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ABSTRACT

The glycemia regulation is a significant challenge in the Artificial Pancreas (AP) scenario. Several control systems have been developed in the last years, many of them requiring meal announcements. Therefore, if the patients skip the meal announcement or make a mistake in the estimation of the amount of carbohydrates, the control performance will be negatively affected. In this extended version of our previous work, we present a Model Predictive Controller (MPC) for the AP in which the meal is treated as a disturbance to be estimated by an Unknown Input Observer (UIO). The MPC constraints are expressed in terms of Signal Temporal Logic (STL) specifications. Indeed, in the AP some requirements result in hard constraints (in particular, absolutely avoid hypoglycemia and absolutely avoid severe hyperglycemia) and some other in soft constraints (avoid a prolonged hyperglycemia) and STL is suitable for expressing such requirements. The achieved results are obtained using the BluSTL toolbox, which allows to synthesize model predictive controllers with STL constraints. We report simulations showing that the proposed approach, avoiding unnecessary restrictions, provides safe trajectories in correspondence of higher unknown disturbance.

KEYWORDS

Artificial pancreas; model predictive control; Signal Temporal Logic; unknown input; observer

Introduction

Glucose is a simple sugar that, circulating in plasma, provides energy to cells. The glucose concentration in blood is important for human health care; in particular, a persistent high glucose-level in blood, also known as hyperglycemia condition, leads to glucose toxicity and therefore to cell dysfunction. On the other hand, a low glucose-level in blood, also referred to as hypoglycemia, may cause potentially fatal conditions. Typically, blood sugar concentration increases after food intake and the body regulates blood glucose levels as a part of metabolic homeostasis, thereby restoring a

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normal value of sugar concentration in blood (around $4.4 - 6.1$ mmol/L). This mechanism is characterized by a hormone regulation: the catabolic hormones increase the blood glucose; the anabolic hormones, such as the insulin, decrease it. The pancreas wisely balances these hormones delivery by using the α and the β cells, respectively. Type 1 Diabetes Mellitus (T1DM) is a metabolic disease induced by the pancreas inability in insulin production. Patients affected by this particular pathology must inject insulin to prevent the increase of glucose level in blood.

The Artificial Pancreas is a wearable device developed to simplify the therapy management for T1DM patients. The main elements of an AP are a Continuous Glucose Monitoring (CGM) system, which provides a real-time measure of glucose level in blood, and a pump, which allows a subcutaneous delivery of insulin. Ideally, a controller has to automatically compute the required amount of insulin starting from the knowledge of blood glucose concentration. Unfortunately, the subcutaneous administration of insulin leads to a delay in its absorption (American Diabetes Association 2013). The resulting effect is a rapid growth of glucose after meal that increases the risk of the hyperglycemia condition (Gingras et al. 2018). The current closed loop devices solve the aforementioned problem by requiring an accurate information about meal carbohydrate-content and meal announcement. These requests are not easy to satisfy, especially for adolescents, and the resulting mistakes can lead to undesirable and dangerous outcomes.

The ongoing research direction is to remove meal announcement by automating meal detection and insulin dose computation. Several approaches in literature have already been proposed. Certain solutions use the glucose level in blood for meal detection and estimation. For example, in Dassau et al. (2008) authors process glucose measurements in parallel by using a glucose rate of change (ROC) and a Kalman Filter. Furthermore, they define a meal detection algorithm in which a voting system selects one among 4 meal detection methods. Lee et al. (2009) employs the first and second glucose derivatives with some threshold criterion to assess the meal bolus. However, some other solutions employ an estimation of the meal absorption dynamic, for example using Kalman Filter (Xie and Wang 2017) or unscented Kalman Filter (Turksoy and Cinar 2015; Ramkissoon et al. 2018). In Sala, Dìez, and Bondia (2018) authors consider the viability of generalized extended state observer (GESO) to estimate the rate of meal glucose appearance. Sliding mode observers (SMO) are employed to reconstruct disturbances by means of the equivalent output injection term (Sun et al. 2017). Sala-Mira et al. (2019) proposes an estimation of the meal glucose appearance rate obtained via a first order sliding mode observer (FOSMO) and a meal detector algorithm based on a super-twisting observer (ST).

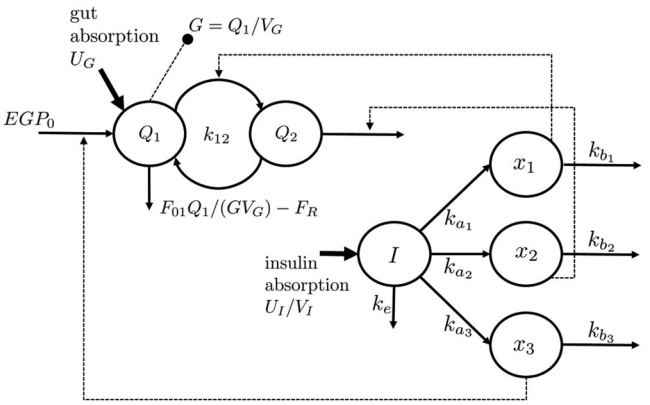

Figure 1. Hovorka compartment model outline.

In a previous work (Cairoli et al. 2019), we have presented a Model Predictive Controller (MPC) for the AP. We have addressed the problem of imposing temporal constraints between events by using the Signal Temporal Logic (STL). Such a solution has allowed us to express both hard (avoid absolutely severe hyperglycemia and avoid absolutely hypoglycemia) and soft constraints (avoid prolonged hyperglycemia), thus increasing the maximum amount of tolerated carbohydrates with respect to some previous works. However, Cairoli et al. (2019) requires information about the meal occurrence and its carbohydrate-content.

In the present work we overcome such limitation by employing an Unknown Input Observer (UIO) (Radke and Gao 2006) to estimate the carbohydrate intake, treated as a (unknown) disturbance. This additional step provides a new complete system that can be useful for large clinical research studies.

The remainder of the paper is organized as follows. In Section *Model of glucose metabolism*, the employed model of the glucoregulatory system is described. Section *Signal Temporal Logic* introduces the general behavior of the STL as a quantitative semantic. In Section *Control problem* the Model Predictive Control Problem including the STL constraints is formulated. Section *Unknown Input Observer* shows the general UIO design. In Section *BluSTL tool* the employed Matlab toolbox is introduced. Section *Implementation and simulation results* describes the implementation procedures and the obtained results in all the considered scenarios. Finally, some conclusions are reported in the last section.

Model of Glucose Metabolism

In order to define the plant model for the implementation of MPC, we choose the Hovorka compartment ODE model (Hovorka et al. 2004). It

Table 1. Hovorka parameters' values.

Parameter	Value	Parameter	Value
w	100	k_e	0.138
k_{12}	0.066	V_I	0.12w
k_{a1}	0.006	A_G	0.8
k_{b1}	0.0034	t_{max_G}	40
k_{a2}	0.06	EGP_0	0.0161w
k_{b2}	0.056	F_{01}	0.0097w
k_{a3}	0.03	t_{max_I}	55
k_{b3}	0.024	F_R	0

represents the glucoregulatory system and includes submodels representing absorption of subcutaneously administered short-acting insulin and gut absorption. The model outline is depicted in Figure 1. Parameter values are listed in Table 1, while the full set of differential equations is the following:

$$\dot{Q}_1(t) = -F_{01} - x_1 Q_1 + k_{12} Q_2 - F_R + EGP_0(1 - x_3) + U_G(t) \tag{1.a}$$

$$\dot{Q}_2(t) = x_1 Q_1 - (k_{12} + x_2) Q_2 \tag{1.b}$$

$$\dot{S}_1(t) = u(t) + u_b - \frac{S_1}{t_{maxI}} \tag{1.c}$$

$$\dot{S}_2(t) = \frac{S_1 - S_2}{t_{maxI}} \tag{1.d}$$

$$\dot{I}(t) = \frac{S_2}{t_{maxI} V_I} - k_e I \tag{1.e}$$

$$\dot{x}_i(t) = -k_{a_i} x_i + k_{b_i} I (i = 1, 2, 3) \tag{1.f}$$

$$y(t) = G(t) = \frac{Q_1(t)}{V_G} \tag{1.g}$$

where

$$U_G(t) = \frac{D_G A_G}{0.18 t_{maxG}^2} \; t \; e^{\left(\frac{-t}{t_{maxG}}\right)}. \tag{2}$$

It is possible to identify three subsystems:

- The Glucose Subsystem (1.a, 1.b) that allows to track the amount of glucose (in mmol) in the accessible and non-accessible compartments ($Q_1(t)$ and $Q_2(t)$ respectively). $G(t)$ (mmol/L) (1.g) represents the glucose concentration in plasma with a given distribution volume V_G (L), EGP_0 (mmol/min) the endogenous glucose production rate and $U_G(t)$ (mmol/min) (2) the glucose absorption rate after consuming the main external disturbance D_G (grams of carbohydrates).
- The Insulin Subsystem (1.c, 1.d, 1.e), defined by two-compartment chain, $S_1(t)$ and $S_2(t)$ measured in U (units of insulin), representing the absorption of subcutaneously administered insulin. The administration of insulin computed by the controller is $u(t)$ (U/min), whereas u_b

(U/min) and $I(t)$ (U/L) are respectively the basal insulin infusion rate and the insulin concentration in plasma.

- The Insulin Action Subsystem (1.f) that models the action of insulin on glucose distribution/transport $x_1(t)$, glucose disposal $x_2(t)$, and endogenous glucose production $x_3(t)$ (unit-less).

In a unified fashion, it can be represented as a non-linear system Σ of the form:

$$\begin{cases} \dot{x}(t) = F(x(t), u(t), d(t)) \\ \qquad\quad = f(x(t)) + B_u \cdot u(t) + B_d \cdot d(t), \\ y_{NL}(t) = cx(t) \end{cases} \tag{3}$$

where $F(x, u, d)$ and $f(x)$ are non-linear functions, $\mathrm{x}(t) \in \mathcal{X} \subseteq R^n$ is the state, $u(t) \in \mathcal{U} \subseteq R$ is the control input, $d(t) \in \mathcal{D} \subseteq R$ is the environment input (also referred to as disturbance, in particular the glucose production rate $U_G(t)$) and $y_{NL}(t) \in \mathcal{Y} \subseteq R$ is the output. For the MPC control system part, the model is linearized around an equilibrium and discretized using a time step Δt (it will be deepened later). The resulting system Σ_L is of the form:

$$\begin{cases} x_{k+1} = Ax_k + B_u u_k + B_d d_k \\ y_{LIN_k} = Cx_k. \end{cases} \tag{4}$$

Signal Temporal Logic

For the examined task the specifications should be independent from the chosen Δt; this is a good reason to prefer STL over Linear Temporal Logic (LTL) (Pnueli 1977).

An atomic predicate π^{μ} is a function of the form $\mathcal{X} \times \mathcal{Y} \times \mathcal{U} \times \mathcal{D} \rightarrow \{0, 1\}$, where 0 and 1 are the Boolean representations of false and true, respectively. The truth value of such atomic predicate depends on the sign of the function $\mu : \mathcal{X} \times \mathcal{Y} \times \mathcal{U} \times \mathcal{D} \rightarrow R$. Any formula can be defined as a recursive combination of atomic predicates with the operators present in the grammar of the considered logic.

The STL grammar is $\varphi ::= \pi^{\mu} \mid \neg\psi \mid \varphi_1 \wedge \varphi_2 \mid \text{alw } \psi \mid \varphi_1 \text{until}_{[a,b]} \varphi_2$, where $\wedge$ indicates the "and" operator, while $\text{alw}_{[a,b]}$ and $\text{until}_{[a,b]}$ are two temporal operator, explained later on.

Given an initial state $x_0 \in \mathcal{X}$ and two sequences $\underline{\mathrm{u}} = \mathrm{u}_0\mathrm{u}_1 \ldots \mathrm{u}_{N-1}$ and $\underline{\mathrm{d}} = \mathrm{d}_0\mathrm{d}_1 \ldots \mathrm{d}_{N-1}$ of N elements, a run $\xi(x_0, \underline{u}, \underline{d}) \in \mathcal{X}^{\mathcal{N}}$ is defined as the 4-uple of sequences $\left(\underline{x}, \underline{y}, \underline{u}, \underline{d}\right)$ obtained by applying the two sequences, $\underline{u}$ and $\underline{d}$, to a system such as Σ_L, starting from x_0. $\xi \vDash \varphi$ denotes that a run $\xi(x_0, \underline{u}, \underline{d})$ satisfies an STL formula φ.

The temporal operators can be explained, informally, as the "always" operator ($\xi \vDash alw_{[a,b]}\psi$ if ψ holds at all times between a and b) and the

"until" operator ($\xi \vDash \varphi_1 \text{until}_{[a,b]} \varphi_2$ if φ_1 holds at every time step before φ_2 holds). An additional temporal operator, known as "eventually" operator, could be derived from the ones present in the STL grammar ($\xi \vDash ev_{[a,b]}\varphi = \text{true until}_{[a,b]}\varphi$ means that φ holds at some time step between a and b). The formal definition of the operators presented in the grammar can be found in Raman et al. (2014).

STL admits *quantitative semantics* which, in addition to Boolean answers to the satisfaction questions, provides a robustness index ρ^{φ} that expresses the quality of the satisfaction or violation. It is a real-valued function of ξ and t such that $\rho^{\varphi}(\xi, t) > 0$ if $(\xi, t) \vDash \varphi$ and $\rho^{\varphi}(\xi, t) < 0$ if $(\xi, t) /\vDash \varphi$ (Raman et al. 2014) and it should be interpreted as how "far" ξ is from violating φ. In other words, it can be viewed as the signed distance of ξ from the set of trajectories satisfying or violating φ, in the space of projections with respect to the function μ that defines the predicates of φ. The recursive definition of function ρ^{φ}, with some practical computation examples, is presented in Raman et al. (2014). The STL specifications are decomposed into a set of inequalities over each time horizon, such that synthesizing a controller fulfilling the formula at each horizon results in satisfaction of the global specification. In Raman et al. (2014), two automatically-generated mixed integer linear programing (MILP) encodings for STL specifications are presented. These encodings are employed to find open-loop control actions that meet the STL properties and that result in the maximization of the robustness score.

Control Problem

Given an STL formula φ, a cost function J, an initial state x_0, a time frame[1] of length N and a reference disturbance signal $\underline{d}$, the STL model predictive control synthesis problem can be stated as follows (Raman et al. 2014), in a deterministic setting:

Given a horizon $0 < H < N$, for all $0 \leq k \leq N - H$, compute $u_k^* = u_k^{H*}$, the first element of the sequence $\underline{u}_k^{H*} = u_k^{H*} u_{k+1}^{H*} \cdots u_{k+H-1}^{H*}$ satisfying

$$\underline{u}_k^{H*} = \text{argmin}_{\underline{u}_k^H \in \mathcal{U}^{\mathcal{H}}} \quad J(x_k, \underline{u}_k^H, \underline{d}_k, \varphi)$$

$$\text{s.t. } \xi_G(x_k, \underline{u}_k^H, \underline{d}_k) \vDash \varphi. \tag{5}$$

An adversarial formulation exists (see also Cairoli et al. (2019), Raman et al. (2014)), which is not used in the present paper.

[1]the time frame is basically the interval where the STL specifications are evaluated and is different from the horizon H of the MPC.

Note that the state of the plant must be accessible and the environment is assumed to be known in advance in the time frame $[0, N]$. As shown in Raman et al. (2014), it is possible to express both the STL requirements and the constraints due to the system dynamics in terms of a MILP problem which can be efficiently solved.

Remark. In the present work *stability* of the overall control system is not of concern. Indeed, obtaining trajectories satisfying the STL specifications is the actual goal (Raman et al. 2014). On the contrary, recursive *feasibility* is necessary, to guarantee that the sequence of optimization problems admits a feasible solutions. In principle, such a problem could be faced by means of set theoretic tools (Blanchini and Miani 2015), in order to characterize the set of initial conditions and disturbances that guarantees the existence of feasible solutions. This is left as a matter of further work.

Unknown Input Observer

The glucose absorption rate (2), defined by Hovorka et al. (2004), can be regarded as an external disturbance/input. In our previous work (Cairoli et al. 2019), we have assumed that the amount of carbohydrates D_G was known and, therefore, also the resulting $U_G(t)$. Instead, we would like this disturbance to be unknown and therefore estimated. The UIO is a state representation of a Disturbance Observer (DO), which differs from state observer for its ability to provide an estimation of both system states and disturbances (Radke and Gao 2006).

Given a nonlinear system Σ as in (3) and considering its linearized description Γ, around an equilibrium:

$$\Gamma : \left\{ \begin{array}{c} \dot{x}(t) = Ax(t) + B_u u(t) + B_d d(t) \\ y(t) = Cx(t) \\ \dot{z}(t) = A_f z(t) \\ d(t) = C_f z(t) \end{array} \right\} : \Omega, \tag{6}$$

where the last two equations represent the model Ω of the disturbance d, the resulting UIO system $\hat{\Gamma}$ takes the form:

$$\hat{\Gamma} : \left\{ \begin{array}{l} \begin{bmatrix} \dot{\hat{x}} \\ \dot{\hat{z}} \end{bmatrix} = \begin{bmatrix} A & B_d C_f \\ 0 & A_f \end{bmatrix} \begin{bmatrix} \hat{x} \\ \hat{z} \end{bmatrix} + \begin{bmatrix} B_u \\ 0 \end{bmatrix} u + L(y - \hat{y}) \\ \hat{d} = C_f \hat{z} \\ \hat{y} = C\hat{x} \end{array} \right., \tag{7}$$

where the matrix gain L has to be properly chosen. A possible approach for designing L is described in Rajamani and Cho (1995). There, under Lipschitz assumptions on the system's nonlinearity, L is found along with a Lyapunov function proving the asymptotic stability, by solving a suitable linear matrix inequality.

In the Artificial Pancreas the state of the system is not accessible (the plasma insulin cannot be measured in real time, and there are non-accessible glucose compartments) but $U_G(t)$, given by (2), takes the form of the natural response of a second order linear system. In this scenario the UIO seems to be an adequate solution to provide both state and disturbance estimations. It can also be seen as an observer of the augmented linearized Hovorka model, in which the meal absorption dynamic model ($\Omega : (A_f, 0, C_f, 0)$) is included. Therefore, we have employed its discretized version to estimate the full state of the system Γ by using the knowledge of the control input (insulin) and of the (non-linear) Hovorka output (glucose concentration). Hence, the resulting estimate $\hat{x}$ is directly employed for the MPC, while the $\hat{z}$ is exploited for computing future values of $U_G(t)$ (needed for solving the optimization problem). Given z_{k_i}, the estimation of the Ω system state in $k_i < N$, $\forall k \in k_i \leq k \leq N$ the disturbance d is computed, according to Ω, and then used by the MPC.

BluSTL Tool

BluSTL (Donzè et al. 2015) is a MATLAB-based tool to automatically generate controllers from specifications written in Signal Temporal Logic (STL) (Donzè et al. 2015). It takes as input a linear system and a set of constraints expressed as STL properties and provides a closed-loop controller that enforces these constraints on the system while minimizing some cost function. The user can tune the robustness of satisfaction of the STL specifications as defined before. The toolbox also supports robust controller synthesis in more classical sense, i.e., robust to variations of some external disturbance input (Problem 2). The approach is based on encoding the system dynamics, the STL constraints and the cost function together in a Mixed-Integer Linear Programing problem. The controller then consists in a precompiled MILP which can be solved efficiently by modern MILP solvers, such as Gurobi (Gurobi Inc. 2015). Given an STL formula φ and a cost function of the form $J(x_0, \underline{u}, \underline{d}, \varphi) \in R$, BluSTL can solve control synthesis problems of the form of (5). In all problems, an initial state $x_0 \in \mathcal{X}$, a horizon H and an estimation of some disturbance signal $\underline{d} \in \mathcal{D}^{\mathcal{N}}$ are given.

Implementation and Simulation Results

Our aim is to apply the MPC-STL approach to the artificial pancreas scenario introduced in Section *Model of glucose metabolism*. The controller receives glucose measurements every Δt minutes and calculates the insulin infusion rate also every Δt minutes although, in principle, non-constant time steps are possible without changes to the controller design. The computed insulin infusion rate is administered as a constant insulin infusion over the Δt minutes window.

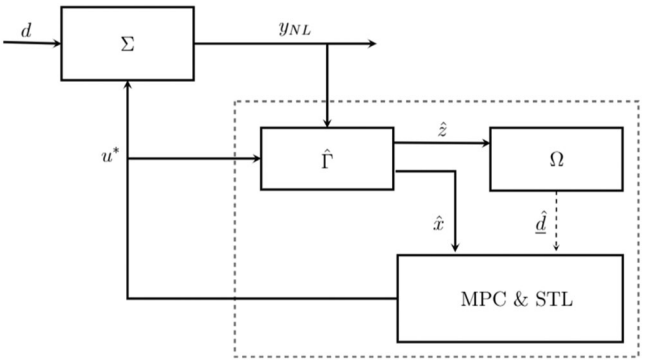

Figure 2. Block scheme describing the closed loop system. The dashed-grey square block includes all the elements of the controller.

The BluSTL requires the plant to be linear. In the following we employ a discrete-time representation of the Hovorka model linearized around a proper equilibrium point. The computed control actions are however applied to the original nonlinear model and the satisfaction of constraints is checked on the trajectory of the nonlinear model. Given a sampling time $\Delta t > 0$, we assume that the system Σ_L admits a discrete-time description $\Sigma_{L_d} : x_{k+1} = Ax_k + B_u u_k + B_d d_k$, where $\forall k > 0$, x_k is shorthand for $x(k\Delta t)$. In the following we use a zero-order hold discretization method, meaning that the control inputs are assumed to be piecewise constant over the sample time Δt. A *run* of Σ_{L_d} is a sequence $\xi_G = (x_0 u_0 d_0)(x_1 u_1 d_1)\cdots$, while a cost function $J(\xi_G(x_0, \underline{u}, \underline{d}))$ maps runs to R. The complete system block diagram is shown in Figure 2: the $\sum$ block represents the nonlinear Hovorka model affected by a disturbance d (unknown to the controller); the Unknown Input Observer Block is $\hat{\Gamma}$, while Ω is an LTI system, modeling the dynamics of the disturbance. At each Δt, a disturbance (U_G) and the control input provided by the controller (u^*) are applied to Σ. The system Σ evolves following its dynamics and returns y_{NL} (the glucose level) as output. Therefore, y_{NL} and u^* are the inputs of UIO ($\hat{\Gamma}$), whose output is the estimation of the states of the linear Hovorka model ($\hat{x}$) and the states of the disturbance model Ω ($\hat{z}$). Hence, $\hat{z}$ is used in Ω to compute an estimation $\hat{d}$ of the future disturbance $d = U_G$, used by the MPC. Therefore, the controller knows only an estimation of the original disturbance U_G. Lastly, the resulting sequence $\hat{d}$ and $\hat{x}$ are used as inputs for the MPC & STL block in order to compute the optimal control input u^*.

Observer Design

The Unknown Input Observer requires to define the Ω system introduced in Section *Unknown Input Observer*. This is easily achieved by observing that (2) is the natural response from initial state $z_0 = \begin{bmatrix} 0 & D_G \end{bmatrix}^T$ of a linear

system. Indeed, it is well-known (Antsaklis and Michel 2006) that the natural response of a linear system of the form

$$\begin{cases} \dot{v}(t) = Mv(t) \\ p(t) = Nv(t) \end{cases} \tag{8}$$

from $v(0) = v_0$ is $p(t) = N \exp(Mt)v_0$.

By taking:

$$M = \begin{bmatrix} -\frac{1}{t_{maxG}} & 1 \\ 0 & -\frac{1}{t_{maxG}} \end{bmatrix}, \; N = \begin{bmatrix} \frac{A_G}{0.18 \; t_{maxG}^2} & 0 \end{bmatrix} \tag{9}$$

and $v_0 = [0 \;\; D_G]^\top$ and by observing that M is in Jordan form, it is immediate to obtain that $p(t) = \frac{D_G A_G}{0.18 t_{maxG}^2} \;\; t \;\; e^{\left(\frac{-t}{t_{maxG}}\right)} = U_G(t) = d(t)$.

Therefore, we are able to design the disturbance system model Ω by considering $A_f = M$ and $C_f = N$.

In all the simulations reported below, in order to estimate the states of (6), we have employed the unknown input observer described in Section *Unknown Input Observer* resulting in the following closed-loop eigenvalues: $\lambda = [-0.133 + 0.222i, \; -0.133 - 0.222i, \; -0.263, \; -0.138, \; -0.097, \; -0.60, \; -0.60, \; -0.30, \; -0.018, \; -0.018]$.

The observer gain values are: $L = [7.541, \; 0.285, \; -1.898 \times 10^{-8}, \; -5.105 \times 10^{-8}, \; -4.281 \times 10^{-7}, \; -2.251 \times 10^{-5}, \; -1.129 \times 10^{-6}, \; -2.153 \times 10^{-7}, \; 670.273, \; 85.488]$.

For simplicity, in the reported simulations, the observer gain L has been designed based on the linearized model, by assigning the eigenvalues λ to the closed loop system (7). The observer is then applied to the nonlinear model. However, the convergence of the estimates can be proven by following Rajamani and Cho (1995), showing the existence of a positive definite matrix P, solution of a proper Linear Matrix Inequality (LMI) involving L, the Γ matrices and assuming $\gamma = 5.35 \cdot 10^{-7}$ as the Lipschitz constant of the nonlinear function F in (3).

Initial Conditions and Basal Insulin

A blood glucose concentration of 110 mg/dL (equivalent to 6.11 mmol/L) is chosen as set point (sp) value, as in Shmarov et al. (2017). Taking into account that the total insulin administered is the sum of the amount computed by the controller $u(t)$ and the basal insulin u_b ($u(t) + u_b$), the latter has been determined to ensure a stationary blood glucose value $y(t) = sp$. The corresponding stationary state has been used as initial state of the system. Since we easily compute Q_1 from the sp value ($\overline{Q_1} = 97.76$ mmol), a

nonlinear equation solver is sufficient to find the initial condition $x(0) = \overline{x}$ and the basal insulin level u_b such that $\dot{x}(0) = F(\overline{x}, u_b) = 0$, assuming no meal occurred, i.e., $\overline{d} = 0$. The obtained equilibrium values are: $\overline{x} = [97.7600, 19.0833, 3.0520, 3.0520, 0.0335, 0.0190, 0.0313, 0.0268]$ and $u_b = 0.0555$.

Cost Function

BluSTL implements cost functions $J(x_k, \underline{u}_k^H, \underline{d}_k, \varphi) = \left|\left|\underline{u}_k^H\right|\right|_\infty - w_r \cdot ||\rho||_\infty$, where w_r is a weight and ρ is the robust satisfaction. By doing so, control sequences with a higher ρ are preferred, since the relative cost function is smaller. Minimizing the ∞-norm of the sequence $\underline{u}_k^H$, instead, aims to minimize the maximum intensity of actions to be performed. All the simulations reported below have been obtained with $w_r = 0$.

Maximum Disturbance Problem

Given a controller developed in a deterministic setting (5), we aim at finding what maximum disturbance is able to tolerate the obtained control system. We define it as *maximum disturbance problem*. This problem is introduced and addressed using a PID controller in Shmarov et al. (2017), where authors define a dangerous state of glucose when its values are not included in the range $[4, 16]$ mmol/L. Translating it as STL property: $y_{NL} \geq 4$ mmol/L $\wedge\, y_{NL} \leq 16$ mmol/L. This restriction must be constantly respected for 12 hours after a meal.

Since both studies use the same Hovorka model to simulate a patient physiologic behavior, we are able to compare the performances of both our MPCs (known and unknown disturbance) with those of the cited PID controller.

C_1 Controller

The C_1 controller imposes the properties introduced in Shmarov et al. (2017), i.e., $y_{NL} \in [4, 16]$ mmol/L, using the STL. The upper bound of the safe range is 11.11 mmol/L yet some hyperglycemia is tolerated *without imposing any temporal requirement*. The use of an MPC controller overtake the results of the PID. In fact, the PID controller is able to guarantee at maximum for a meal of 88 g. We are able to safely reach the performances guaranteed by the PID controller and to overcome them. The maximum disturbance reached by our MPC controller is $D_{G,C_1}^{max} = 93.6$ g (Figure 3(a)). In this scenario the disturbance is known in advance in order to work in the same framework as Shmarov et al. (2017).

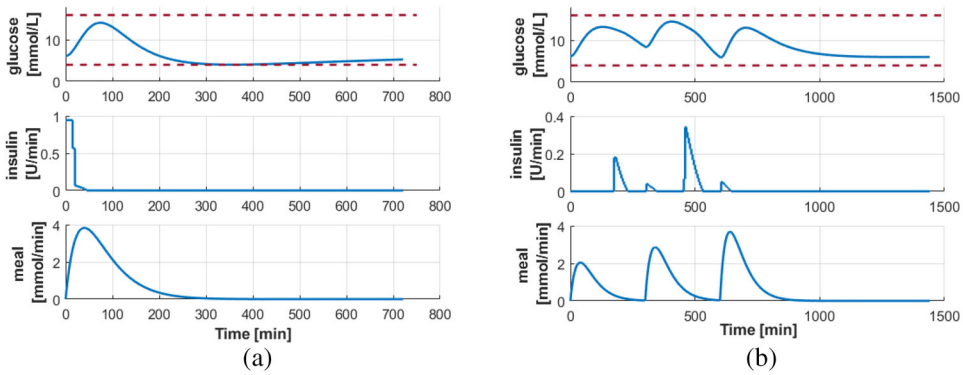

Figure 3. Trajectories of blood glucose (regulated output y_{NL}), insulin (controlled input u^*) and meal (disturbance d) over time under controller C_1. (a) Maximum disturbance $D_{G,C_1}^{max} = 93.6$ g : $H = 40$ min, $\Delta t = 5$ min. (b) In case of three subsequent meals with different carbohydrates intake, $D_G^1 = 50$ g, $D_G^2 = 70$ g, $D_G^3 = 90$ g, occurring at time $T_1 = 0$ min, $T_2 = 300$ min and $T_3 = 600$ min : $H = 40$ min, $\Delta t = 5$ min. Hard constraints are represented by the red dashed lines.

C_2 Controller

The MPC-STL approach we have implemented in Cairoli et al. (2019) allows temporal constraints to be imposed on postprandial hyperglycemia. The safety range for glucose concentration G is $y_{NL} \in [4, 20]$ mmol/L, thus G should never reach values higher than 20 mmol/L. However, the allowed hyperglycemia ($G > 11.11$ mmol/L) should not last for more than three consecutive hours. These requirements may be summarized as:

- avoid hypoglycemia: $\text{alw}_{[0,\ N]}\big(y_{NL}(t) > 4\big)$, meaning that during the whole time frame ($[0,\ N]$) it must be always true that the glucose concentration in plasma is greater than 4 $mmol/L$.
- avoid severe hyperglycemia: $\text{alw}_{[0,\ N]}\big(y_{NL}(t) < 20\big)$, with the same previous formalism, it is imposed the upper bound for the glucose concentration in plasma (20 mmol/L).
- avoid prolonged hyperglycemia (Cameron et al. 2015): $\neg\text{ev}_{[0,N]}\text{alw}_{[0,180]}\big(y_{NL}(t) > 11.11\big)$, meaning that a glucose concentration in plasma greater than 11.11 mmol/L for 3 consecutive hours (always in $[0,\ 180]$ min) must never occur (not eventually) during the whole time frame ($[0, N]$).

Recall that the control is computed based on the linearized system, whose variables represent the displacement from the equilibrium point, which is $\bar{y} = \frac{97.76}{V_G} = 6.11$ mmol/L. Therefore, the STL constraints should be translated as well, the resulting requirements are:

- lower and upper bounds: $\text{alw}_{[0,N]}\big[\big(y_{LIN}(t) > 2.11\big) \wedge \big(y_{LIN}(t) < 13.89\big)\big]$
- prolonged hyperglycemia: $\neg\text{ev}_{[0,N]\text{alw}_{[0,180]}}\big(y_{LIN}(t) > 5\big)$.

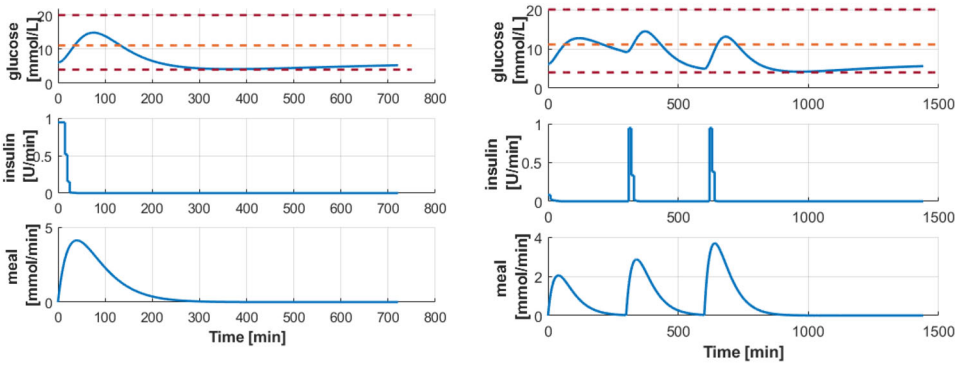

Figure 4. Trajectories of blood glucose (regulated output y_{NL}), insulin (controlled input u^*) and meal (disturbance d) over time under controller C_2. (a) Maximum disturbance $D_{G,C_2}^{max} = 100.8$ g : $H = 40$ min, $\Delta t = 5$ min. (b) In case of three subsequent meals with different carbohydrates intake, $D_G^1 = 50$ g, $D_G^2 = 70$ g, $D_G^3 = 90$ g, occurring at time $T_1 = 0$ min, $T_2 = 300$ min and $T_3 = 600$ min : $H = 20$ min, $\Delta t = 10$ min. Hard constraints are represented by the red dashed lines, while soft constraint is the orange dashed line.

C_2 is the controller with these STL constraints. Even in this case the disturbance is known in advance. Its maximum disturbance is higher than before $D_{G,C_2}^{max} = 100.8\ g$ (Figure 4(a)), which represents a meal very abundant in carbohydrates and furthermore the blood glucose trajectories now comply with more meaningful and problem-specific requirements.

C_3 Controller

The C_3 controller imposes the same properties introduced in C_2 (Cairoli et al. 2019) but considering an unknown disturbance: for the sake of clarity, we have assumed that the dynamic of the disturbance is known, whereas, the *amount* of carbohydrates D_G and the *time-instant* in which it occurs are unknown.

The maximum disturbance tolerated by C_3 overcomes all the previous performances: $D_{G,C_3}^{max} = 107.3$ g (Figure 5(a)). Nevertheless, the greatest contribution of this last solution is its ability to properly control the AP even when the controller doesn't know exactly the amount of carbohydrates ingested. Introducing a controller increases the maximum disturbance with respect to the basal case and the control, in addition, decreases the blood glucose level sufficiently enough to allow the consumption of a meal of similar size without incurring in severe hyperglycemia. This behavior can be seen in Figures 3(b), 4(b), and 5(b), where the C_1, C_2 and C_3 controllers respectively show three different control approaches leading to successfully safe scenarios during 24 hours.

We conclude this section by reporting the time required for performing the simulations (Table 3, "elapsed time"). The technical specifications of the hardware/software platform employed are reported in Table 2.

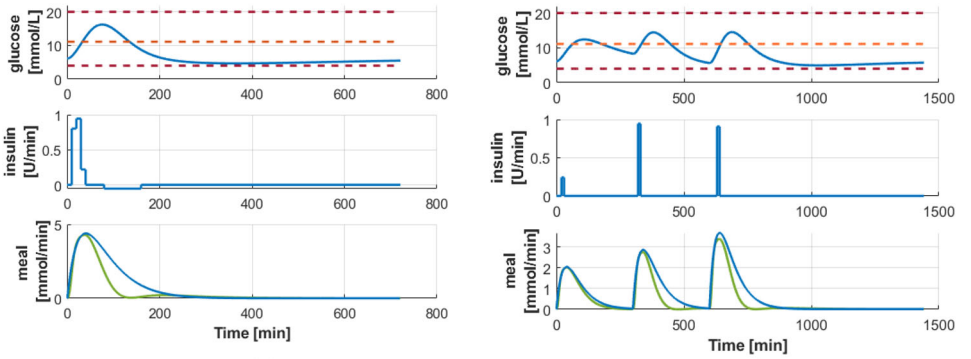

Figure 5. Trajectories of blood glucose (regulated output y_{NL}), insulin (controlled input u*) and meal (disturbance d) over time allowed under controller C_3 . (a) Maximum disturbance $D_{G,C3}^{max} = 107.3$ g : $H = 20$ min, $\Delta t = 10$ min. (b) In case of three subsequent meals with different carbohydrates intake, $D_G^1 = 50$ g, $D_G^2 = 70$ g, $D_G^3 = 90$ g, occurring at time $T_1 = 0$ min, $T_2 = 300$ min and $T_3 = 600$ min : $H = 20$ min, $\Delta t = 10$ min. Hard constraints are represented by red dashed lines, while soft constraint is the orange dashed line. Green line is the disturbance estimation of the UIO ($\hat{d}$).

Table 2. Hardware and software specifications.

Hardware:	Intel Core i7 – 4770 @3.4 GHz RAM 16 Gb
Software:	MATLAB R2018b YALMIP→MILP parser Gurobi→MILP solver Windows 8.1 Pro

Table 3. Computational effort required by the developed controllers.

Problem	H (min)	Δt (min)	N (h)	Elapsed time (sec)
C_1 **1 meal**	40	5	12	147.68
C_1 **3 meals**	40	5	24	169.58
C_2 **1 meal**	40	5	12	55.04
C_2 **3 meals**	20	10	24	96.34
C_3 **1 meal**	20	10	12	55.04
C_3 **3 meal**	20	10	24	96.34

Conclusions

In the present extended version of Cairoli et al. (2019), we started from a control framework in which the patient is involved by announcing meal, and then we address the problem of meal estimation by means of an unknown-disturbance observer. The employed control technique is MPC with STL constraints that turned out to be particularly suitable for AP. The resulting controller is able to provide safe trajectories without any information about meal amount (D_G) and its occurrence. Furthermore, it is able to cope with soft constraints, thanks to STL. The performed simulations

provide encouraging results. However, different aspects still need to be investigated. In particular, a study on the robustness to model uncertainty should be conducted in order to take into account different gluco-regulatory system behaviors. Moreover, the applicability of the proposed method to other more sophisticated models, for example the UVA/Padova (Messori et al. 2019), will be subject of future research.

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