Impulsive Zone MPC for Type I Diabetic Patients based on a long-term model

Alejandro H. González [*] **Pablo S. Rivadeneira** [*,**]
Antonio Ferramosca [***] **Nicolas Magdelaine** [****] **Claude H. Moog** [****]

[*] *CONICET - INTEC - Facultad de Ingeniería Química, Grupo de Control Avanzado de Procesos, Güemes 3450, Santa Fe, Argentina. -psrivade,alejgon@santafe-conicet.gov.ar*
[**] *Universidad Nacional de Colombia, Facultad de Minas, Grupo GITA, Cra. 80 65-223, Medellín, Colombia.*
[***] *CONICET - UTN Facultad Regional Reconquista, Calle 27 de Abril, 1000 (3560), Reconquista, Santa Fe.*
[****] *L'UNAM Université, IRCCyN, UMR-CNRS 6597, BP 92101, 44321 Nantes Cedex 3, France.*

Abstract: In this work the problem of regulating glycemia in type I diabetic patients is studied by means of an impulsive zone model predictive control (impulsive ZMPC) based on a novel long-term glucose-insulin model. Taking advantage of the model - which features real life properties of diabetes patients that some other popular models do not - the proposed control ensures the stability under moderate-to-severe disturbances. A long-term scenario - including meals - are simulated, and the results appear to be satisfactory as long as every hyperglycemia and hypoglycemia episodes are suitably controlled.

Keywords: Type I diabetes model, zone model predictive control, impulsive systems.

1. INTRODUCTION

Type 1 diabetes mellitus (T1DM) is an autoimmune disease, affecting approximately 18 million people in the world, characterized by the destruction of the pancreatic $\beta-$cells. As a consequence, the natural endogenous production of insulin disappears, thus results in a dysfunctional glycemic regulation. T1DM was a fatal disease until the discovery of insulin in 1921. Nowadays, the current treatment consist of a number of daily insulin injections - depending on the measurements of glycemia and on carbohydrate intake - or of continuous subcutaneous insulin infusion (CSII) via a pump, with the objective of maintaining glycemia in a safe zone (between 70 mg/dl and 120 mg/dl) (Magdelaine et al., 2015).

The germinal idea of an artificial pancreas (AP) for T1DM patients was first envisioned 30 years ago (Doyle III, 2012). In the last decade, Model Predictive Control (MPC) received an increasing attention as an advanced control strategy to be implemented in an AP device (Magni et al., 2009; Grosman et al., 2010; Gondhalekar et al., 2014). In general, these formulations use discrete-time control actions, and are based on the model of T1DM patient presented in (Bergman et al., 1981) and its linealizations (Dalla Man et al., 2007; Cobelli et al., 2009, 2014). The drawback of these models, as shown in (Magdelaine et al., 2015), is their modeling of apparent equilibria in fasting periods, in such a way that for each value of blood glucose (BG), a different insulin infusion rate is needed in order to maintain a constant BG level. In (Magdelaine et al., 2015) it is shown that in fact this is not true in real life, where patients display only one single-insulin infusion rate, called the basal rate, which does not depend on the value of glycemia, and which is capable of ensuring the equilibrium for any value of the glycemia in fasting periods.

In this note, an Impulsive Zone Model Predictive Control with artificial variables for T1DM patients is presented. The contribution is twofold. First, to exploit the anticipative benefits of the optimizing constrained controllers, a novel long-term glucose-insulin model is considered (Magdelaine et al., 2015). This model has the advantage of representing the patient realistically, which mainly means that it has a critically stable equilibrium manifold (instead of a stable one). This equilibrium corresponds to a basal insulin injection level, and small disturbances destabilize the system producing both, hyper and hypoglycemia episodes, if no actions are taken.

Then, in a second stage, an Impulsive Zone Model Predictive Controller that takes advantage of long-term forecasts that can be done with the latter model is designed. An impulsive scheme of the continuous-time original model is developed, which is devoted to control the entire system by only injecting control actions at given time instants. So, based on the design proposed in (Rivadeneira. et al., 2015), which uses artificial equilibrium variables (Limon et al., 2008; Ferramosca et al., 2010), a controller was designed to impulsively steer the glycemia to its safety interval. The controller has an enlarged domain of attraction, thanks to the use of artificial variables, and it ensures recursive feasibility and closed-loop stability. It is worth remarking that the use of a zone control strategy - which ensures that no control penalization is made when the glucose is inside the desired zone - is not a trivial fact, since every time the glucose is in the normoglycemia zone, no matter at which point it is, no unnecessary control action (insulin delivery) will be taken.

To evaluate the proposed strategy, the application of the proposed Impulsive Zone MPC strategy on five different T1DM patients is presented. To this aim, a long-term scenario - includ-

ing meals - is simulated. The results appear to be satisfactory as long as smooth variable behaviors are obtained, while hyperglycemia and hypoglycemia episodes are avoided.

The outline of this note is as follows. Section 2 presents the preliminaries, while Section 3 introduces the impulsive model. In Section 4 the proposed Zone MPC is presented, while in Section 5, the results of the *in silico* trials are given. Finally, some concluding remarks are proposed in Section 6.

2. PRELIMINARIES

According to (Magdelaine et al., 2015), we consider the following affine continuous time model:

$$\dot{x}(t) = Ax(t) + B_u u(t) + B_r r(t) + E, \;\; x(0) = x_0, \quad (1)$$

where $x(t) = [G(t) \;\; I(t) \;\; \dot{I}(t) \;\; D(t) \;\; \dot{D}(t)]'$, being G the glycemia (mg/dl), I the plasma insulin (insulinemia) (U/l) and D the digestion of CHO (g/dl). Furthermore, $u(t)$ is the insulin infusion rate (U) and $r(t)$ is the meal delivery rate (g/min). E is a constant term denoting the difference between the liver endogenous glucose production k_1 and the glucose absorption rate by the brain k_b.

The model matrices are given by:

$$A = \begin{pmatrix} 0 & -k_{si} & 0 & 1 & 0 \\ 0 & 0 & 1 & 0 & 0 \\ 0 & -\frac{1}{T_u^2} & -\frac{2}{T_u} & 0 & 0 \\ 0 & 0 & 0 & 0 & 1 \\ 0 & 0 & 0 & -\frac{1}{T_r^2} & -\frac{2}{T_r} \end{pmatrix}, \; B_u = \begin{pmatrix} 0 \\ 0 \\ \frac{k_u}{V_i T_u^2} \\ 0 \\ 0 \end{pmatrix},$$

$$B_r = \begin{pmatrix} 0 \\ 0 \\ 0 \\ 0 \\ \frac{k_r}{V_B T_r^2} \end{pmatrix}, \quad E = \begin{pmatrix} \theta \\ 0 \\ 0 \\ 0 \\ 0 \end{pmatrix}, \quad (2)$$

where k_{si} represents the sensitivity to insulin, T_u and $\frac{k_u}{V_i}$ are respectively the time constant and static gain of the relationship between the input $u(t)$ (insulin rate) and the insulinemia $I(t)$, with V_i being the insulin distributed volume, and T_r and $\frac{k_r}{V_B}$ are respectively the time constant and static gain of the relationship between the CHO in meal $r(t)$ and the digestion of CHO, $D(t)$, with V_B being the blood volume. Furthermore, the parameter θ of the constant term is given by $\theta = k_1 - k_b$.

Constraints for both, states and inputs are considered, in such a way that $u \in \mathcal{U}$, $x \in \mathcal{X}$ and $r \in \mathcal{R}$, where $\mathcal{U}$, $\mathcal{X}$ and $\mathcal{R}$ are assumed to be polyhedrons.

The main advantages of this model is that it is an integrating model (A has an eigenvalue at zero, which means that it is not stable) and so it better represents the evolution of the variable in real life diabetic patients. For instance, any equilibrium point corresponding to the fasting state ($r_s = 0$) is given by an arbitrary value of G, fixed values for the other states, and a fixed (and unique) value of insulin, $u_s \triangleq u_b$, which is known as the basal insulin rate. These characteristics, that make the model essentially different from other models used in the literature (mainly the Bergman model, (Bergman et al., 1981)), allow us to make long term predictions. This way, it is argued that every undesirable episode can be better anticipated and corrected.

The general control objective is **to maintain the glycemia in a safety range, $\mathcal{X}^{Tar}$, while keeping the other variables fulfilling the constraints, which are mainly positive values**. An interesting point is that the hypoglycemia episodes (when glycemia is below this safety range) is much more dangerous than hyperglycemia episodes (when the glycemia is above this safety range). Furthermore, the insulin infusion u is considered as the control variable, while the carbohydrate (CHO) in meals r is considered as a disturbance. This disturbance, however, is neither a completely known nor a completely unknown disturbance. In fact, in this work we assume that disturbance is unknown, which avoids the alternative to predict or anticipate the disturbance effect. A completely different problem arises - mainly in the context of predictive control - if disturbances (meals) are assumed to be (even partially) anticipated by means of a signal entering the controller. This issue is not in the scope of this paper, but a perspective for future research.

3. IMPULSIVE SCHEMES

In many cases it is desirable to control the glycemia by means of insulin bolus, instead of by a continuous delivery. This is not a limitating factor as the basal rate can be easily produced by a sequence of frequent microboluses (every minute). If we assume that the insulin infusion u is injected to the system **only at certain time instants** given by $\tau_k \triangleq kT$, where T is the fixed period, and $k \in \mathbb{N}$, then it is possible to work under the impulsive system framework. Formally, assume that the input is given by

$$u(t) = u(kT)\delta(t - kT), \;\; t \in [kT, (k+1)T], \;\; k \in \mathbb{N}, \quad (3)$$

where $\delta(t)$ is a generalized function (or distribution) Dirac delta [1], that fulfills $\delta(t) = \infty$ for $t = 0$, $\delta(t) = 0$ for $t \neq 0$, and

$$\int_{-\infty}^{\infty} g(\zeta)\delta(\zeta)d\zeta = g(0), \quad (4)$$

for all continuous, compactly supported, function g. This way, the solution of (1) at each periods T can be divided into two parts, the first one, describing the system in the period $[kT, \; kT + \Delta T]$, and the second one describing the system in the period $(kT + \Delta T, \; (k+1)T)$, for a positive and arbitrary small Δ:

$$\begin{aligned} \varphi(t; x(kT), u, r) = {} & e^{A(t-kT)}x(kT) \\ & + \int_{kT}^{kT+\Delta T} e^{A(t-\zeta)}B_u u(\zeta)\delta(\zeta - kT)d\zeta \\ & + \int_{kT}^{kT+\Delta T} e^{A(t-\zeta)}B_r r(\zeta)d\zeta \\ & + \int_{kT}^{kT+\Delta T} e^{A(t-\zeta)}d\zeta E, \end{aligned} \quad (5)$$

for $t \in [kT, \; kT + \Delta]$, and

[1] The Dirac delta is only an abstraction to formulate the impulsive problem. The idea behind this concept is that quick insulin injections can be properly approximated by impulses, if compared to T.

$$\varphi(t;x(kT+\Delta T),u,r)=e^{A(t-kT)}x(kT+\Delta T) + \int_{kT+\Delta T}^{(k+1)T} e^{A(t-\zeta)}B_r r(\zeta)d\zeta + \int_{kT+\Delta T}^{(k+1)T} e^{A(t-\zeta)}d\zeta E, \quad (6)$$

for $t \in (kT+\Delta,\ (k+1)T)$.

Now, if we consider the limits of this solution for $\Delta \to 0$, it follows that

$$x(kT^+) \triangleq \lim_{\Delta\to 0} \varphi(t;x(kT),u,r) = x(kT)+B_u u(kT), \quad (7)$$

and

$$x(t) \triangleq \lim_{\Delta\to 0} \varphi(t;x(kT^+),u,r) = e^{At}x(kT^+) + \int_{kT^+}^{(k+1)T} e^{A(t-\zeta)}B_r r(\zeta)d\zeta + \int_{kT^+}^{(k+1)T} e^{A(t-\zeta)}d\zeta E, \quad (8)$$

for $t \in (kT^+,\ (k+1)T)$. This latter solution is the one corresponding to the continuous time system $\dot{x}(t) = Ax(t) + B_r r(t) + E$, $x(0) = x_0$. So, the hybrid system evolution can be described as an impulsive system of the form:

$$\begin{cases} \dot{x}(t) &= Ax(t)+B_r r(t)+E,\ \ x(0)=x_0,\ t\neq\tau_k, \\ x(\tau_k^+) &= x(\tau_k)+B_u u(\tau_k), \qquad\qquad k\in\mathbb{N}, \end{cases} \quad (9)$$

Remark 1. An interesting point here is that the **impulsive system has not formal equilibrium points**. In fact, there are not triplets (x_s^i, u_s^i, r_s^i) fulfilling the condition:

$$Ax_s^i + B_r r_s^i + E = 0, \quad (10)$$

$$x_s^i = x_s^i + B_u u_s^i, \quad \text{(no jump)}, \quad (11)$$

because the first equation has not solution, for $r_s^i = 0$ (fasting condition).

An interpretation of the latter situation is that it is not possible to maintain the system in a given point by only applying impulsive inputs, even when this input is null. However, as it will be shown in the next section, it is possible to maintain the system (switching) **inside** a given region. The condition for that is: (i) to find states before and after the jump, that although different between them, remain constant, and (ii) to ensure that the transient state trajectories between these states remain inside a given set.

Remark 2. We assume for simplicity that the disturbance $r(t)$ remains constant for $t \in [kT,(k+1)T)$, $k \in \mathbb{N}$; i.e., $r(t) \equiv r(k)$ for $t \in [kT,(k+1)T)$ (zero order hold). This means that the continuous-time equation in (9) can be written as

$$\dot{x}(t) = Ax(t) + B_r r(k) + E,\ \ t\in(\tau_k,\tau_{k+1}),\ k\in\mathbb{N},$$

where the starting state of the evolution is given by $x(\tau_k^+) = x(\tau_k) + B_u u(\tau_k)$.

3.1 Underlying discrete time subsystems

According to the impulsive scheme developed in (Rivadeneira. et al., 2015), two underlying discrete-time subsystems associated to (9) can be defined to characterize the states $x(\tau_k)$ and $x(\tau_k^+)$ evolution [2]:

$$x^\bullet(k+1) = A^\bullet x^\bullet(k) + B_u^\bullet u^\bullet(k) + B_r^\bullet r^\bullet(k) + E^\bullet,\ x^\bullet(0) = x(\tau_0),$$

$$x^\circ(k+1) = A^\circ x^\circ(k) + B_u^\circ u^\circ(k) + B_r^\circ r^\circ(k) + E^\circ,\ x^\circ(0) = x(\tau_0^+),$$

where $A^\bullet = A^\circ \triangleq A^d = e^{AT}$, $B_u^\bullet = e^{AT}B_u$, $B_u^\circ = B_u$. Furthermore, the input and disturbance are related by $u^\circ(k+1) = u^\bullet(k) = u(\tau_k)$, $r^\circ(k) = r^\bullet(k) = r(k)$, and $E^\bullet = E^\circ \triangleq \int_0^T e^{A\zeta}d\zeta E$, $B_r^\bullet = B_r^\circ \triangleq \int_0^T e^{A\zeta}d\zeta B_r$.

3.2 Extended equilibrium for the impulsive representation

The extended equilibrium points of the impulsive representation are characterized by the equilibrium points of the **Underlying Subsystems**, $(x_s^\bullet, u_s^\bullet, r_s^\bullet)$ and $(x_s^\circ, u_s^\circ, r_s^\circ)$, respectively, in such a way that they must fulfill the conditions:

$$x_s^\bullet = A^\bullet x_s^\bullet + B_u^\bullet u_s^\bullet + B_r^\bullet r_s^\bullet + E^\bullet,$$
$$x_s^\circ = A^\circ x_s^\circ + B_u^\circ u_s^\circ + B_r^\circ r_s^\circ + E^\circ.$$

So, the equilibrium sets corresponding to the two subsystems are given by

$$\mathcal{X}_s^\bullet \triangleq \{x_s^\bullet \in \mathcal{X} : \exists u_s^\bullet \in \mathcal{U}, r_s^\bullet = 0 \text{ such that } A^\bullet x_s^\bullet + B_u^\bullet u_s^\bullet + B_r^\bullet r_s^\bullet + E^\bullet = 0\}, \quad (12)$$

$$\mathcal{X}_s^\circ \triangleq \{x_s^\circ \in \mathcal{X} : \exists u_s^\circ \in \mathcal{U}, r_s^\circ = 0 \text{ such that } A^\circ x_s^\circ + B_u^\circ u_s^\circ + B_r^\circ r_s^\circ + E^\circ = 0\}, \quad (13)$$

$$\mathcal{U}_s^\bullet \triangleq \{u_s^\bullet\} = \{u_b^\bullet\}, \quad \mathcal{U}_s^\circ \triangleq \{u_s^\circ\} = \{u_b^\circ\}. \quad (14)$$

Furthermore, given that $u^\circ(k+1) = u^\bullet(k)$ and $r^\circ(k) = r^\bullet(k)$ by definition (and $E^\circ = E^\bullet$), we have that at steady state it is $u_s^\bullet = u_s^\circ$ and $r_s^\bullet = r_s^\circ$. For simplicity, we denote the equilibrium input and disturbance of both subsystems as $u^\bullet(k)$ and $r_s^\bullet$, respectively. This means that we need to find variables $(x_s^\bullet, x_s^\circ, u_s^\bullet, r_s^\bullet)$ fulfilling

$$x_s^\bullet = A^\bullet x_s^\bullet + B_u^\bullet u_s^\bullet + B_r^\bullet r_s^\bullet + E^\bullet, \quad (15)$$

$$x_s^\circ = A^\circ x_s^\circ + B_u^\circ u_s^\bullet + B_r^\circ r_s^\bullet + E^\bullet. \quad (16)$$

Remark 3. An important point here is that both triplets $(x_s^\bullet, u_s^\bullet, r_s^\bullet)$ and $(x_s^\circ, u_s^\bullet, r_s^\bullet)$ are **in general different from** the continuous-time (or discrete-time) equilibrium (in particular, $u_s = u_b \neq u_s^\bullet = u_b^\bullet$). This fact is rather intuitive, given that the **impulsive input** necessary to keep the system in an extended equilibrium (or equilibrium orbit) is not the same to the one necessary to keep the system in an equilibrium point by applying a continuous (or piecewise constant) input signal.

Remark 4. Note that $(x_s^\bullet, u_s^\bullet, r_s^\bullet) \to (x_s, u_s, r_s)$ only for $T \to 0$, whose limit represents the continuous time case.

A final condition that the equilibrium quadruplets $(x_s^\bullet, x_s^\circ, u_s^\bullet, r_s^\bullet)$ must fulfill to be a **feasible extended equilibrium**, is that the free response corresponding to them (the orbit) must be feasible; i.e., $o_s(x_s^\bullet, u_s^\bullet, r_s^\bullet) \in \mathcal{X}$, where $o_s(x_s^\bullet, u_s^\bullet, r_s^\bullet) \triangleq \{\phi(t; x_s^\bullet, u_s^\bullet(t), r_s^\bullet(t)), t \in [\tau_k, \tau_{k+1}), k \in \mathbb{N}\}$, $u_s^\bullet(t)$ is the impulsive input and $r_s^\bullet(t)$ the constant disturbance, in a period T, i.e., $u_s^\bullet(t) = u_s^\bullet \delta(t-\tau_k)$ and $r_s^\bullet(t) = r_s^\bullet$, for $t \in [\tau_k, \tau_{k+1}),\ k \in \mathbb{N}$.

In this context, we can characterize the extended equilibrium by redefining the equilibrium set $\mathcal{X}_s^\bullet$ as [3]

[2] The state $x(\tau_k)$ is denoted as $x^\bullet(k)$, while $x(\tau_k^+)$ is denoted as $x^\circ(k)$.

[3] Note that condition (12) (and (16)) is implicitly accounted for definition (17).

$$\mathcal{X}_s^\bullet \triangleq \{x_s^\bullet \in \mathcal{X} : \exists u_s^\bullet \in \mathcal{U}, r_s^\bullet = 0 \text{ such that}$$
$$A^\bullet x_s^\bullet + B_u^\bullet u_s^\bullet + B_r^\bullet r_s^\bullet + E^\bullet = 0,\ o_s(x_s^\bullet, u_s^\bullet, r_s^\bullet) \in \mathcal{X}\} \quad (17)$$

Furthermore, $\mathcal{U}_s^\bullet$ is a singleton for the diabetes system, i.e., $\mathcal{U}_s^\bullet \triangleq \{u_s^\bullet\} = \{u_b^\bullet\} \neq \{u_b\}$.

The same procedure can be followed to define the equilibrium sets corresponding to the **target** or **therapeutic window**, $\mathcal{X}_s^{\bullet Tar}$ and $\mathcal{U}_s^{\bullet Tar} \triangleq \{u_b^\bullet\}$.

4. IMPULSIVE ZMPC FORMULATION

The control objective is to steer, and to maintain, the system in the therapeutic window, avoiding significant hyper an hypoglycemia episodes. The therapeutic window is characterized - for the impulsive scheme - by sets $\mathcal{X}_s^{\bullet Tar}$ and $\mathcal{U}_s^{\bullet Tar}$ while $\mathcal{X}_s^\bullet$ and $\mathcal{U}_s^\bullet$ denote the equilibrium sets.

The proposed MPC formulation is the one described in (Rivadeneira. et al., 2015), adapted to the integrating affine system (1). The cost of the optimization problem that MPC solves online is

$$V_N(x, \mathbf{r}, \mathcal{X}_s^{\bullet Tar}, \mathcal{U}_s^{\bullet Tar}; \mathbf{u}, u_a, x_a) \triangleq V_{dyn}(x, \mathbf{r}; \mathbf{u}, u_a, x_a) + V_f(\mathcal{X}_s^{\bullet Tar}, \mathcal{U}_s^{\bullet Tar}; u_a, x_a),$$

where $V_{dyn}(x, \mathbf{r}; \mathbf{u}, u_a, x_a) = \sum_{j=0}^{N-1} (x(j) - x_a)^T C'QC (x(j) - x_a) + (u(j) - u_a)^T R (u(j) - u_a)$, with $Q > 0$ and $R > 0$, is a term devoted to steer the system to a certain **artificial open-loop equilibrium variable** given by the **artificial pairs** $(u_a, x_a) \in \mathcal{U}_s^\bullet \times \mathcal{X}_s^\bullet$, and $V_f(\mathcal{X}_s^{\bullet Tar}, \mathcal{U}_s^{Tar}; u_a, x_a) = p\left(dist_{C\mathcal{X}_s^{\bullet Tar}}(Cx_a) + dist_{\mathcal{U}_s^{\bullet Tar}}(u_a)\right)$, with $p > 0$, is a terminal cost devoted to steer Cx_a to the whole sets $C\mathcal{X}_s^{\bullet Tar}$ and u_a to $\mathcal{U}_s^{\bullet Tar}$, respectively. Matrix C is an output matrix that decides which states will be controlled (**we consider in this case the first** 3 **states, which represent the controllable part of the system**).

Note that in the latter cost, the current state x, the (possibly unknown) predicted disturbance $\mathbf{r} = \{r(0), r(1), \cdots, r(N-1)\}$, and the target sets $\mathcal{X}_s^{\bullet Tar}$ and $\mathcal{U}_s^{\bullet Tar}$ are **optimization parameters**, while $\mathbf{u} = \{u(0), u(1), \cdots, u(N-1)\}$, u_a and x_a are the **optimization variables** (being N the control horizon).

Remark 5. The latter cost is a zone-symmetric quadratic cost, that penalizes the distance to the desired target set (zone), in a symmetric form. Many alternatives can be analyzed to improve this cost, in order to penalize harder the hypoglycemia episodes, and to prevent excursions far from the zone. See (Gondhalekar et al., 2015) for an example.

The optimization problem to be solved at time k by the MPC is given by

$P_{MPC}(x, \mathbf{r}, \mathcal{X}_s^{\bullet Tar}, \mathcal{U}_s^{\bullet Tar})$:

$$\begin{aligned}
\min_{\mathbf{u}, u_a, x_a}\ & V_N(x, \mathbf{r}, \mathcal{X}_s^{\bullet Tar}, \mathcal{U}_s^{\bullet Tar}; \mathbf{u}, u_a, x_a) \\
s.t.\ & \\
& x(0) = x, \\
& x(j+1) = A^\bullet x(j) + B_u^\bullet u(j) + B_r^\bullet r(j) + E^\bullet, j \in \mathbb{I}_{0:N-1} \\
& x(j) \in \mathcal{X},\ u(j) \in \mathcal{U}, \qquad j \in \mathbb{I}_{0:N-1} \\
& x(N) = x_a, \\
& x_a \in \mathcal{X}_s^\bullet,\ \ u_a \in \mathcal{U}_s^\bullet.
\end{aligned}$$

The constraint $x(N) = x_a$ is the terminal constraint that forces the terminal state - at the end of control horizon N - to reach the artificial equilibrium state x_a. Furthermore, the last constraint forces the artificial variable pair (u_a, x_a) to be in $\mathcal{X}_s^\bullet \times \mathcal{U}_s^\bullet$, and it is equivalent to force the pair (u_a, x_a) to fulfill the equilibrium condition $x_a = A^\bullet x_a + B^\bullet u_a$. This means that the state at the end of the horizon is only forced to be any feasible equilibrium state.

Once the Problem $P_{MPC}(x, \mathbf{r}, \mathcal{X}_s^{\bullet Tar}, \mathcal{U}_s^{\bullet Tar})$ is solved, the (optimal) solution is denoted as $(\mathbf{u}^0, u_a^0, x_a^0)$, while the optimal cost function is given by $V_N^0(x, \mathbf{r}, \mathcal{X}_s^{\bullet Tar}, \mathcal{U}_s^{\bullet Tar}) \triangleq V_N(x, \mathbf{r}, \mathcal{X}_s^{\bullet Tar}, \mathcal{U}_s^{\bullet Tar}; \mathbf{u}^0, u_a^0, x_a^0)$. The control law, derived from the application of a **receding horizon control** policy (RHC), is given by $\kappa_{MPC}(x, \mathbf{r}, \mathcal{X}_s^{\bullet Tar}, \mathcal{U}_s^{Tar}) = u^0(0; x)$, where $u^0(0; x)$ is the first element of the solution sequence $\mathbf{u}^0(x)$. The domain of attraction of the closed loop, $\mathcal{X}_N^\bullet$, is given by the controllable set in N steps to the **entire equilibrium set** $\mathcal{X}_s^\bullet$.

Remark 6. In this work, for brevity, we consider only the (worst) case in which $\mathbf{r}$ is unknown for the MPC, and so, $\mathbf{r} = 0$, which means that no information is passed to the MPC regarding the meals.

5. IN SILICO: NUMERICAL RESULTS

The impulsive ZMPC controller is tested to regulate glycemia using the T1DM patient model described above, together with the constraints and the target window. The simulation horizon is settled in 50 h. This horizon is larger than the one used in other works (Gondhalekar et al., 2014; Grosman et al., 2010; Doyle III, 2012), since the used linear model is able to reproduce accurately the behaviors for long-time intervals. In spite of the simplicity of the model, this is an advantage when control strategies are designed.

Five patients are considered as in (Magdelaine et al., 2015). According to their parameters, some information can be collected for the future tuning of the MPC controller. The gain and settling time of the response of each patient to the insulin injection and food intake are calculated, being G_u, ST_u, G_r, and ST_r, respectively, and shown in Table 1.

Table 1. Insulin - Glycemia - Food intake response parameters

Patient	G_u	$ST_u(h)(\approx 6T_i)$	G_r	ST_r (h)
IF2	10.69	13	2.4	19
IF3	17.2	9	2	5
LR	81.53	7	4.9	4
IF9	44.46	7	7	8
BE	9.87	6	2.7	4

Note that only Patient IF2 has ST_u smaller than ST_r (significantly smaller in fact). This fact makes this patient very easy to be controlled (as it will be shown next), since clearly, the food effect can be quickly compensated by the insulin injection. For the other patients, the limitations for a good closed-loop performance are harder, because the food effect is faster than the insulin one. However, it should be noted that these limitation (together with the input and state limits) represents limitation of the system itself, and not of the controller.

The state and input constraints are given by $\mathcal{X} = \{x : [0\ 0\ -0.1\ 0\ -0.1]^T \preceq x \preceq [500\ .5\ 0.1\ 1\ 0.1]^T\}$ and $\mathcal{U} = \{u :$

$0 \leq u \leq 30\}$, respectively. The state target window should be decided by the treating physician. In the simulation below it is defined by $\mathcal{X}^T = \{x : [80\ 0\ -0.1\ 0\ -0.1]^T \preceq x \preceq [100\ 0.2\ 0.05\ 0.5\ 0.05]^T\}$. It is clear that, if the glycemia remains most of the time within the boundaries of $\mathcal{X}^T$, then the insulin therapy is satisfactory. The time period was selected to be $T = 15$ (min) (in many cases it could be modified with good results). In general, this period should be selected according the speed of the response of the system (to the insulin and food). This is so because the controller can inject insulin only at the period times kT, $k \in \mathbb{N}$. If a disturbance enters the system at time, for instance, $t = kT + \Delta$, with $\Delta << T$, then the controller must wait for almost T minutes to compensate it. In this context, and given the time responses, patient IF2 can be almost perfectly controlled with $T = 60$ min - if only meals are considered as a disturbances - while patient IF3 cannot.

The **control/prediction horizon N should be large enough to account for the entire insulin effect** (given that overdoses are hard to compensate, because of its positiveness). So, according to the insulin response settling time, the control/prediction horizon (which is the number of periods considered for the predictions) is selected in these simulations to be $N \approx \frac{ST_u \times 60}{T}$, which is only a **practical rule**. Note however that, as it is usual in MPC, the use of larger horizons N needs a high computational effort. The MPC parameters are selected to be: $Q = 500$; $R = 1$; $p = 500000$. A detailed analysis for the selection of these parameters, according to the patient parameters, still needs to be done.

The therapeutic windows (target zone) for the glycemia values is selected to be $[80 - 100]$, which is a zone strictly inside the **normoglycemia** zone of $[60 - 140]$. This is so to improve the performance, since the controller makes no distinction between points inside the zone, and so, it tends to maintain the glycemia at the boundary of the therapeutic window (not at a middle point) that is closer to the current value. If a disturbance pushes the system above the zone, the controller only steers the system back to the upper bound of the zone. As a result, any disturbance in the same direction will produce a transitory evolution that can take the glycemia far from the upper bound. So selecting the bounds of the target zone inside the normoglycemia zone could be a good practice.

The simulated meal schedule is the one shown in (Magdelaine et al., 2015). Notice that the meals/disturbances enter the system at arbitrary times (in minutes), and the MPC controller only "sees" its effect at the next time period. The results - for three of the patients simulated - can be seen in Figures 1-6. Note that the meals enter the system as a pulse of $T = 15$ min of duration; so, the amount of CHO of each meal should be computed as the value on the right hand side scale of Figures 1, 3 and 5, multiplied by 15. As it can be seen, the glycemia evolutions is significantly better than the one obtained by the manual injection of insulin bolus.

6. CONCLUSIONS

The contributions of the paper are in two-folds: an Impulsive Zone MPC controller is designed based on a new impulsive affine model that accurately describes the Type I diabetic patient. The main attributes of the model (in contrast with other popular ones) that make it suitable for the proposed MPC are: i) It shows a non-stable equilibrium region (integrating behavior), uniquely characterized by a set of glucose levels and fixed value of insulin injection. This allows to get a reliable description of the true T1DM patient, mainly from the point of view of the anticipative characteristics of MPC controllers. In fact, anticipating an eventual unstable behavior allows the controller to take preventive action faster. ii) It is a long-term model, and so the well-known anticipative benefits of predictive strategies is much better exploited. This way, eventual hyper and hypo glycemia episodes that may happen in the future can

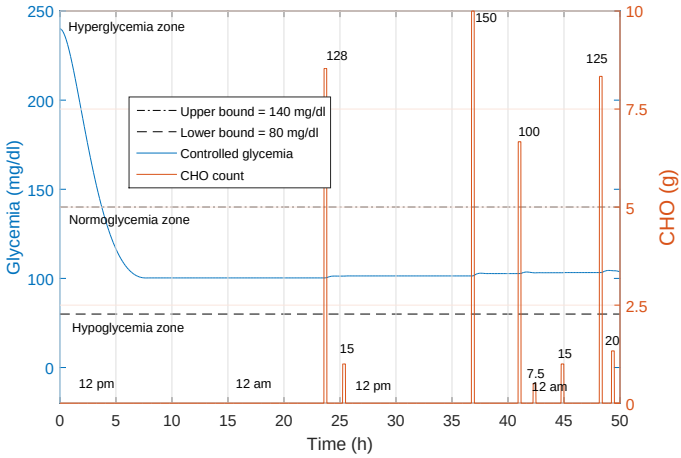

Figure 1. IF2 patient. Glycemia evolution (blue line) and meals (red line).

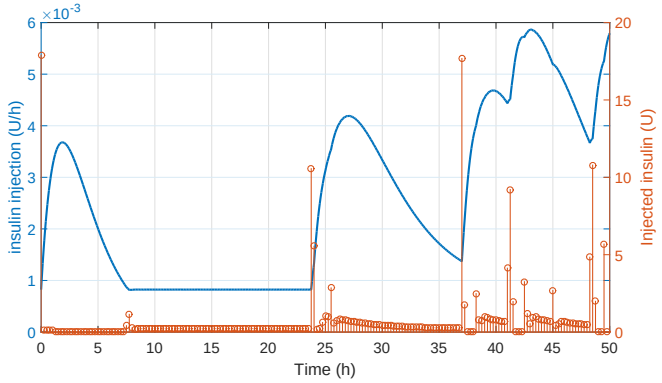

Figure 2. IF2 patient. Insulinemia evolution (blue line) and Bolus (red line).

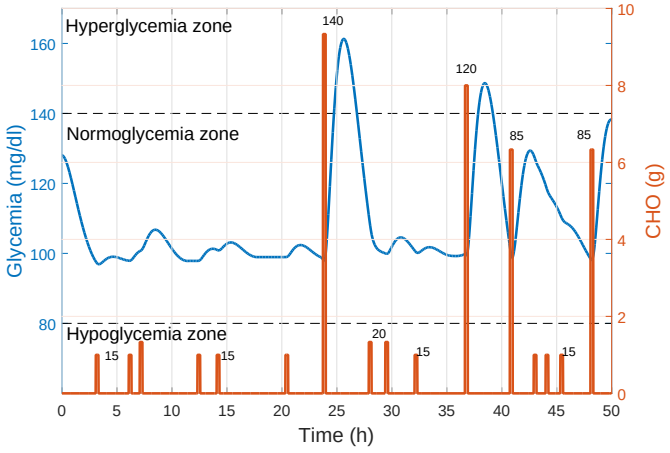

Figure 3. IF3 patient. Glycemia evolution (blue line) and meals (red line).

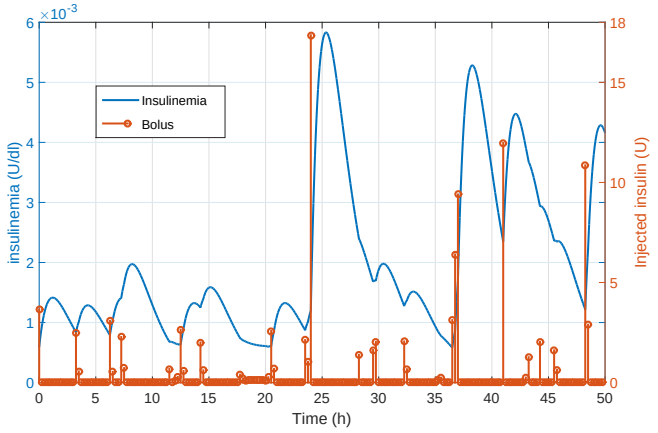

Figure 4. IF3 patient. Insulinemia evolution (blue line) and Bolus (red line).

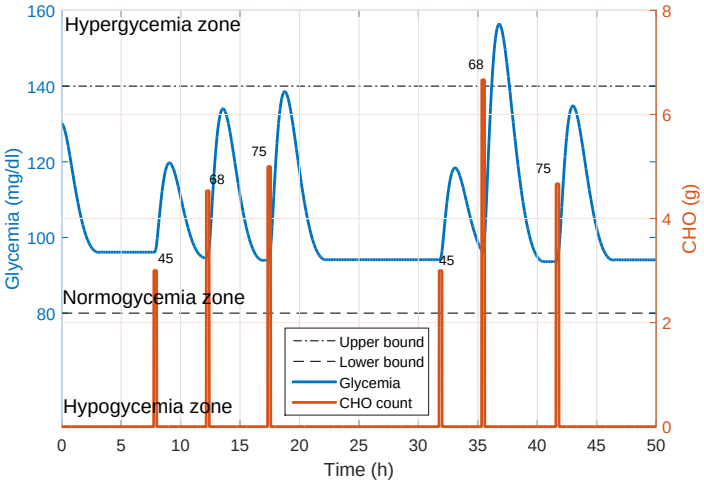

Figure 5. BE patient. Glycemia evolution (blue line) and meals (red line).

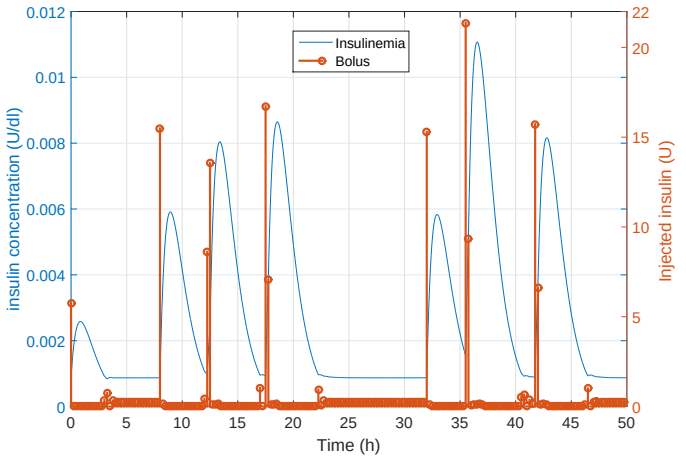

Figure 6. BE patient. Insulinemia evolution (blue line) and Bolus (red line).

be predicted - and avoided - faster by means of a smooth insulin delivery. iii) It is an affine model, and so, no approximation is needed for the impulsive representation. Opposite to other MPC strategies, which needs a permanent insulin injection (zero-order hold), here the insulin is delivered by boluses, which can prevent insulin overdoses.

The main features of this new MPC controller are: i) The use of artificial variables produces a large domain of attraction. This means that disturbances that steer the system far from the desired equilibrium target can also be controlled. ii) It works by zones in such a way that no control penalization is made when the glucose is inside the desired zone. This is not a trivial achievement, since every time the glucose is in the zone, no matter in which point it is, no unnecessary control action (insulin delivery) will be taken. iii) Although the selection of the main impulsive ZMPC parameters may be not trivial, it allows a variety of closed-loop behaviors.

Although the proposal shows promising preliminary results that come from the formulation itself, they must still be tested in more realistic scenarios. The first step is to make a comparison with other available models (i.e., Bergman linearized model, (Bergman et al., 1981)) under MPC schemes. This way, conclusion can be drawn about the performance obtained with both approaches and how it is impacted by the choice of the model.

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