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Nonlinear MPC for Insulin Titratio2shn of Type 2 Diabetes ⋆

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Abstract: This paper explores the development and application of both linear and nonlinear model predictive control (MPC) strategies for insulin titration in type 2 diabetes (T2D) subjects. By utilizing daily blood glucose measurements, alongside information on insulin injections and meal intake from the previous day, we adjust the insulin sensitivity parameter of the internal model of the controller. This adjustment is based on the steady-state glucose error between the internal model and the plant model. The performance of these strategies was assessed using a high-fidelity T2D model, demonstrating their potential in enhancing the management of T2D.

Keywords: Nonlinear MPC, Biological systems, Diabetes, Human-in-the-loop Control

1. INTRODUCTION

Individuals suffering from type 2 diabetes (T2D) are characterized by the inability of their endogenous insulin system to regulate the level of glucose in their blood. Over time, T2D subjects risk developing severe detrimental effects if left untreated, such effects include cardiovascular and kidney diseases or damage to eyesight. According to the World Health Organization (WHO), the number of people suffering from diabetes worldwide rose from 108 million in 1980 to 422 million in 2014. Moreover, the number of people suffering from diabetes worldwide is projected by IDF (2021) to increase to 643 million by 2030. If behavioral changes or oral medication do not provide sufficient results for a given T2D subject, injection of long-acting insulin is a possible next step in treatment. The exact effect of an injected insulin dose varies from one individual to another, and therefore great care must be taken when choosing the size of the dose administered to a given subject. Conventionally, titrating the dosage has been done by medical professionals based on glucose levels at specific times, e.g., before meals or while fasting. However, these titration strategies can be time-consuming and may take a relatively long time for glucose levels to reach a safe level. To address these challenges, several algorithms for insulin dosage titration based on control theory were suggested in the literature. The works in Ahdab et al. (2023, 2022); Krishnamoorthy et al. (2021) propose model-free algorithms to adjust the long-acting insulin doses based on either self-monitored blood glucose (SMBG) measurements or continuous glucose monitoring (CGM) devices.

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On the other hand, algorithms that utilize models capturing the interaction between insulin and glucose have been investigated. The work Eringis et al. (2020) utilized Linear Parameter Varying (LPV) tools to design a model-based dosing strategy where the control design model was the same as the model used for simulation. The work in Aradóttir et al. (2019) investigated the feasibility of a model predictive control (MPC) approach for insulin titration. The work was a proof-of-concept in which the same physiological parameters were shared between the simulated model and the model used for the MPC design. Recently, Fathi et al. (2023) proposed a receding horizon approach which provides more validity to the MPC approaches for long-acting insulin dosing strategies.

The MPC strategies in the literature for long-acting insulin dosing are all based on a linear internal model for the MPC strategy.

In this paper, we contribute to the field by

- Proposing and comparing both linear and nonlinear MPC strategies for insulin titration of T2D subjects.
- Introducing a straightforward online parameter adjustment method to align the internal MPC model with data from T2D subjects.

The structure of the paper is as follows. In Section 2 we define and discuss the T2D models used. Section 3 contains a description of the MPC scheme and state estimation. The main contributions of this paper are found in Section 4 where the parameter adjustment is described, and the performance of the linear and nonlinear MPC strategies are evaluated using a high-fidelity model. We end the paper with a discussion of the results in Section 5.

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2. CONTROL AND SIMULATION MODELS

This paper revolves around the use of MPC for T2D treatment. In this paper, the dynamical system describing the glucose-insulin relation used for designing the MPC can be summarized as follows

$$\frac{d\tilde{I}_{sc}(t)}{dt} = \frac{1}{\tau_{in}}u(t) - \frac{1}{\tau_{in}}\tilde{I}_{sc}(t) \tag{1a}$$
$$\frac{d\tilde{I}_{p}(t)}{dt} = \frac{1}{\tau_{in}}\tilde{I}_{sc}(t) - \frac{1}{\tau_{in}}\tilde{I}_{p}(t) \tag{1b}$$
$$\frac{d\tilde{I}_{eff}(t)}{dt} = p_2(\tilde{I}_p(t) + \tilde{\beta}G(t)) - p_2\tilde{I}_{eff}(t) \tag{1c}$$
$$\frac{dG(t)}{dt} = -(G_{EZI} + \tilde{S}_I\tilde{I}_{eff}(t))G(t) + E_{GP} + \frac{D_2(t)}{V_G\tau_m} \tag{1d}$$
$$\frac{dD_1(t)}{dt} = \frac{1000}{M_{wG}}d(t) - \frac{1}{\tau_m}D_1(t) \tag{1e}$$
$$\frac{dD_2(t)}{dt} = \frac{1}{\tau_m}D_1(t) - \frac{1}{\tau_m}D_2(t) \tag{1f}$$

Here, time t is measured in days. Equations (1a) - (1d) model how the injected insulin $u(t)$ affects the subcutaneous insulin $\tilde{I}_{sc}(t)$, which affects the plasma insulin $\tilde{I}_p(t)$, which finally affects the blood glucose level $G(t)$. Equations (1e) and (1f) model how the consumption of meals affects the blood glucose. Meal consumption, captured in $d(t)$, varies between subjects. However, for simulation purposes, we assume that the subjects are consuming four types of meals: A breakfast meal with a size $m_{s,1}$ [g] drawn each day from $\mathcal{N}(70, 10^2)$ and time $m_{t,1}$ [hour] drawn from $\mathcal{N}(7, 0.37^2)$ with a probability of 0.1 to skip the meal, a lunch meal with size $m_{s,2}$ [g] drawn each day from $\mathcal{N}(100, 12^2)$ and time $m_{t,2}$ [hour] drawn from $\mathcal{N}(12, 0.27^2)$ with a probability of 0.1 to skip it, an afternoon snack with size $m_{s,3}$ [g] drawn each day from $\mathcal{N}(40, 20^2)$ and time $m_{t,3}$ [hour] drawn from $\mathcal{N}(15, 1.5^2)$ with a probability of 0.4 to skip it, and a dinner meal with size $m_{s,4}$ [g] drawn each day from $\mathcal{N}(140, 40^2)$ with a time $m_{t,4}$ [hour] drawn from $\mathcal{N}(18, 0.87^2)$ with a probability of 0.05 to skip it. Note that we assume $D_1(0) = D_2(0) = d(0) = 0$. For the control design, the model is discretized using a fourth-order Runge-Kutta integration scheme from Butcher (1996).

Furthermore, in this paper, we consider the effect of medication adherence on the performance of the developed methods. To achieve this, we first determine whether the T2D subject will adhere to medication with a probability of 0.567. If the subject is not adherent, then their k'th prescribed insulin dose $u(k)$ is modified to be

$$u_a(k) = \phi(k)\eta(k)u(k) \tag{2}$$

where $\phi(k) \in \{0, 1\}$ is a random variable to account for skipping a dose with probability 0.2, and $\eta(k) = 1 - |\varepsilon(k)|$, $\varepsilon(k) \sim \mathcal{N}(0, 0.5)$ is a random variable which scales down the prescribed insulin dose. The probabilities were chosen according to García-Pérez et al. (2013) and Trief et al. (2016).

The system (1) was first described in Aradóttir et al. (2017), where a detailed description of the states and parameters can be found. A summary of these can be found in the appendix.

For simplicity write (1) as (3a) below and add to it the output equation (3b) to obtain the input-output system

$$\dot{x} = f(x, u, d) \tag{3a}$$
$$z = h(x) \tag{3b}$$

with $f(x, u, d)$ the right-hand side of (1), state $x = (\tilde{I}_{sc}, \tilde{I}_p, \tilde{I}_{eff}, G, D_1, D_2)$, and h projection onto the fourth coordinate (that is, we can only measure blood glucose level $z = G$). As indicated above, we will treat d as an exogenous input and view the injected insulin $u(t)$ as the input. Note that $f(x, u, d)$ is nonlinear due to the bi-linear term $\tilde{I}_{eff}(t)G(t)$ in (1d).

Besides using the nonlinear dynamics (3a) we will also use a linearized version of (3a) to produce the linear input-output system

$$\begin{aligned}\dot{x} =& D_x f(x', u', d')(x - x') + D_u f(x', u', d')(u - u') \\ &+ D_d f(x', u', d')(d - d')\end{aligned} \tag{4a}$$
$$z = h(x) \tag{4b}$$

with (x', u', d') an equilibrium point of (3a), that is $f(x', u', d') = 0$. Clearly (x', u', d') can be parameterized by u', G' and d'. Several linearization schemes were considered, and the following was chosen for the best performance: $d' = 0$ and linearize around different operating points u' and G' as time passes. More specifically, we chose G' to be the fasting blood glucose level measured every morning at 7 AM, and $u' = \frac{E_{GP} - G_{EZI}G'}{\tilde{S}_I G'} - \tilde{\beta}G'$

To demonstrate, assume that (3) represents a T2D subject (below, we explain how we, in general, represent a (virtual) subject using a high-fidelity model). Fig. 1 shows how the linearized system (4) nicely tracks the nonlinear system (3) in a simple simulation of a T2D subject with no meal intake ($d = 0$). For comparison, Fig. 2 shows the performance of linearizing only once at a blood glucose level of 5 [mmol/L] ($G' = 5$) and insulin injection of 30.65 [U/day] ($u' = 30.65$).

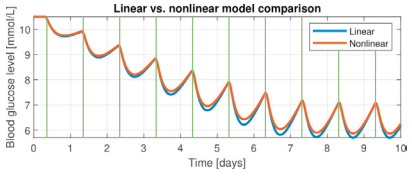

Fig. 1. Comparison of (4) and (3) for the chosen linearization scheme. Linearization happens at 7 AM each day, that is , at 0.29 days, 1.29 days etc. (indicated by the green lines)

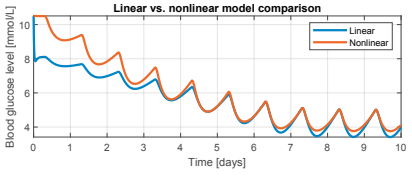

Fig. 2. Comparison of (4) and (3) when linearizing only once around $G' = 5$ and $u' = 30.65$

As a stand-in for a T2D subject, the high-fidelity T2D model described in Ahdab et al. (2021) of the glucose-insulin dynamic is used. The high-fidelity T2D model has 33 compartments, 57 states, and 128 variables and acts as a virtual patient in the MPC scheme. That is, a blood glucose level is produced by the high-fidelity T2D model, which is passed to an estimation procedure (see section 3.1 and Fig. 4), giving an initial state that is used to initialize

the MPC calculations, which then produce an insulin dose (input) to the high-fidelity T2D model.

3. MPC FORMULATION

We will synthesize control of the blood glucose level using an MPC scheme. Before providing the details, we describe how the receding horizon works in this setup (see also Fig. 4). We assume that the T2D subject provides an SMBG measurement y every day, 5 minutes before breakfast. Let $t_b = t_b(k)$ denote this time of day, at day k, and note that it is a stochastic variable according to the discussion below (1). Once the SMBG measurement $y = y(t_b)$ is obtained, an optimal control problem involving reference tracking of blood glucose level is solved, with a prediction horizon of 288 corresponding to the next 24 hours with a sampling time of $\Delta t = 5$ [min]. A scaled version of the optimal input (amount of injected insulin) is then recommended to the T2D subject, and this cycle is then repeated the next day when a new SMBG measurement arrives. The details of this procedure can be summarized in the following MPC scheme (with $k = 1, 2, \ldots$ denoting day number)

$$\min_{u(0|k),\,\xi} V(k) = \sum_{i=1}^{288} ||\mathsf{z}(i|k) - r(i)||_Q^2 + Ru(0|k)^2 + \rho||\xi||_1 \tag{5a}$$

subject to

$$\mathsf{x}(i+1|k) = F(\mathsf{x}(i|k), u(i|k), d(i|k)),\ \mathsf{x}(0|k) = \hat{x}_k \tag{5b}$$
$$\mathsf{z}(i|k) = h(\mathsf{x}(i|k)) \tag{5c}$$
$$u(i|k) = 0,\ i \neq 0, \tag{5d}$$
$$0 \leq u(0|k) \leq 300 \tag{5e}$$
$$r(i) = 7,\ i \notin \mathcal{J} = \{48, 49, \ldots, 84\} \tag{5f}$$
$$r(i) = 5,\ i \in \mathcal{J} \tag{5g}$$
$$3.9 - \xi_1 \leq \mathsf{z}(i|k) \leq g(i) + \xi_2, \tag{5h}$$
$$\mathsf{z}(0|k) - \mathsf{z}(288|k) \leq c + \xi_3 \tag{5i}$$

where $\hat{x}_k$ indicates an estimated value of $x(t_b(k))$ (at day k), (5b) represents a discretized version of (3a) or (4a) (using a fourth-order Runge-Kutta), the set $\mathcal{J}$ contain time instances between 4 AM and 7 AM,

$$g(i) = \begin{cases} 5.6 & i \in \mathcal{J} \\ 10 & i \notin \mathcal{J} \end{cases},$$

and $\xi = (\xi_1, \xi_2, \xi_3)$ is a vector of slack variables. In the above, g accounts for the fact that blood glucose level, on average, is allowed to be much higher during day time (because of meal consumption), and c is the maximum drop allowed in glucose for consecutive daily SMBG measurements (to avoid pseudo hypoglycemia). The parameter c is patient-dependent and is included as an optional constraint if desired. However, for the results shown in this paper, the constraint is effectively disabled by setting $c = 2000$. Moreover, the meal consumption $\{d(i|k)\}_{i=\{0,1,\ldots,287\}}$ is chosen to be the mean meal sizes at mean times described below (1). The slack variables are introduced since the problem often will violate the upper bound on glucose levels due to the inclusion of meals. The MPC scheme is solved using Yalmip from Lofberg (2004) when the linearized control model (4) is used, and CasADI from Andersson et al. (2019) when a nonlinear control model (3) is used. The weights in the cost $V(k)$ are chosen as $Q = 50/\Delta t$, $R = 0.1/\Delta t$, and $\rho = 10^{10}$.

Henceforth, we will let nonlinear MPC (resp. linear MPC) mean (5) with the discretized version of (3a) (resp. (4a)) in (5b).

3.1 State estimation

For a real-life setup, the only measurable state is the blood glucose $G(t)$. State estimation is used to estimate the rest of the states of the model in (1a) - (1f) based on measurements of $G(t)$. We use three different methods for estimation: the full-order observer, the unscented Kalman filter, and the particle filter. Several comparisons between these three methods have been made under uncertain meals, nonadherence, and a mismatch between the values of the parameters of the model in (3) and the version of it used by the estimators. Based on these comparisons, the particle filter provided the best performance and has therefore been chosen as the method to obtain state estimates of the model in (3) and (4).

4. UPDATING THE INSULIN SENSITIVITY

A model mismatch between the MPC and the real patient will cause the MPC to have poor prediction capabilities for the effect of insulin on glucose. In Fig. 3, the linear MPC was tested on a virtual patient simulated using a perturbed version of (3), where parameters E_{GP}, $\tilde{S}_I$, and $\tilde{\beta}$ were each reduced by three times their estimated standard deviation (3σ) from the mean values. It can be seen from the figure that the mismatch between the model (4) of the MPC and the model (3) representing the virtual patient causes a persistent error to be present between the predicted and measured blood glucose.

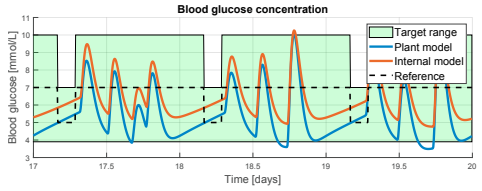

Fig. 3. Linear MPC on (3) with perturbed parameters.

To alleviate these types of persistent errors, it is proposed to implement a mechanism that, over time, corrects the accuracy of the prediction based on error feedback. Namely, the parameter $\tilde{S}_I$ will be adjusted to $\hat{S}_I$ for the internal model used in the (linear or nonlinear) MPC since this parameter in the model (3) modulates the effect of insulin on the blood glucose levels in the simulated T2D subject.

The implemented mechanism will operate in the following way (see Fig. 4):

(1) At day k, adjust the parameter $\hat{S}_I$ using the deviation $\delta(t_b(k))$.
(2) At day k, recommend a scaled version of the insulin dose $\alpha(t_b(k))u(t_b(k)|k)$ from the MPC to the T2D subject.
(3) At day $k+1$, obtain the actual administered insulin dose $u_a(t_b(k)|k+1)$ from day k and the meal times $m_t(k|k+1)$ and sizes $m_s(k|k+1)$ from day k.

(4) At day $k+1$, simulate day k with the internal model using $u_a(t_b(k)|k+1)$, $m_t(k|k+1)$ and $m_s(k|k+1)$.
(5) At day $k+1$, obtain the deviation $\delta(t_b(k+1))$ between the simulated SMBG $\mathsf{z}(t_b(k+1)|k+1)$ and the measured SMBG $y(t_b(k+1))$.

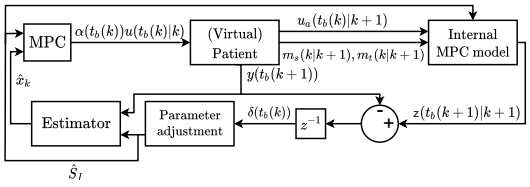

Fig. 4. The proposed MPC scheme with parameter adjustment.

The adjusted value $\hat{S}_I$ is updated as:

$$\hat{S}_I \longleftarrow \hat{S}_I + \gamma\delta(t_b(k)), \tag{6}$$

where $\delta(t_b(k))$ is the blood glucose deviation defined as $\delta(t_b(k)) = \hat{z}(t_b(k)|t_b(k)) - y(t_b(k))$, and $\gamma \geq 0$ is the modification gain. See Fig. 4 for an overview of the setup. The variables $m_s(k|k+1)$ and $m_t(k|k+1)$ represent 4-dimensional vectors of the reported meal sizes and meal times, respectively, from $t_b(k)$ until $t_b(k+1)$ and reported at time $t_b(k+1)$. The variable $\alpha(t_b(k))$ is chosen to be $\alpha(t_b(k)) = \min(\frac{1}{4}k, 1)$ and it is used to scale down the proposed insulin dose $u(t_b(k))$ at the beginning of the treatment. The scaling down at the beginning is implemented to help with cases when the insulin dose could be too large due to having the initial guess of $\tilde{S}_I$ (the first $\hat{S}_I$ on the right-hand side of (6)) being far from the true one.

The sensitivity is repeatedly updated with a scaled version of the deviation $\gamma\delta(t_b(k))$ added to the previously obtained parameter value. This implements an integral effect, where the parameter will continue to change as long as a steady-state error is present.

4.1 Finding the gain γ

A simple test is performed to find the best gain for the sensitivity update seen above. For this test, linear MPC is used, and the measurement is then taken from the simulated nonlinear model. The nonlinear model's insulin sensitivity $\tilde{S}_I$ has been set to 3.6. The insulin sensitivity for the model in the MPC is initialized with $\hat{S}_I = 1.8$. Fig. 5 shows how the insulin sensitivity of the linearized model changes over time with different gain γ values, and Fig. 6 shows how the deviation δ in the fasting blood glucose level between the prediction of the MPC and the measurements change over time.

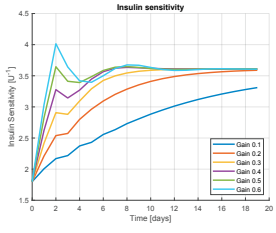

Fig. 5. Change of insulin sensitivity adjustment $\hat{S}_I$ throughout the simulation.

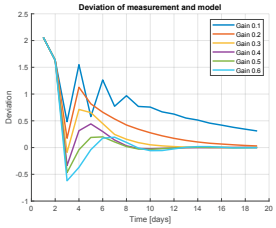

Fig. 6. Change of model deviation of fasting blood glucose δ throughout the simulation.

When it comes to T2D treatment, it is always best to be conservative since drastic changes could have fatal consequences. It can be seen in Fig. 5 that the larger the gain is, the more erratically the insulin sensitivity behaves. Since it is impossible to know how the sensitivity would behave for all T2D subjects, a conservative gain of 0.2 is chosen. As seen in Fig. 6, the deviation is erratic for the first 3-4 days. The variable $\alpha(t_b(k))$ scaling the proposed insulin dose in the first three days will help in avoiding aggressive insulin suggestions due to a large initial mismatch between the estimated insulin sensitivity $\hat{S}_I$ and the actual one $\tilde{S}_I$.

The effect of the sensitivity update can be seen by comparing Fig. 3 and Fig. 7. The results are only shown from days 15 to 20 of the simulation since the sensitivity changes slowly and does not converge within the first week or two.

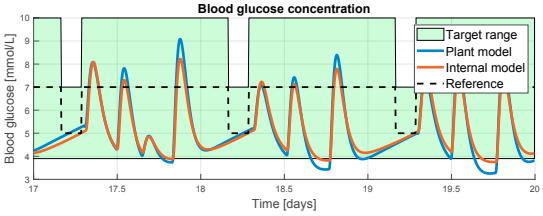

Fig. 7. Linear MPC on (3) with perturbed parameters, and sensitivity update enabled.

It can be seen that the offset between the MPC model and simulated virtual patient in Fig. 3 has been greatly reduced in Fig. 7, where the sensitivity update has been enabled. This indicates that it has a positive effect on the performance of the treatment. Note that some hypoglycemia events are observed, but this is of no concern since this is only a proof of concept.

4.2 Test of sensitivity update on high fidelity T2D model

With the system behaving well in the test based on (3), it is desired to investigate whether a similar performance can be obtained in simulations using the high-fidelity T2D model as a virtual patient. Therefore, it is decided to simulate nonlinear and linear MPC on the high-fidelity T2D model. In each of these cases, a run with and without the sensitivity update will also be performed to illustrate if this method will yield the benefits observed in the simulations in which the virtual patient is obtained according to (3). In the following simulations (Fig. 8-11) we set ϕ and η from (2) to 1, and meal times and sizes are the mean values.

The results obtained with linear and nonlinear MPC on the high fidelity model without enabling the sensitivity update can be seen in Fig. 8 and Fig. 9, respectively.

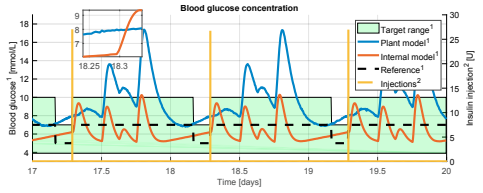

Fig. 8. Linear MPC on the high-fidelity model, without sensitivity update enabled

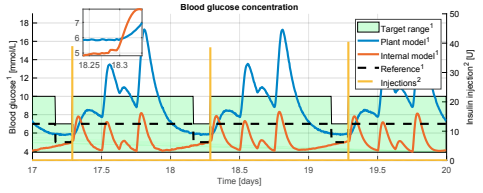

Fig. 9. Nonlinear MPC on the high-fidelity model, without sensitivity update enabled

When comparing the linear and nonlinear MPC simulations, it was observed that the largest doses administered in the linear MPC are approximately 27 U. In comparison, the nonlinear MPC administers doses up to 41 U.

In these simulations, this causes the linear MPC to be unable to lower the high-fidelity model's SMBG value to the desired level.

The results obtained with linear and nonlinear MPC on the high fidelity model with the sensitivity update being enabled can be seen in Fig. 10 and Fig. 11, respectively.

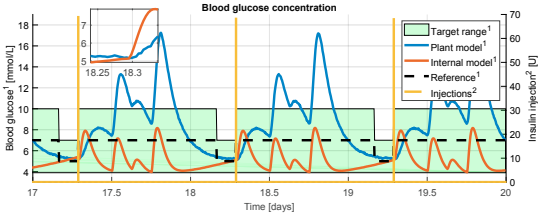

Fig. 10. Linear MPC on the high-fidelity model, with sensitivity update enabled

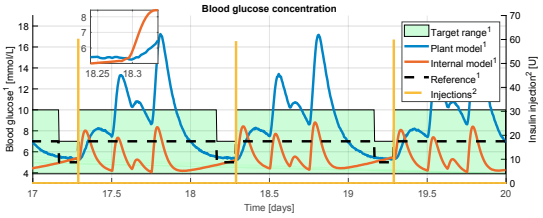

Fig. 11. Nonlinear MPC on the high-fidelity model, with sensitivity update enabled

It is observed here that the sensitivity update causes doses in both the linear and nonlinear MPC to increase (not shown). This is a desired behaviour to implement for the linear MPC, especially since the linear MPC can now bring the SMBG level of the high-fidelity model into the correct range. When inspecting the doses administered since the first day of treatment, the doses almost reach 70 U, where the previous highest dose observed was 27 U. Similarly, for the nonlinear MPC, the doses are slightly higher, with the largest dose increasing from 41 U to 61 U, but the nonlinear MPC seems to settle more quickly than the linear MPC.

To test the capability of this method to estimate insulin sensitivity, only the performance in scenarios involving adherent patients is explored. These patients are identified as those who closely follow the treatment regimen. Therefore, the simulations do not consider the occasional missed dose or stochastic meal timings. The results for both linear and nonlinear MPC when including these considerations are illustrated in Fig. 12 and Fig. 13.

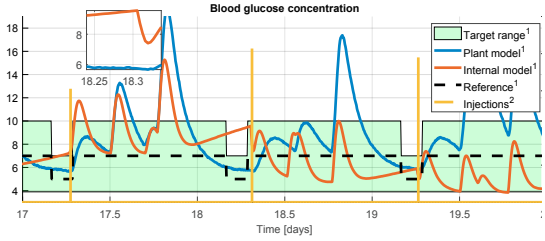

Fig. 12. Linear MPC on the high-fidelity model of the non-adherent patient, with sensitivity update enabled

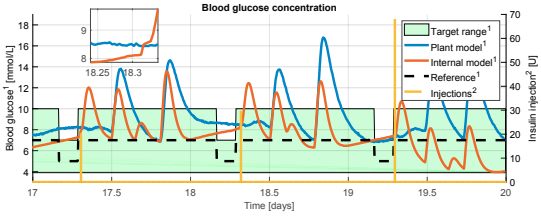

Fig. 13. Nonlinear MPC on the high-fidelity model of the non-adherent patient, with sensitivity update enabled

The simulations revealed that non-adherence to the prescribed treatment significantly decreases the efficacy of both MPC strategies. The fasting glucose levels were often outside the desired range, demonstrating the importance of patient adherence in managing diabetes effectively.

Through extensive simulations, it has been discerned that an insulin sensitivity parameter value of 4 yields behaviour in both the model from Ahdab et al. (2021) and the model expressed in (3) that exhibits a notable degree of similarity. As a result of this observation, the parameter values selected for the model from Ahdab et al. (2021) will be strategically distributed around the pivotal value of 4. These values will be determined in ten uniform increments of 3.2 to 4.8. This meticulous approach ensures a judicious exploration of the titration method's robustness across a spectrum of clinically relevant insulin sensitivity scenarios. The acceptable range of glucose values for a T2D subject in treatment is between 3.9 $[\frac{\text{mmol}}{\text{L}}]$ and 10 $[\frac{\text{mmol}}{\text{L}}]$. Table 1 shows the 25th, 50th, and 75th percentile of the TIR, TBR, and TAR of the ten patients with varying sensitivities to insulin. Linear and nonlinear MPC with and without sensitivity update is compared to the standard or care method

Method	TIR		TBR		TAR	
Standard of Care	25%	0.5736	25%	0	25%	0.3550
	50%	0.6055	50%	0	50%	0.3945
	75%	0.6450	75%	0	75%	0.4264
Linear No Update	25%	0.6201	25%	0	25%	0.3164
	50%	0.6479	50%	0	50%	0.3521
	75%	0.6836	75%	0	75%	0.3799
Linear Update	25%	0.6423	25%	0	25%	0.2855
	50%	0.6692	50%	0	50%	0.3308
	75%	0.7145	75%	0	75%	0.3577
Nonlinear No Update	25%	0.6308	25%	0	25%	0.3054
	50%	0.6594	50%	0	50%	0.3406
	75%	0.6946	75%	0	75%	0.3692
Nonlinear Update	25%	0.6421	25%	0	25%	0.2835
	50%	0.6689	50%	0	50%	0.3311
	75%	0.7165	75%	0	75%	0.3579

Table 1. Results of TIR, TBR, and TAR of blood glucose, with the 5 insulin titration methods described.

described in Chun et al. (2019). For each simulated patient, ten repeats of each titration method are performed, each running for a period of 30 days. It can be observed that the proposed online parameter estimation method provides an increase in TIR and a decrease in TAR for both the linear and nonlinear cases.

5. CONCLUSION AND FUTURE WORK

We have proposed a linear and a nonlinear MPC scheme for the problem of calculating long-acting insulin doses for individuals with T2D. Additionally, a strategy for handling model mismatch by adjusting the insulin sensitivity parameter is proposed and evaluated with both the model in (3) and the high fidelity model from Ahdab et al. (2021). It is observed that the adjustment of the insulin sensitivity parameter improves the performance of the titration strategies for both the linear and the nonlinear MPC. Future work can include a more extensive performance evaluation by simulating virtual subjects using different T2D models. Additionally, one can consider adjusting different parameters from the model (3) such as V_G and τ_1.

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Appendix A. APPENDIX

Variables: $\tilde{I}_{sc}$ subcutaneous insulin [U/day]; $\tilde{I}_p$ plasma insulin [U/day]; $\tilde{I}_{eff}$ effect of insulin [U/day]; G glucose concentration [mmol/L]; D_1 and D_2 1st and 2nd compartment for ingested carbs [mmol].

Parameters: $\tau_{in} = 0.5$ insulin injection [day]; $\tilde{\beta} = 1.68$ glucose sensitivity for secreted insulin [U L/mmol/day]; $p_2 = 15.8$ effect of insulin rate [1/day]; $\tilde{S}_I = 1.8$ insulin sensitivity [1/U]; $G_{EZI} = 3.31$ rate constant for the insulin-independent lowering effect of glucose [1/day]; $E_{GP} = 368$ endogenous glucose production [mmol/L/day]; $\tau_m = 0.03$ time constant for the ingested carbohydrates compartments [day]; $V_G = 22$ Glucose distribution [L]; $M_{wG} = 180.1559$ Molar weight of glucose [g/mol].