Long-Term Diabetes Prevention via Physical Activity: An Output-Feedback MPC Approach

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***Abstract*—Extensive clinical evidence supports the beneficial role of physical activity in delaying the progression of type-2 diabetes. However, current clinical recommendations remain largely qualitative, failing to account for the patient's evolving condition and lacking a quantitative framework for real-time, personalized prescriptions. In this letter, we propose an original model-based approach to the control of diabetes progression via physical activity, based on a control-theoretical formulation of the benefits of the exercise, leveraging a sampled-data observer-based model predictive control framework. We design the control law on a compact, widespread model of diabetes evolution, whilst the effectiveness of the proposed control strategy is tested *in silico* by closing the loop on a population of virtual subjects simulated by a different, higher-dimensional model of diabetes regulation under exercise. The validation procedure also accounts for the effect of additional non-idealities, including quantized measurements and disturbances, and clearly shows the efficacy of a suitably designed physical activity to prevent diabetes progression. To the best of our knowledge, this letter proposes for the first time an output-feedback approach leveraging physical activity for long-term glucose regulation.**

***Index Terms*—Healthcare and medical systems, predictive control for nonlinear systems, sampled-data control, diabetes.**

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I. Introduction

TYPE 2 diabetes (T2D) is a chronic disease with a rising global prevalence, entailing huge medical and social challenges due to its severe complications and growing strain on healthcare systems [1]. T2D is primarily characterized by impairments in glucose-insulin regulation, such as defective insulin secretion and reduced insulin-mediated glucose uptake [2]. Clinical evidence strongly associates T2D onset with prolonged unhealthy lifestyle habits, gradually promoting insulin resistance and beta-cell mass degradation, that ultimately results in chronic hyperglycemia and related issues. Nevertheless, since lifestyle factors are primarily involved in the onset and progression of the disease, targeted interventions – especially increased physical activity – can significantly delay or even prevent the course of the disease [3], [4], [5].

Over the past years, diabetes management has mainly focused on the short-term glucose control, giving rise to the research field of the Artificial Pancreas (AP), aiming at regulating plasma glycemia by means of insulin infusion therapies, whose design strongly benefits of advanced control methodologies allowing to properly account for model uncertainties and physiological or design constraints, such as symbolic or model predictive control [6], [7], [8]. Similarly to most AP approaches, we exploit mathematical models describing the glucose-insulin feedback loop to design the closed-loop control therapy; differently from short-term glucose-control strategies, relying on exogenous insulin administration to overcome insufficient or inefficient pancreatic insulin release, dealing with long-term therapies aiming at Type 2 diabetes prevention, we leverage the beneficial effect of exercise to design the control law. To our knowledge, quantitative therapy for controlling diabetes progression through structured physical activity remains underexplored, primarily due to the lack of suitable long-term physiological models. To address this, we recently developed a novel mathematical model [9], [10] that quantifies the cumulative long-term impact of physical activity on T2D progression. The model builds on recent studies identifying interleukin-6 (IL-6) as a key mediator of exercise-induced improvements in insulin sensitivity and beta-cell function, due to its anti-inflammatory effects. A first attempt to design a model-based closed-loop control for the long-term diabetes prevention has been presented in [11] where, however, the control law required an unfeasible complete knowledge of the model, including real-time measurements of the state variables. Here we overcome the previous drawback by proposing an output-feedback, model-based control scheme that exploits a widespread minimal model of diabetes progression [12] and adapts it to suitably account for the

physical activity. More in detail, the contribution of this letter is multi-fold: i) first, starting from the original formulation in [9], [10], we derive a Quasi-Steady-State Approximation (QSSA) of the effects of the exercise on the long-term period, encoding all the related features (intensity, duration, period) in a compact way; then ii) we endow a well-acknowledged, compact, diabetes progression model [12], with the aforementioned effect of physical activity, and we design an output-feedback model predictive control (MPC) law by suitably exploiting a nonlinear observer to provide a real-time estimation of the current state; finally, iii) to assess the effectiveness of our approach, we validate the designed control law through an extensive simulation campaign involving the closed-loop control of a population of virtual subjects simulated by means of a different, higher-dimensional model combining diabetes progression and physical activity [9], [10], also accounting for additional non-idealities. To the best of our knowledge, we provide in this letter the first output-feedback approach for long-term T2D control via physical activity.

The remainder of this letter is organized as follows: Section II introduces the modeling framework, including the extended (high-dimensional) virtual patient model and the compact model used for control purposes; Section III addresses the MPC control design based on the compact model; Section IV shows an extensive *in silico* validation on the extended model in non-ideal scenarios; Section V briefly outlines the conclusions and further developments.

II. A Compact QSSA Model Formulation for the Control Via Physical Activity

A. Extended Model

The model in [9], [10] is exploited to derive the QSSA model of the physical activity required for the control design, as well as to build the population of virtual patients on which to close the loop and test the proposed control law. We report here the equations of the model (time dependencies are omitted):

$$\dot{G} = R_0 + \frac{W}{V_g}\left(G_{prod} - G_{up}\right) - \left(E_{g0} + S_I I\right)G, \quad (1a)$$

$$\dot{I} = \frac{\beta}{V} ISR - kI - I_e, \quad (1b)$$

$$\dot{\beta} = \frac{\bar{P}(ISR) - \bar{A}(M)}{\tau_\beta}\beta, \quad (1c)$$

$$\dot{\gamma} = \frac{\gamma_\infty(G) - \gamma}{\tau_\gamma}, \quad (1d)$$

$$\dot{\sigma} = \frac{\sigma_\infty(ISR, M) - \sigma}{\tau_\sigma}, \quad (1e)$$

$$\dot{S}_I = \frac{-\left(S_I - S_{I,target}\right)\left(1 - \zeta_3 \frac{Vl}{kn_{si} + Vl}\right)}{\tau_{SI}}, \quad (1f)$$

$$\dot{Vl} = IL_6 - k_s Vl \quad (1g)$$

$$\dot{G}_{\text{prod}} = a_1 PVO_2^{\max} - a_2 G_{\text{prod}}, \quad (1h)$$

$$\dot{G}_{\text{up}} = a_3 PVO_2^{\max} - a_4 G_{\text{up}}, \quad (1i)$$

$$\dot{I}_e = a_5 PVO_2^{\max} - a_6 I_e, \quad (1j)$$

$$\dot{IL}_6 = SR \cdot\ PVO_2^{\max} - K_{IL6} \cdot IL_6, \quad (1k)$$

$$\dot{PVO}_2^{\max} = -0.8\ PVO_2^{\max} + 0.8\ u, \quad (1l)$$

where G, I, β, S_I represent respectively basal glucose concentration, basal insulin concentration, beta-cell mass and insulin sensitivity, whereas γ and σ represent the shift in glucose response and the insulin secretion capability, respectively. Eqs. (1a)–(1g) are associated with long-term dynamics and diabetes progression, whereas Eqs. (1h)–(1l) are related to the short-term dynamics of physical activity. Specifically, variable $PVO_2^{\max}$ in (1l) represents the *sovrabasal* istantaneuos oxygen consumption required by the exercise session expressed as a fraction of the maximum oxygen consumption. Exercise is represented in the model by means of the control $u(t)$ that constitutes the target level for the oxygen consumption dynamics that triggers the fast dynamics associated with physical activity and its long-term effect by means of the state variable Vl, which acts on beta cells and insulin sensitivity. Note that, in diabetes progression models, the parameter R_0 provides a net balance among different terms, including basal hepatic glucose production, zero-order glucose tissue uptake and the average daily effect of meals. For the meaning of the short-term state variables $(G_{prod}, G_{up}, I_e, IL_6)$, the model parameters and the shape of the nonlinear functions $\bar{P}(\cdot)$, $\bar{A}(\cdot)$, $\gamma_\infty(\cdot)$, $\sigma_\infty(\cdot)$, $ISR(\cdot)$, the interested reader can refer to [9], [10], [13]. In our setting, we consider a control input defined as a piecewise-constant (PWC) input representing the exercise intensity:

$$u(t) = \begin{cases} 0 & t \in [kT, (k+1)T - D_k) \\ \bar{u}_k & t \in [(k+1)T - D_k, (k+1)T) \end{cases} \qquad k \in \mathbb{N}, \quad (2)$$

where D_k and $\bar{u}_k$ are durations and activity levels, respectively, of the exercise sessions in the k-th interval, which are repeated every training period T, assumed to be constant. Finally, we assume that glucose measurements are taken at the beginning of each training period, i.e., the sequence of sampling instants is $\{kT\}_{k\in\mathbb{N}}$.

Despite the model in (1) has not been validated against data, it is capable of reasonably reproducing most of the effects of physical activity on diabetes progression and model predictions are well aligned with real-world evidence. Specifically, the model accurately captures: 1) the effect of different exercise programs at varying intensity and weekly duration, according to the well-established dose-response effect of the exercise [14]; 2) the effect of different World Health Organization (WHO) recommendations for chronic disease prevention [15]; 3) the effect of de-training, as reported in different diabetes prevention programs [16], [17].

We refer to [10] for further details, where a comprehensive description of the tuning of the model and its validity in describing the long-term effect of exercise is provided.

B. Approximately Equivalent Definition of Physical Activity

In this section we aim at approximating the control law (2) by means of an equivalent law which is constant over each period:

$$u_{eq}(t) = \bar{u}_{eq,k}, \qquad t \in \left[kT, (k+1)T\right), \qquad k \in \mathbb{N}. \quad (3)$$

To this end, we consider a quasi-steady-state approximation of the short-term dynamics (1k)–(1l) ($\dot{IL}_6 \simeq 0$, $\dot{PVO}_2^{\max} \simeq 0$), resulting in

$$IL_6(t) = \frac{SR}{K_{IL6}}\ PVO_2^{\max}(t) = \frac{SR}{K_{IL6}} u(t), \quad (4)$$

which we substitute into (1g) to obtain an approximate scalar dynamics linking directly the physical activity to its cumulative effect:

$$\dot{Vl}(t) = \frac{SR}{K_{IL6}} \cdot u(t) - k_s Vl(t). \tag{5}$$

Proposition 1 (Equivalence of the QSSA Model): Denote by Vl_{PWC} and Vl_C the solutions of Eq. (5) at the end of each training period, starting from initial condition $Vl_0 \in \mathbb{R}_{\geq 0}$, with control laws (2) and (3), respectively. If the following condition is satisfied

$$\bar{u}_{eq,k} = \frac{1 - e^{-k_s D_k}}{1 - e^{-k_s T}} \cdot \bar{u}_k \qquad \forall k \in \mathbb{N}, \tag{6}$$

then the two solutions coincide at sampling intervals, that is

$$Vl_{PWC}(kT) = Vl_C(kT), \qquad \forall k \in \mathbb{N}. \tag{7}$$

Proof: Comparing the two solutions of the linear equation (5) at time T (end of the first interval) for the different control inputs (2) and (3), we obtain:

$$Vl_{PWC}(T) = e^{-k_s T} V_{l0} + \frac{SR}{k_s K_{IL6}} \bar{u}_0 \left(1 - e^{-k_s D_0}\right) \tag{8}$$

and

$$Vl_C(T) = e^{-k_s T} V_{l0} + \frac{SR}{k_s K_{IL6}} \bar{u}_{eq,0} \left(1 - e^{-k_s T}\right), \tag{9}$$

respectively, whose equality is implied by (6) (with $k = 0$). By iterating the procedure for $k > 0$ and still exploiting (6), Eq. (7) is implied, which concludes the proof. ∎

Remark 1: We observe that, in Eq. (1g), the parameter k_s takes a very small value ($2.76 \cdot 10^{-6}$[1/min] [9], [10]). This renders the products $k_s D_k$ and $k_s T$ significantly smaller than one for the typical values of D_k and T exploited in this letter. In turn, according to the first-order Taylor approximation $e^x \simeq 1+x$, the approximate equalities $1-e^{-k_s D_k} \simeq 1-(1-k_s D_k) = k_s D_k$ and $1 - e^{-k_s T} \simeq k_s T$ hold. Hence, Eq. (6) can be well approximated by

$$\bar{u}_{eq,k} = \frac{1 - e^{-k_s D}}{1 - e^{-k_s T}} \cdot \bar{u} \simeq \frac{k_s D}{k_s T} \cdot \bar{u}_k = \delta_k \bar{u}_k, \qquad k \in \mathbb{N}, \tag{10}$$

where $\delta_k := \frac{D_k}{T} \in [0, 1]$ is the *duty cycle* of the PWC input (2).

C. Control Model

As discussed, in this letter we consider the model (1) as the *virtual patient* to be controlled, whereas we exploit a compact model for the design of the control law. Specifically, we consider the widespread model of diabetes progression [12], which shares with model (1) some basic features as basal glycemia and insulinemia, and which is here suitably modified to account for the effect of the exercise. For this model the state vector is $\chi(t) = [G(t), I(t), \beta(t), S_I(t)]^{\mathrm{T}}$, whose dynamics is given by

$$\dot{\chi}_1 = R_0 - \left(E_{g0} + \chi_4 \chi_2\right)\chi_1, \tag{11a}$$

$$\dot{\chi}_2 = \chi_3 \sigma \frac{\chi_1^2}{\alpha + \chi_1^2} - k\chi_2, \tag{11b}$$

$$\dot{\chi}_3 = \left(-d_0 + r_1 \chi_1 - r_2 \chi_1^2\right)\chi_3, \tag{11c}$$

$$\dot{\chi}_4 = -c\left(\chi_4 - S_{I,target}\right) \cdot (1 - u_v), \tag{11d}$$

with measured output

$$y = \Gamma \chi, \qquad \Gamma = [1 \quad 0 \quad 0 \quad 0]. \tag{12}$$

System (11) accounts for the effect of exercise in a compact form by means of the (normalized) virtual input function $u_v : \mathbb{R}_{\geq 0} \longrightarrow [0, 1]$, representing the relative reduction of the insulin sensitivity decay rate due to the effect of exercise, whereas we omit the additional contribution of physical activity on the fast dynamics and on beta cells. Moreover, coherently with (1), we introduce here the positive steady state value $S_{I,target}$ for S_I as in [13] to avoid the unrealistic unbounded increase in beta-cell mass that the original model [12] may exhibit. The parameters of the model are inherited from [12], with $S_{I,target} = 0.028$.

III. Observer-Based MPC Design

In this section, we propose a model predictive control approach, based on model (11), for the design of the optimal physical activity strategy, expressed in terms of the equivalent input function $u_v(\cdot)$.

A. State-Feedback MPC

For optimization purposes, we define the cost function

$$J(\chi, u_v)\big|_{[t_1,t_2]} \triangleq \|\chi_1(\cdot) - G_d\|^2_{L^2([t_1,t_2])} + \lambda(t_2 - t_1)|u_v - u_{v,b}|^2, \tag{13}$$

where $[t_1, t_2]$ is the time interval of interest, G_d is the desired glycemia and u_v is the control input predicted by the MPC, assumed constant in the period of interest, whereas $u_{v,b} \in [0, 1]$ is a feedforward baseline control. The cost function $J(\chi, u_v)$ is designed to balance the best trade-off between optimal glucose levels and the practical feasibility of the amount of the required exercise. Penalizing the deviation from a baseline level $u_{v,b}$ ensures that the optimizer drives the control to track the baseline amount of physical exercise, while allowing for dynamical adjustments. The optimizer computes the optimal virtual control sequence $\{u^*_{v,k}\}_{k\in\mathbb{N}}$ such that

$$\begin{aligned} u^*_{v,k} = \arg\min & J(\chi, u_v)\big|_{[kT,(k+N)T]} \\ \text{s.t.} \quad & (11), \\ & u_v \in [0, 1], \\ & u(t) = u^*_{v,k}, \qquad t \in [kT, (k+1)T), \quad k \in \mathbb{N}, \end{aligned} \tag{14}$$

where T is the training period and N represents the integer length of the prediction window in terms of number of training periods considered in the optimization horizon.

B. Output-Feedback MPC

The optimization in (15) requires the full knowledge of the state χ of system (11), which for the subsequent developments we recast in compact notation as

$$\dot{\chi}(t) = f(\chi(t)) + g(\chi(t))u_v(t). \tag{15}$$

Unfortunately, only plasma glycemia is a measurable output, therefore we exploit an observer to estimate in real time the other components of the state χ. To this end, in order to deal with the discrete-time feature of the sampled measurements, we model them as continuous outputs acquired with the following time-varying observation delay

$$y(kT) = \Gamma \chi(t - \delta(t)) \tag{16}$$

with $\delta(t) = t - kT$, $t \in [kT, (k+1)T)$, $k \in \mathbb{N}$. For these systems, we consider an observer scheme originally proposed in [18], [19]. The design is performed according to the following dynamics, using only the output $y(kT)$, $k = 1, 2, \ldots,$ measured at sampling times:

$$\dot{\hat{\chi}} = f\big(\hat{\chi}(t)\big) + g\big(\hat{\chi}(t)\big)u_v(t) + e^{-\eta\delta(t)} \cdot Q^{-1}\big(\hat{\chi}(t)\big)\Lambda\big(y(kT) - \Gamma\hat{\chi}(kT)\big) \quad (17)$$

where $\eta > 0$ is a design parameter, giving progressively less weight to the latest measurement, and Λ is the observer gain and assigns the eigenvalues associated with the error matrix $A_b - \Lambda\Gamma$, with A_b the Brunowski matrix $A_b = \begin{bmatrix} 0_{3\times1} & I_3 \\ 0 & 0_{1\times3} \end{bmatrix}$. For the development of the observer, it is required that the *drift-observability* map $\Psi(\chi) \triangleq \begin{bmatrix} \chi_1 & L_f\chi_1 & L_f^2\chi_1 & L_f^3\chi_1 \end{bmatrix}^{\mathrm{T}}$, where $L_f^k\chi_1$ denotes the k-th order Lie-derivative for $k = 1, 2, 3$, is a diffeomorphism in $\mathbb{R}^4_{\geq 0}$, implying that its Jacobian $Q(x) = \frac{\partial\Psi(x)}{\partial x}$, exploited in (17), is invertible. Such a property has been proven to hold true locally, by finding the Jacobian $Q(\cdot)$ invertible in the state space region explored by simulation. In [18], [19] there can be found sufficient conditions to ensure global/semiglobal convergence of the observer. Without a separation principle ensuring to treat the control and state estimation problems separately, these conditions do not guarantee the same properties for the observer in closed-loop.

In the spirit of the separation principle, we are now ready to recast the MPC problem (14) in an output-feedback fashion by replacing the true (unknown) state by its real-time estimation (17), with the optimal virtual control sequence now given by $\{u^*_{v,k}\}_{k\in\mathbb{N}}$ such that

$$\begin{aligned} \hat{u}^*_{v,k} = \arg\min\, & J\big(\hat{\chi}, u_v\big)\big|_{[kT,(k+N)T]} \\ \text{s.t.} \quad & (17), \\ & u_v \in [0, 1], \\ & u(t) = \hat{u}^*_{v,k}, \qquad t \in [kT, (k+1)T), \quad k \in \mathbb{N}. \end{aligned} \quad (18)$$

The problem formulation makes use of a dynamical system evolving in continuous-time to model the plant (i.e., the glucose-insulin long term evolution), along with a piecewise-constant MPC exploiting quantized measurements acquired at discrete times. The continuous-time model for the plant reflects a more accurate choice, since it accounts for the intersample behavior that would have been overlooked according to a simpler, though less accurate, discrete-time model.

In light of its formulation, the proposed MPC optimization problem is inherently both initially and recursively feasible.

IV. Validation in a Non-Ideal Setting

In this section, we demonstrate the output-feedback design method from the previous section by applying it to the extended model (1) and presenting simulation results. These include both a nominal virtual patient and a virtual population generated via random parameter perturbations, with added non-idealities like quantized measurements and disturbances. Validating control on a more accurate model than that used in design is a standard approach in Artificial Pancreas and disease control research [6], [8], [20], [21]. Before closing the loop on model (1), the optimal output-feedback MPC must be converted into a piecewise-constant input as in (2). To this end, we decide to modulate physical activity by pulses of optimal duration D^*_k, which we consider to be realistically implemented by multiples of $\mu_D = 5$ minutes. Therefore, we fix the activity level $\bar{u}_k = \bar{u} = 60$ for all intervals, simulating moderate-to-vigorous exercise [9], [22]. The optimal solution coming from the MPC is treated as the proper fraction of maximal $\bar{u}_{eq,k}$ so that, exploiting the main result of Proposition 1, by means of (10), we have

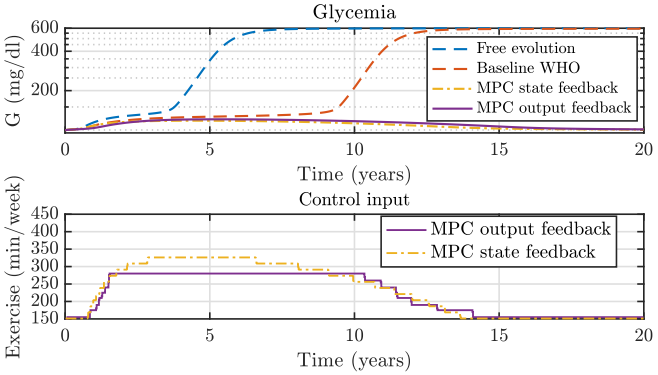

Fig. 1. Top panel: trend of the basal glucose concentration over the 20-year horizon. Bottom panel: trend of the control input in terms of recommended exercise per week.

$$\frac{D^*_k}{T}\bar{u} = \hat{u}^*_{v,k} \cdot u_{eq,\max}. \quad (19)$$

From this, accounting also for the quantization, we get

$$D^*_k = \left[\frac{u_{eq,\max}\ T}{\bar{u}} \cdot \hat{u}^*_{v,k}\right]_{\mu_D}, \qquad k \in \mathbb{N}, \quad (20)$$

where we defined the quantization operator $[\,\cdot\,]_\mu : \mathbb{R}_{\geq 0} \longrightarrow \mu\mathbb{N}$, defined by $[x]_\mu = \mu[\frac{x}{\mu}]$, with $[\,\cdot\,]$ denoting rounding to the nearest natural number. In the following simulations, we choose $T = 2$ [days] (period of physical activity, coincident with sampling and actuation period), $N = 10$ (length of the MPC prediction window), corresponding to a prediction horizon of 20 days; the MPC weight parameter λ in (13) is set to 150, and $u_{eq,\max} = 2.5$, corresponding, in agreement with (20), to a maximal exercise duration $D_{\max} = 120$ [min]. We set $G_d = 100$ (mg/dl) and we set $u_{v,b} = 0.36$. We remark that by means of (20) the general information of the effect of physical activity embedded in the virtual control $u^*_{v,k}$ is translated into a duration D^*_k spanning from a minimum of 0 to a maximum of around 400 minutes/week (i.e., the threshold at which the benefits of physical activity seems to saturate according to clinical evidence [14]). Analogously, by means of (20), the baseline reference of the virtual control input $u_{v,b}$ tracks the minimum amount of exercise of around 150 minutes/week suggested by the WHO recommendations [15]. We assume that the conditions predisposing to diabetes arise at $t = 0$, with a severe insulin sensitivity decay according to Eq. (1f). The initial condition for the extended model (1a)–(1l) is assumed to be $x(0) = [99.7604\ 9.025\ 1000.423\ -0.00666\ 536.67\ 0.8\ 0\ 0\ 0\ 0\ 0\ 0]^{\mathrm{T}}$, whereas the initial condition for the observer (17) is $\hat{\chi}(0) = [100\ 4\ 990\ 0.72]^{\mathrm{T}}$. As a further non-ideality with respect to the theoretical framework, we also consider quantized glucose measurements, i.e., $y(kT) = [G(kT)]$, i.e., glycemia [mg/dl] is rounded to the nearest integer. We consider a time span of 20 years, consistent with most of the clinical evidence and prevention studies on diabetes progression, assessing that

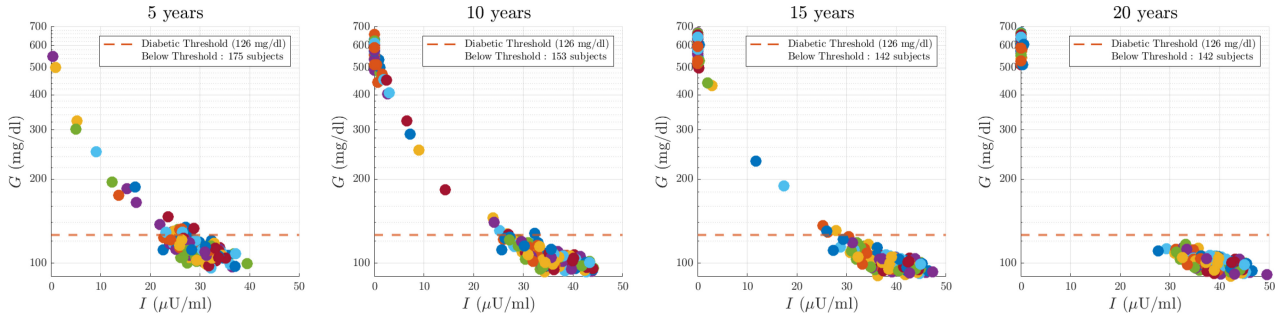

Fig. 2. Scatter plots of G and I for the 200 virtual subjects simulated by means of log-normal parameter perturbations at 5,10,15,20 years.

diabetes course develops on a time horizon ranging from five years onward [4], [14], [17].

A. Simulations on the Average Patient Model

Fig. 1 (top panel) shows the results obtained when simulating the extended model in the open loop case (blue dashed line), in the case of baseline feedforward control associated with WHO guidelines (i.e., 150 min/week) (red dashed line), in the MPC state feedback case (yellow dotted line) and in the MPC output feedback case (purple solid line), when closing the loop on the extended model (1).

As it can be observed from the plot, in the open-loop case and in the case of baseline WHO feedforward control, the simulated subject goes diabetic from the third and seventh year of simulation onwards respectively, with the disease course becoming irreversible, and the system reaches its hyperglycemic equilibrium point at $G = 600$ over the 20-year simulation (mg/dl); on the other hand, in the MPC controlled case, both state feedback and output feedback, the control law is able to delay diabetes progression and even to reverse the course restoring safe glycemia values within the 20-year time horizon, with the basal glucose concentration never exceeding the diabetic threshold of 126 (mg/dl). Fig. 1 (bottom panel) illustrates the trends of the control input expressed as total amount of exercise in minutes required per week. As it can be easily observed, both the MPC state feedback (yellow dotted line) and the MPC output feedback (purple solid line) predict similar amount of exercise over the 20-year simulation, with the state feedback case exhibiting a slightly higher average and this results in lower glucose concentration values with respect to the output feedback controller (as clearly visible from the top panel of Fig. 1). Note that the MPC state feedback exhibits a lower overall cost with respect to the MPC output feedback ($J_{sf} = 1.47 \cdot 10^6$ vs $J_{of} = 1.66 \cdot 10^6$) as reasonably expected. It should be pointed out that these results are perfectly consistent with what suggested in the general WHO guidelines, recommending a minimum of 150 min/week of moderate exercise for chronic disease prevention and explicitly suggesting to go beyond the minimum recommendations as larger benefits are expected from larger amount of exercise [15]. It can be shown that the output feedback controller ensures that the glucose concentration remains within a safe and acceptable range, even when accounting for random fluctuations of the basal glycemia in the range $[-10, 10]\%$, (as in [23], [24]).

B. Validation on a Population of Virtual Subjects

To further investigate the performance of the output feedback control law, we perform a validation by closing the loop on a population of 400 virtual patients generated applying perturbations to the nominal value of the parameters of the extended model (1). The goal is to find out, on the 20-year horizon, how many individuals reverse the diabetes progression. Specifically, 200 virtual subjects have been simulated by means of log-normal independent random samples for the set of parameters with standard deviation of 5% with respect to the nominal values as in [25], whereas the remaining 200 have been simulated accounting for uniform independent random samples over the set of parameters within the range $[-5, 5]\%$ of the nominal values [25]. Analogous range for the parameter perturbations is considered in the work in [6], [26]. A summary of the overall results for the validation on the whole virtual population of 400 subjects is provided in Table I, where the three columns refer to the percentage of subjects reversing diabetes, their basal glycemia at the end of the 20 years, and the physical activity required by the control action. These results are similar in both the parameter distributions, showing a promising percentage of success. The overall average duration of the recommended exercise is aligned with the previously discussed general recommendations on exercise for diabetes prevention. Higher success percentages may be achieved by setting a lower penalty λ in the MPC cost function (13), at the cost of increased recommendations in terms of minutes of weekly physical activity. In Fig. 2 we show the scatter plots of basal glucose and insulin concentrations obtained for the 200 virtual subjects associated with log-normal parameter perturbation. These plots allow to understand how fast diabetes proceeds (or is reversed by means of sustained physical activity): the fate of diabetes progression seems to be definitely set after the first 10 years.

TABLE I
VALIDATION RESULTS FOR THE COHORT OF 400 VIRTUAL SUBJECTS

	% of success	G (mg/dl)	Exercise (min/week)
U	75	106 (4.3)	201 (39.3)
Log	71	104 (3.7)	199 (38.5)

V. CONCLUSION AND OPEN ISSUES

In this letter we have proposed a novel control approach for long-term diabetes progression via physical activity. Results are consistent with the literature. Our approach is aimed at quantitatively assessing and complementing the general population-level guidelines on physical activity [15] with personalized and adaptive recommendations. In this way, the proposed method provides a way to translate the public health guidance into actionable and individualized targets.

This letter presents some limitations that deserve to be addressed in the future developments. First, upcoming efforts will aim at validating the model against real clinical data. Subsequent developments will involve further formal investigations of the proposed control scheme and more extensive simulation campaigns, also closing the loop on additional higher-dimensional models, as those adopted in [6], [7], [8]. Moreover, to further improve the output-feedback implementation future research will investigate the possibility of leveraging alternative observers, such as Moving Horizon Estimators.

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