pi$ and $\omega_2 = 0.8\pi$. The initial value of the high-pass filter is $\zeta(0) = 0.68$. The parameter of the high-pass filter h has to be $0 < h < 1$. Here we choose $h = 0.2$. Generally, the algorithm in (4) with a larger h has a slower convergence, but more robustness against the measurement noise $\xi(k)$, because the system (4a) has a pole closer to the unit circle in the complex plain and a stronger averaging effect. In contrast, a smaller h results in a faster convergence but increased sensitivity to the measurement noise. $\hat{\theta}(0)$ is initialized as $[180, 70]^T$ mg/dL, a clinically acceptable zone. This choice with the existence of regularizer prevents $\text{rGPI}(1)$ from reaching zero, which would result in an ill-definition of $\text{rrGPI}(k)$. Intuitively, the optimal upper bound would be lower than 180 mg/dL. Thus, its modulation phase φ_1 is designed as 0 to have a negative search direction in the beginning. The modulation phase of lower bound φ_2 is selected as π to give a positive initial search direction to prevent unnecessary hypoglycemia.

The feedback gain $\gamma_i(k)$ and the perturbation amplitude $\alpha_i(k)$ are the two most important tuning parameters in the proposed method. However, they play different roles in the optimization performance and convergence. Generally, the increase of $\gamma_i(k)$ and $\alpha_i(k)$ boosts the convergence rate but results in a large variation around the limit solution. In this application, considering the asymmetry of glycemic intervals, the amplitude of perturbation on the upper bound $\alpha_1(k)$ should be chosen larger than that on the lower bound $\alpha_2(k)$. In the classic ESC, $\alpha_i(k)$ should be large enough to allow the gradient information extractable from the noises. In this sense, $\alpha_1(k)$ and $\alpha_2(k)$ are selected to be 2 and 1, respectively. In order to formulate the first effective gradient estimate (requiring at least two rrGPI measurements), $\gamma_i(k)$ are selected to steer $\theta(1)$ close to $[140, 80]$ mg/dL to measure rrGPI therein, because the zone $[80, 140]$ mg/dL is clinically plausible. The corresponding values of $\gamma_i(k)$ are given in Table 1. Moreover, it should be remarked that sufficiently large values of $\alpha_i(k)$ may make the classic ESC pass through a local minimum [21]. In other words, large values of $\alpha_i(k)$ help the method converge to a global minimum. Considering the classic ESC, achieved by employing $\gamma_i(k) = \gamma_i, \alpha_i(k) = \alpha_i$ as constants independent of k , given a pair γ_i, α_i that stabilizes the entire system, if one doubles γ_i and halves α_i in (4b), this new $(\gamma_i^\wedge, \alpha_i)$ pair may not result in ESC convergence. On the other hand, halving γ_i and doubling α_i usually results in a stable pair [23].

Note that in reality the variations of meal time and meal size are large. These uncertainties may compromise the stability of the ESC system. An alternative to improve the robustness against these uncertainties is the ESC scheme with $\alpha_i(k)$ and $\gamma_i(k)$ decaying with k . This *decay ESC* scheme basically cuts off the feedback update and perturbation (becomes open loop), terminating the zone adaptation for a sufficiently large k . An interesting question that follows from this is under what conditions the limit point becomes the optimal solution to J . The theorem in [26] answered this question.

Theorem 4.1: [26] Define $\varepsilon_i(k)$ as the product of $\gamma_i(k)$ and $\alpha_i(k)$. If the following conditions are satisfied, then $\theta(k)$ will converge to $\theta^* := \arg\min J(\theta)$ almost surely:

C1) the decreasing sequences $\epsilon_i(k)$, $\alpha_i(k)$ satisfy that $\epsilon_i(k) > 0$, and $\alpha_i(k) > 0$, and $\lim_{k \rightarrow \infty} \epsilon_i(k) = 0$,

$$\lim_{k \rightarrow \infty} \alpha_i(k) = 0;$$

C2) the two sequences are also subject to $\sum_{k=1}^{\infty} \epsilon_i(k) \alpha_i(k) = \infty$

C3) the sequence $\epsilon_i(k)$ needs to meet the condition $\sum_{k=1}^{\infty} \epsilon_i^2(k) < \infty$

The values of $\gamma_i(k)$ and $\alpha_i(k)$ for the classic ESC, and also the decay ESC studied in this paper, selected according to Theorem 4.1, are tabulated in Table 1. The product $\epsilon_i(k)$ is $O(k^{-0.75})$, the summation of whose squared sequence $O(k^{-1.5})$ is bounded. The sequence $\epsilon_i(k) \alpha_i(k)$ is $O(k^{-1})$, whose summation is unbounded. Hence, the conditions C1-C3 are satisfied for the selection in Table 1. The decaying of feedback gain $\gamma_i(k)$ and perturbation signal $\alpha_i(k)$ is expected to slow down the convergence of the decay ESC. To make the convergence rate of the decay ESC comparable to the classic ESC, the initial values of $\gamma_i(k)$ are tuned large by a factor of 10/7. It should be remarked that a slowly decaying sequence of $\gamma_i(k)$ with sufficiently large initial values may be helpful for avoiding local minima, as pointed out in [21] and analyzed in [46].

V. IN-SILICO TRIALS

This section is divided into two parts: the first part studies the proposed decay ESC method for the standard scenario; the second part tests the proposed method's robustness with respect to two types of uncertainties - the variations of meal size and meal time. The in-silico trials in this paper are conducted using the US *Food and Drug Administration* (FDA) accepted academic version of the Universities of Virginia/Padova (UVA/Padova) metabolic simulator [47]. The simulations include additive, stochastic CGM noise. Note that the simulator's limitation is that it only allows a constant basal profile.

A. Standard scenario

The *standard scenario* is defined as consuming three meals of size M grams of carbohydrates (gCHO) every day at 6:30, 12:00, 18:00, where $M \in \{60, 90\}$ is employed to model small and large meals, respectively. The in-silico trials have a duration of 30 days. Fig. 4 shows the results of the decay ESC method on Subject 1 in the simulator. In each subplot, the blue solid line represents the blood glucose or insulin dosage, the green area depicts the zone used by zone-MPC, and the red bar is the feedforward insulin bolus dosage when meals are announced. The blood glucose plot in every subplot of Fig. 4 shows that the blood glucose trajectory is shifted downward towards the highly desirable zone [80, 140] mg/dL, and the zone converges quickly, within 5 days. The insulin dosage plots show that more insulin is delivered as the upper bound is lowered, which is consistent with the glucose results. Comparing subplots (a), (b) with (c), (d), the improvements for unannounced meals are more distinguishable than those for announced meals. The explanations for this phenomenon are two-fold. First, the glucose dynamics in announced meals are dominated by the feedforward control - the bolus dosages, and the magnitudes of the feedback and the feedforward actions

are not on the same scale. Second, the IOB constraint suppresses the feedback actions longer after the bolus dosage in the announced meals, thus there is less room for performance improvement by adjusting zone boundaries in the announced meals.

Table 2 summarizes the sought final zone for the standard scenario. The final zone for each subject is calculated by averaging the zones during Days 26–30, since 5 days is roughly two periods for the selected dither signal. There are three observations to be made from Table 2. First, the upper bound is much more sensitive than the lower bound to the changes of meal size. Second, the upper bound increases, and the lower bound decreases but less significantly, as the meal size

These three observations are confirmed again in the meal size spectrum test shown in Fig. 5, in which we investigate the relation between the meal sizes and zone boundaries. In the meal size spectrum test, the meal size ranges from 10 gCHO to 120 gCHO; this range covers snacks (tiny meals), normal meals, and festival meals (enormous meals). In Fig. 5, the linear fitting to the data points is acceptable, particularly the upper bound's fitting, whose R^2 (quantitatively describing linear fitting performance) exceeds 0.7 for both announced and unannounced meals. Interestingly, it is suggested that the zone [80,120] mg/dL may be a wiser option compared to the current one [80,140] mg/dL. Compared to the upper bound's fitting, the smaller slope of the lower bound's fitting arises for two reasons. First, the change of meal size does not have direct influence on the lower bound. Second, the imposed regularizer plays the role of a soft constraint, making the lower bound insensitive to the meal size change. The two slopes in the case of unannounced meals are more distinguishable than those in the case of announced meals. This observation matches our expectation. The longer restriction, induced by IOB constraints, on the insulin delivery after the bolus dosage in the case of announced meals makes changing the bounds less effective. The reason for the positive correlation between the upper bound and meal size is that it is much safer with respect to hypoglycemia to increase the upper bound for large meals. As the meal size is increased, if the upper bound maintains the same value, or even decreases, more insulin is delivered, subsequently increasing the hypoglycemia risk. The linear fitting in the case of announced meals is above that in the case of unannounced meals over the entire meal-size spectrum. This is due to the fact that for the case of announced meals more insulin (feedforward bolus) has been delivered into the body, and a higher upper bound can substantially reduce the amount of insulin delivery except the bolus dosage, in order to prevent an overdose.

Fig. 6 uses the mean of ten subjects' rrGPI values to compare three ESC methods in four scenarios. The three ESC methods are classic ESC, the proposed decay ESC, and ES-ESC (*early-stopping ESC*), a decay ESC scheme that terminates adaptation after a week. All subplots show that the classic ESC and the decay ESC achieve an almost monotonically decreasing rrGPI. Compared to the decay ESC, the classic ESC decreases more slowly initially, and outperforms the decay ESC eventually, because the feedback gain of the classic ESC is smaller in the beginning and becomes greater than that of the decay ESC due to the decay effect. Even though the classic ESC performs better than the decay ESC ultimately, it will be shown in the next subsection that the classic ESC is so sensitive to uncertainties that it may not be safely deployable in practice. The results of the decay ESC and the ES-ESC

indicate that there is only a marginal benefit for continuing adaptation. This observation suggests that the zone after one week of adaptation is very close to the final. This is important because it is difficult in practice for T1D patients to maintain a highly repeatable daily routine, particularly meal plan, in the long term. In fact, it suggests an iteration-based termination criterion. There exist various alternative termination criteria in the optimization literature, such as threshold criterion, which terminates the optimization when the difference between two consecutive costs is less than the threshold. This method cannot be applied here, because each patient requires an individually tailored threshold, which may not be practically feasible to characterize.

In Table 3, we calculate and compare the time-in-range percentages during the Days 26–30 (two periods of the dither signal) for the proposed decay ESC method and the clinical intuition derived constant zone [80,140] mg/dL, which has been tested in clinical trials [12]–[14]. The p-values are calculated for the two indices - [70,180] mg/dL time-in-range percentage and BGRI, which are of great importance in practice. The decay ESC performs better than the zone [80,140] mg/dL with respect to almost every index. The proposed method increases by at most 3% and at least 0.5% (p-value < 0.05) in the range [70,180] mg/dL. Similar improvements are achieved for the range [80,140] mg/dL as well. The proposed decay ESC method reduces the BGRI by at most 9.6% (60 gCHO unannounced meals, p-value < 0.05) and at least 1.3% (90 gCHO announced meals). The closer performance on BGRI for 90 gCHO announced meals is understandable, because in this scenario the optimal bounds are very close to [80,140] mg/dL (see Fig. 5a). Overall, it can be concluded that the proposed decay ESC method is effective and advantageous compared to the constant zone [80,140] mg/dL with a slight increase of the hypoglycemic risk.

B. Uncertainty scenarios

This section focuses on testing the robustness of the decay ESC method for the uncertain scenarios. There are two scenarios that will be discussed - uncertain meal size and uncertain meal time. The uncertain meal size scenario consists of three meals per day at exactly 6:30, 12:00, 18:00, where the size of each meal is subject to a uniform distribution [0.8M, 1.2M]. That means the variation on meal size is $\pm 20\%$. The uncertain meal time scenario is the standard scenario in which the meal time variations are drawn from a uniform distribution [-2 hr, 2 hr]. Fig. 7 shows the comparisons of the decay ESC and the constant zone [80,140] mg/dL for both the uncertain scenarios with the two different meal sizes. The proposed decay ESC method achieves a lower mean GPI in every subplot. There are larger variations in the uncertain meal size scenario. This is understandable, because the change of meal size has more direct and larger effects on the blood glucose trajectory, or equivalently the clinical index GPI.

Instead of the clinical risk index GPI, Table 4 contains the performance of decay ESC by the blood glucose time-in-range percentages. For 60 gCHO meals, compared to the fixed zone [80,140] mg/dL, the decay ESC increases the [70,180] mg/dL time-in-range percentage by about 3% and 1% (p-value < 0.05) for the case of unannounced and announced meals, respectively, both in the uncertain meal size and meal time scenario. Similar observations can be made for 90 gCHO meals. The increment is approximately 2% and 0.7% (p-value <

0.05) for unannounced and announced meals, respectively. Similar arguments used previously apply to explain the greater performance improvement for unannounced meals: the dominance of feedforward control (bolus dosage) on the glucose dynamics. Furthermore, it is also noted that the hyperglycemia risk (the $(180, +\infty)$ mg/dL and $(250, +\infty)$ mg/dL time-in-range percentages) is reduced significantly by the decay ESC. The cost for these improvements is the slight increase of hypoglycemia risk for the large unannounced meals, e.g., less than 0.2% increase in the $(0, 70)$ mg/dL time-in-range percentage. For announced meals, the proposed method reduces the BGRI by at most 6.7% (p-value < 0.05). The proposed method is more effective for unannounced meals; it reduces the BGRI by at most 9.7% (p-value < 0.05) and at least 4.8% (p-value < 0.05).

Fig. 8 depicts the zone boundaries' 30-day trajectories of the ten subjects for the decay ESC in both the uncertain meal size and meal time scenarios. The variations of the upper bound trajectories are larger in the uncertain meal size scenario than in the uncertain meal time scenario, because the effect of meal size is larger than timing on blood glucose, and so does the index GPI. In spite of the existence of uncertainties on meal size or meal time, the upper bound trajectories eventually reach a close proximity of the final bound of the standard scenario.

This result is quantitatively verified in Table 5, which employs the error of final bound to compare the decay ESC and the classic ESC in the uncertain meal size scenario. The error of the final bound is defined as the absolute difference between the mean of the final bounds in the uncertain scenario and the standard scenario (cf. Table 2). Mathematically, it is $\left| \sum_{k=26}^{30} b_{k,a} - b_{k,b} \right| / 5$, where $b_{k,a}$ is either $\bar{b}_k$ or $\underline{b}_k$ for the decay ESC in the standard scenario, and $b_{k,b}$ is $\bar{b}_k$ or $\underline{b}_k$ for the corresponding method in the uncertain scenario. It shows that there is a significant error in the final bound for the classic ESC, while that of the decay ESC is uniformly small. Such a significant error of final bound is undesirable and risky, because it may induce hypoglycemia. For example, in the scenario of unannounced 90 gCHO with uncertain meal size, the classic ESC achieves the mean percentage time in the interval $(0, 60)$ mg/dL of 0.27% (compared to that of decay ESC, which is 0 in Table 4), indicating the occurrence of severe hypoglycemia. The sensitivity of the classic ESC arises from the existence of the constant feedback gain, which admits continuous updating on the zone boundaries based on the calculated rrGPI index. Besides, as mentioned before, rrGPI or equivalently GPI is sensitive to the meal size change. Therefore, it subsequently results in the sensitivity of classic ESC to the meal size uncertainties.

VI. SUMMARY

In this paper an ESC based zone adaptation method that can converge to the optimal zone for a zone-MPC strategy in terms of a clinical glycemic risk index - rrGPI was proposed. The proposed decay ESC scheme steers the bounds very close to the optimal ones within one week of adaptation. The in-silico trials on 10 virtual subjects demonstrated that the proposed method yields "optimized" zones that are different enough from one another to indicate that personalization is, as many would expect, important. Crucially, in this paper we demonstrate that the task of personalized zone optimization can be automated, driven only by the

measurements of glucose outcomes, and does not rely on cumbersome physiological measurements, or clinical insight and rules of thumb.

In the future, it is of great value to investigate the effects of exercise on the final zone using the proposed method. Other uncertain factors, such as routinely skipped meals and irregular exercise, are also worth investigation in future ESC studies. In this preliminary in-silico study the uVA/Padova simulator is used, and the simulator has time-invariant parameters and dynamics. Hence, the decaying dither signal demonstrates that an optimal value can be reached provided that C1-C3 in Theorem 4.1 are satisfied. However, in practice this would need to be re-set (or introducing other advanced techniques) whenever a major change in lifestyle (or subject) is performed, e.g., after initial purchase.

Table 3: Blood glucose time-in-range percentages, HBGI, LBGi and BGRI for the decay ESC and the fixed zone [80,140] mg/dL during Days 26–30.

Table 4: Blood glucose time-in-range percentages, HBGI, LBGi and BGRI for the decay ESC and the fixed zone [80,140] mg/dL in the uncertain scenarios during Days 26–30. UMS: uncertain meal size, and UMT: uncertain meal time.

Table 5: Error of final bound for the decay ESC and classic ESC in the uncertain meal size scenario.

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Fig. 1:
Penalty functions of GPI and BGRI

Fig. 2:

Illustration of the mechanism of extremum seeking control: the top subplot (a) shows the closed loop of the classic extremum seeking; the bottom subplot (b) delivers a graphical explanation [43].

Fig. 3:

Schematic of the zone-adaptation closed loop: in reality, J , the rrGPI index calculated from CGM measurements, is a function of $\theta(k)$ and $d(k)$, i.e., $J(\theta(k), d(k))$. $d(k)$ represents the disturbance, comprising all the information of meal-time variation, uncertainty of meal sizes, exercise effects, stress, etc. To simplify the analysis, we approximate $J(\theta(k), d(k))$ as $J(\theta(k)) := J(\theta(k), 0) + \xi(k)$, which is obtained by the first-order Taylor expansion on the second argument $d(k)$. $J(\theta(k))$ is the rrGPI corrupted by “noise” $\xi(k)$, which is introduced only for conceptual analysis, assumed as zero-mean noise and denoted by a dashed line. $J(\theta(k))$ sequentially goes through a high-pass filter parameterized by h , demodulator, and a low-pass filter, yielding $\hat{\theta}(k)$. $\hat{\theta}(k)$ is perturbed sinusoidally and processed by $\mathbb{P}$ operator. The resulting $\theta(k)$ is sent to the zone-MPC controller. The system in the dash-dotted box is operated every 5 minutes, and the outer loop is updated daily. This achieves the *time-scale separation*, a key argument for stability of the entire ESC loop [19]. increases. Third, the upper bound is higher in the case of announced meals than in the case of unannounced meals.

Fig. 4:

Snapshots of the evolutions of blood glucose, zone, insulin dosage in a 30-day in-silico trial: (a) 60 gCHO announced meals, (b) 90 gCHO announced meals, (c) 60 gCHO unannounced meals, (d) 90 gCHO unannounced meals. The zone is updated daily. Most convergence occurs during the first week. Days 4–29 are removed to aid clarity; the changes during omitted days are not graphically discernible.

Fig. 5:

Relation between the final zone boundaries and meal size: (a) announced meals, (b) unannounced meals. Blue circle is each subject's final upper bound determined by the decay ESC, and red square is the lower bound. The blue solid line is the upper bounds' linear fitting versus meal-size, while the red solid line is the lower bounds' linear fitting. The green fill denotes the interval $[80, 140]$ mg/dL.

Fig. 6: Comparison of three ESC methods in terms of rrGPI: (a) 60 gCHO announced meals, (b) 90 gCHO announced meals, (c) 60 gCHO unannounced meals, (d) 90 gCHO unannounced meals.

Fig. 7:

GPI comparison of the decay ESC and fixed zone [80,140] mg/dL in a 30-day in-silico trial: Blue solid line represents the GPI mean of the decay ESC method, while the red solid line stands for the GPI mean of the fixed zone [80,140] mg/dL. The blue dashed line signifies the *standard error of the mean (SEM)* of the decay ESC method, and the red dashed line is for the SEM of the fixed zone [80,140] mg/dL. The downward peaks in (b)(d)(f)(h) are caused by small meal size generated by randomness. The subplots are organized as follows:

- (a) 60 gCHO announced meals with meal-time uncertainties (b) 60 gCHO announced meals with meal-size uncertainties
- (c) 60 gCHO unannounced meals with meal-time uncertainties (d) 60 gCHO unannounced meals with meal-size uncertainties
- (e) 90 gCHO announced meals with meal-time uncertainties (f) 90 gCHO announced meals with meal-size uncertainties
- (g) 90 gCHO unannounced meals with meal-time uncertainties (h) 90 gCHO unannounced meals with meal-size uncertainties

Fig. 8:

Evolution of the bounds of the decay ESC in a 30-day in-silico trial: Blue solid line represents the mean of the upper bound $\bar{b}_k$, while the red solid line stands for the mean of the lower bound $\underline{b}_k$. The blue dashed line signifies the range of the upper bound $\bar{b}_k$, and the red dashed line is for the range of the lower bound $\underline{b}_k$. The subplots are organized as follows:

- (a) 60 gCHO announced meals with meal-time uncertainties (b) 60 gCHO announced meals with meal-size uncertainties
- (c) 60 gCHO unannounced meals with meal-time uncertainties (d) 60 gCHO unannounced meals with meal-size uncertainties
- (e) 90 gCHO announced meals with meal-time uncertainties (f) 90 gCHO announced meals with meal-size uncertainties
- (g) 90 gCHO unannounced meals with meal-time uncertainties (h) 90 gCHO unannounced meals with meal-size uncertainties

Table 1:Selections of $-\gamma_i(k)$ and $\alpha_i(k)$

	Classic ESC	Decay ESC
$\gamma_1(k)$	78	$78/0.7k^{0.5}$
$\gamma_2(k)$	28	$28/0.7k^{0.5}$
$\alpha_1(k)$	2	$2/k^{0.25}$
$\alpha_2(k)$	1	$1/k^{0.25}$

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Table 2:

Final zone for the standard scenario (Days 26–30).

Scenario Meal size (gCHO)	Announced						Unannounced					
	60			90			60			90		
	Mean	Max.	Min.	Mean	Max.	Min.	Mean	Max.	Min.	Mean	Max.	Min.
Upper bound (mg/dL)	120.1	126.6	111.1	121.7	130.9	121.7	112.1	131.5	103.8	120.0	129.8	113.3
Lower bound (mg/dL)	79.4	80.5	77.1	79.2	80.0	78.3	80.2	81.7	77.1	79.3	80.1	78.0

Table 3:

Blood glucose time-in-range percentages, HBGI, LBGI and BGRI for the decay ESC and the fixed zone [80,140] mg/dL during Days 26–30.

Scenario		Announced				Unannounced			
Meal size	(gCHO)	60		90		60		90	
Method		Decay ESC	[80,140]	Decay ESC	[80,140]	Decay ESC	[80,140]	Decay ESC	[80,140]
BG [mg/dL] % time	€[80, 140]	63.20	61.27	58.45	57.97	52.05	48.75	47.86	45.71
	€[70, 180]	93.19	92.32	80.06	79.64	71.14	68.06	62.26	60.68
	< 80	0	0	0	0	0.02	0	0.62	0.56
	< 70	0	0	0	0	0	0	0.2	0
	< 60	0	0	0	0	0	0	0	0
	> 180	6.81	7.68	19.94	20.36	28.85	31.94	37.53	39.32
	> 250	0	0	0.24	0.32	2.45	3.40	13.05	14.14
mean HBGI		2.13	2.29	3.51	3.57	5.14	5.70	8.61	9.15
mean LBGI		0.05	0.03	0.12	0.11	0.06	0.05	0.19	0.16
mean BGRI		2.18	2.32	3.63	3.68	5.20	5.75	8.80	9.31
p-value of BG-€[70, 180]		0.0275		0.0209		0.0019		0.0084	
p-value of mean BGRI		0.0018		0.1789		0.0006		0.0002	

Table 4:

Blood glucose time-in-range percentages, HBGI, LBGI and BGRI for the decay ESC and the fixed zone [80,140] mg/dL in the uncertain scenarios during Days 26–30. UMS: uncertain meal size, and UMT: uncertain meal time.

(a) Announced meals									
Scenario	60 gCHO UMS		60 gCHO UMT		90 gCHO UMS		90 gCHO UMT		
Method	Decay ESC	[80,140]	Decay ESC	[80,140]	Decay ESC	[80,140]	Decay ESC	[80,140]	
BG [mg/dL] % time	€[80, 140]	63.29	61.31	63.95	61.79	58.31	57.54	58.85	57.77
	€[70, 180]	93.49	92.55	93.71	92.91	80.87	80.25	81.08	80.11
	< 80	0	0	0	0	0	0	0	0
	< 70	0	0	0	0	0	0	0	0
	< 60	0	0	0	0	0	0	0	0
	> 180	6.51	7.45	6.29	7.09	19.13	19.75	18.93	19.89
	> 250	0	0	0	0	0.50	0.34	0.17	0.24
mean HBGI	2.09	2.24	2.05	2.22	3.43	3.50	3.36	3.36	3.48
mean LBGI	0.05	0.03	0.05	0.03	0.11	0.10	0.14	0.14	0.12
mean BGRI	2.14	2.27	2.10	2.25	3.54	3.60	3.50	3.50	3.60
p-value of BG €[70, 180]	0.0260		0.0417		0.0388		0.0642		
p-value of mean BGRI	0.0102		0.0103		0.1102		0.0274		
(b) Unannounced meals									
Scenario	60 gCHO UMS		60 gCHO UMT		90 gCHO UMS		90 gCHO UMT		
Method	Decay ESC	[80,140]	Decay ESC	[80,140]	Decay ESC	[80,140]	Decay ESC	[80,140]	
BG [mg/dL] % time	€[80,140]	51.83	48.79	51.78	48.84	48.42	46.24	48.08	46.28
	€[70,180]	71.90	68.91	70.88	67.70	62.56	60.91	61.98	60.34
	< 80	0.11	0.01	0.06	0	0.34	0.26	0.67	0.44
	< 70	0	0	0	0	0.05	0.02	0.25	0.06
	< 60	0	0	0	0	0	0	0	0.02
	> 180	28.10	31.09	29.12	32.30	37.39	39.07	37.78	39.60

(a) Announced meals									
Scenario	60 gCHO UMS		60 gCHO UMT		90 gCHO UMS		90 gCHO UMT		90 gCHO UMT
	Decay ESC	[80,140]	Decay ESC	[80,140]	Decay ESC	[80,140]	Decay ESC	[80,140]	
	> 250	2.55	3.33	2.51	3.46	12.97	13.90	13.15	14.45
mean HBGI	5.04	5.57	5.17	5.74	8.49	8.95	8.62	9.17	
mean LBGI	0.06	0.06	0.06	0.05	0.17	0.15	0.21	0.17	
mean BGRI	5.10	5.63	5.23	5.79	8.66	9.10	8.83	9.34	
p-value of BG-€[70, 180]	0.0023	0.0013	0.0016	0.0039					
p-value of mean BGRI	0.0010	0.0006	0.0002	0.0002					

Table 5:

Error of final bound for the decay ESC and classic ESC in the uncertain meal size scenario.

Scenario	Announced				Unannounced			
	60		90		60		90	
	Decay ESC	Classic ESC	Decay ESC	Classic ESC	Decay ESC	Classic ESC	Decay ESC	Classic ESC
Upper bound mean error	1.78	16.7	5.37	11.71	1.53	16.49	2.29	6.74
Lower bound mean error	1.23	9.98	1.64	10.13	1.29	7.73	1.42	8.21