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CHoKI-based MPC for blood glucose regulation in Artificial Pancreas

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Abstract: This work presents a Model Predictive Control (MPC) algorithm for the artificial pancreas able to autonomously manage basal insulin injections in type 1 diabetic patients. The MPC goal is to maintain the blood glucose inside the safe range (70-180 mg/dL) acting on the insulin amount, using a model to make predictions of the system behavior and satisfying operational constraints. The complexity of diabetes complicates the identification of a general physiological model, so a data-driven learning method is proposed, the Componentwise Hölder Kinky Inference (CHoKI), leading to customized controllers. For the data collection phase and also to test the proposed controller, the FDA-accepted UVA/Padova simulator is exploited. The final results are promising since the proposed controller reduces the time in hypoglycemia if compared to the standard constant basal insulin therapy, satisfying also the time in range requirements.

Keywords: Artificial Pancreas, MPC, learning-based control

1. INTRODUCTION

Type 1 Diabetes (T1D) is a common chronic metabolic disorder characterized by the body inability to correctly balance the blood glucose (BG) level, due to a complete deficiency of insulin production by the pancreatic cells. Its treatment consists of daily insulin injections to restore the physiological range of the BG values (i.e. 70-180 mg/dL). Above this threshold, the patient is in a state of hyperglycemia, and below it, in a state of hypoglycemia. The Artificial Pancreas (AP) implements such a treatment in closed loop. AP consists of three components: the Continuous Glucose Monitoring (CGM, the sensor that measures the glucose at the interstitial level every few minutes), the insulin pump (that delivers insulin in the subcutaneous tissue), and the control algorithm (which computes the insulin quantity). The APs currently on the market are Hybrid Closed Loop systems, since the administration of the basal insulin (injected to manage the BG in fasting periods) is automatic, while for postprandial boluses it still requires the manual intervention of the patients (Moon et al., 2021).

The AP requires the presence of a control algorithm and Model Predictive Control (MPC) is among the most utilised. MPC is a control method that uses a dynamic model to forecast the future behavior of a system, and to compute the best sequence of control moves at each time as a solution of a finite horizon optimal control problem. Only the first value is applied to the plant and the procedure is then repeated at each sampling instant, in a receding horizon fashion (Rawlings et al., 2009). The use of MPC as a control algorithm for AP has been widely studied and tested in the last few years (Del Favero et al., 2019; Toffanin et al., 2013; Hovorka et al., 2004; Abuin et al., 2020; Gondhalekar et al., 2016; González et al., 2020; Shi et al., 2018; Hajizadeh et al., 2019), thanks to its ability to anticipate undesired glucose variation and to compute the amount of insulin injections, respecting all the imposed constraints.

The BG response to meals or insulin varies significantly according to the daily condition and from one patient to another, thus making difficult to identify a general model to describe this system. The aim of this work is to exploit data-driven methods and to use current and past data of a patient to obtain the future BG. This way, a customized MPC algorithm for the AP is obtained, to ease and improve the T1D management. Various types of learning-based MPCs have been recently proposed in literature Hewing et al. (2020). In this work, we resort to the Componentwise Hölder Kinky Inference (CHoKI) method, a nonparametric learning technique which favours the design of robust MPCs that are stable by design (Manzano et al., 2021).

The data to learn the system are collected exploiting the virtual adult patients of the UVA/Padova simulator (The Epsilon Group, 2016). The same simulator will be used to test the proposed control algorithm.

The rest of this note is structured as follows. In Section 2 the learning method is presented and tailored to the insulin-glucose system. In Section 3, the proposed MPC problem is introduced. Section 4 shows the in-silico

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simulation results and Section 5 drawn some conlcusion.
Notation: A set of integers $[a, b]$ is denoted $\mathbb{I}_a^b$, $\mathbb{R}^n$ is the set of real vectors of dimension n and $\mathbb{R}^{n\times m}$ is the set of real $n \times m$ matrices. Given $v, w \in \mathbb{R}^{n_v}$, the notation (v, w) implies $[v^T, w^T]^T$ and $v \leq w$ implies that the inequality holds for every component. $\|v\|$ stands for the Euclidean norm of v and $|v| = \{w : w_i = |v_i|, \forall i\}$. Given two sets A, B, $A \ominus B$ denotes the Pontryagin difference. Their Cartesian product is denoted $A \times B = \{(x, y)|x \in A, y \in B\}$. The box $\mathbb{B}(v) \subset \mathbb{R}^{n_v}$ is defined as $\mathbb{B}(v) = \{y : |y| \leq v\}$ and the ball $\mathcal{B}(v) \subset \mathbb{R}^{n_v}$ is defined as $\mathcal{B}(v) = \{y : 0 \leq y \leq v\}$. An n, m-dimensional matrix of ones is denoted $\mathbf{1}_{n\times m}$. The ith row of a matrix M is denoted M_i.

2. PROBLEM STATEMENT

The system under study is a sampled continuous-time system, described by an a priori unknown discrete-time model, where $y(k) \in \mathbb{R}^{n_y}$ is the measured output (in our case, $n_y = 1$: the glucose level, in mg/dL) and $u(k) \in \mathbb{R}^{n_u}$ is the input. In this case, there are two inputs ($n_u = 2$): the meal (u_1, the not controllable one, in g of carbohydrates) and the insulin (u_2, the controllable one, in pmol). A sampling time of 5 minutes is considered.
The measured output can be modelled as a NARX regression of previous inputs and outputs, with the following state-space representation:

$$y(k+1) = f(x(k), u_1(k), u_2(k)) + e(k), \tag{1}$$

where the regression state $x \in \mathbb{R}^{n_x}$ is

$$x(k) = \big(y(k), \dots, y(k-n_a), u_1(k-1), \dots, u_1(k-n_b), u_2(k-1), \dots, u_2(k-n_c)\big), \tag{2}$$

for some memory horizons n_a, n_b and $n_c \in \mathbb{N}_0$ (where n_a is the memory horizon for the glucose values, n_b for the meals and n_c for the basal injections) and $e(k) \in \mathbb{R}^{n_y}$ is process noise. The arguments of f are then aggregated into $w = (x, u_1, u_2) \in \mathbb{R}^{n_w}$ so that it is possible to construct a data set of $N_\mathcal{D}$ observations, denoted $\mathcal{D} = \{(w_k, y_{k+1})\}$, for $k = 1, \dots, N_\mathcal{D} - 1$.

2.1 Componentwise Hölder Kinky Inference (CHoKI)

The aim of this subsection is to describe the chosen learning method. Kinky Inference (KI) (Manzano et al., 2020) is a class of learning approaches that includes Lipschitz interpolation, a technique based on Lipschitz continuity of the function to be learned. There exists an extension of the Lipschitz continuity, named Hölder continuity, in which the function has to satisfy the following more generalized condition:

Definition 1. *A function $f : \mathcal{W} \to \mathcal{Y}$ is Hölder continuous if there exist two real constants $L \geq 0$ and $0 < p \leq 1$ such that for all $w_1, w_2 \in \mathcal{W}$,*

$$\|f(w_1) - f(w_2)\| \leq L\|w_1 - w_2\|^p, \tag{3}$$

where L represents the smallest Lipschitz constant and p is called the Hölder exponent, $\mathcal{W} \subseteq \mathbb{R}^{n_w}$ is the input space and $\mathcal{Y} \subseteq \mathbb{R}^{n_y}$ is the output space. In the case of $p = 1$, it means to have Lipschitz continuity (Manzano et al., 2021).

In Manzano et al. (2021), the Componentwise Hölder Kinky Inference (CHoKI) was introduced, as a method that considers matrices $(\mathcal{L}, \mathcal{P})$ instead of the Hölder constant L and exponent p. This is done in order to find the effect that each component of the regressor has on each output, taking into consideration that a function may have abrupt variations along one dimension of the input and have smoothly changes along another one. This is based on the componentwise Hölder continuity, defined as follows:

Definition 2. *Given the matrices $\mathcal{L}$ and $\mathcal{P} \in \mathbb{R}^{n_y\times n_w}$, a function $f : \mathcal{W} \to \mathcal{Y}$ is componentwise $\mathcal{L}$-$\mathcal{P}$-Hölder continuous if $\forall w_1, w_2 \in \mathcal{W}$ and $\forall i \in \mathbb{I}_1^{n_y}$*

$$|f_i(w_1) - f_i(w_2)| \leq \sum_{j=1}^{n_w} \mathcal{L}_{ij}|w_{1,j} - w_{2,j}|^{\mathcal{P}_{ij}}. \tag{4}$$

This can be written in a more compact form, using:

$$\mathfrak{d}_\mathcal{L}^\mathcal{P}(w) := (a : a_i = \sum_{j=1}^{n_w} \mathcal{L}_{i,j} w_j^{\mathcal{P}_{i,j}}, \forall i \in \mathbb{I}_1^{n_y}) \tag{5}$$

and thus (4) becomes:

$$|f(w_1) - f(w_2)| \leq \mathfrak{d}_\mathcal{L}^\mathcal{P}(|w_1 - w_2|). \tag{6}$$

Then, assuming that f is Hölder continuous and given a data set $\mathcal{D}$ of inputs/outputs observations, the CHoKI predictor is defined as follows, for a query $q \in \mathbb{R}^{n_w}$:

$$\hat{f}(q; \Theta, \mathcal{D}) = \frac{1}{2} \min_{i=1,\dots,N_\mathcal{D}} (\tilde{y}_i + \mathfrak{d}_\mathcal{L}^\mathcal{P}(|q - w_i|)) + \frac{1}{2} \max_{i=1,\dots,N_\mathcal{D}} (\tilde{y}_i - \mathfrak{d}_\mathcal{L}^\mathcal{P}(|q - w_i|)), \tag{7}$$

where $\Theta = \{\mathcal{L}, \mathcal{P}\}$. In case matrices $\mathcal{L}$ and $\mathcal{P}$ are unknown a priori, they must be estimated solving an optimization problem offline, exploiting the available input-output data (see (9)) (Manzano et al., 2021).

According to (7) it is possible to predict a new output $\hat{y}(k+1) = \hat{f}(w(k); \Theta, \mathcal{D})$ given $\Theta = \{\mathcal{L}, \mathcal{P}\}$. Then, the prediction model can be formulated in state-space as follows:

$$\begin{aligned} \hat{x}(k+1) &= \hat{F}(x(k), u_1(k), u_2(k)) \\ \hat{y}(k) &= M\hat{x}(k) \end{aligned} \tag{8}$$

where $\hat{F}(x(k), u_1(k), u_2(k)) = (\hat{f}(x(k), u_1(k), u_2(k)), y(k), \dots, y(k-n_a+1), u_1(k), \dots, u_1(k-n_b+1), u_2(k), \dots, u_2(k-n_c+1))$ and $M = [I_{n_y}, 0, \dots, 0]$.

2.2 CHoKI implementation for T1D patient

Since the goal is to automatically manage the basal insulin, while postprandial boluses are assumed to be delivered manually, only the relation between BG, meals and basal insulin will be considered.
To exploit the CHoKI strategy, an initial phase of data collection is necessary. This is done by means of the UVA/Padova simulator. In particular, for each of the available virtual adult patients, several simulations were made, varying the initial BG value, the amount of the basal insulin and of the carbohydrates of the meals (with the corresponding insulin boluses). These were set in order to obtain an appropriate distribution of the points in the space, looking at the input-output representation. Also some noises were added, to make simulations more realistic. Specifically, as sensor, the available virtual typical commercial CGM was selected, with auto-regressive noise with inverse Johnson transform distribution. The virtual pump's noise follows a Gaussian distribution, with mean 0 pmol and standard deviation of 0.1. Also a noise

to the meal carbohydrate estimation was added, using a normal distribution with standard deviation of 30% of the meal amount. The data collection is a fundamental phase, since the quality of the data set will affect the performance of the CHoKI predictions and of the controller.

To identify the model orders (n_a, n_b, n_c) a cross validation procedure has been performed, selecting the combination that returned the lowest mean squared error between the predictions and the real values, considering also a trade-off with model complexity, to avoid the risk of overfitting. The chosen orders were $n_a = 5$, $n_b = 9$ and $n_c = 3$.

To obtain the predictions employing (7), the hyperparameters $\Theta = \{\mathcal{L}, \mathcal{P}\}$ must be estimated. To this aim, an optimization problem is solved offline, splitting $\mathcal{D}$ of each patient into two disjoint data sets ($\mathcal{D}_{\text{train}}$ for estimation and $\mathcal{D}_{\text{test}}$ for validation):

$$\Theta = \arg\min_{\Theta} g(\Theta, \mathcal{D}_{\text{train}}, \mathcal{D}_{\text{test}}) \tag{9a}$$

$$\text{s.t. } |\tilde{y}_i - \tilde{y}_j| \leq \mathfrak{d}_{\mathcal{L}}^{\mathcal{P}}(|w_i - w_j|), \tag{9b}$$

$$\forall w_i, w_j \in \mathcal{W}_{\mathcal{D}}, w_i \neq w_j$$

$$0 < \mathcal{P}_{ij} \leq 1, \mathcal{L}_{ij} > 0, \tag{9c}$$

$$i \in \mathbb{I}_1^{n_y}, j \in \mathbb{I}_1^{n_w},$$

where $\mathcal{W}_{\mathcal{D}}$ are the input data points in $\mathcal{D}$, and the cost function to be minimized is:

$$g(\Theta, \mathcal{D}_{\text{train}}, \mathcal{D}_{\text{test}}) = \frac{1}{N_{\mathcal{D}_{\text{test}}}} \sum_{i=1}^{N_{\mathcal{D}_{\text{test}}}} \|\hat{f}(w_i; \Theta, \mathcal{D}_{\text{train}}) - \tilde{y}_i\|^2,$$

being $\hat{f}(w_i; \Theta, \mathcal{D})$ the predictions made with the CHoKI (7) and $\tilde{y}_i$ the measured values of the noisy data set $\mathcal{D}_{\text{test}}$.

It is assumed to have $\mathcal{P} = \mathbf{1}_{n_y \times n_w}$ and thus the optimization problem is set to obtain just the values of the matrix $\mathcal{L}$. In this case, only three values are estimated: one for the glucose part, one for the meals and one for the insulin, denoted $L_a, L_b, L_c \in \mathbb{R}$, respectively. Hence, $\mathcal{L}$ contains those 3 values repeated, i.e. $\mathcal{L} = [L_a \mathbf{1}_{n_a}; L_b \mathbf{1}_{n_b}; L_c \mathbf{1}_{n_c}]$.

To set the constraints of the optimization problem, some a priori knowledge has been exploited, for example establishing as initial value of the $\mathcal{L}$, the one obtained with the LACKI (Lazily Adapted Constant Kinky Inference) method (Manzano et al., 2020), based on the Hölder continuity property (i.e. L). Thanks to previous analyses, the upper and lower bounds are defined for L_a, L_b and L_c as [10;10;10] and [0;0.9;0.09], respectively.

The *fmincon* MATLAB function was used to solve the optimization problem (9) and the results are different for every virtual patient. For each of them, once the $\mathcal{L}$ is selected, the model is validated on a new data set, to verify its ability to predict future BG values. For each patient, the resulting $\mathcal{L}$, the u_{ref} and the L are reported in Table 1.

3. CHOKI-BASED ROBUST MPC

The control objective is to steer the BG level $y(k)$ to the desired euglycemic zone, given by $70 \leq y \leq 180\,\text{mg/dL}$, fulfilling input and output constraints. The glucose must not reach hyper- or hypoglycemia states, that is, $y(k)$ should be maintained in the set $\mathcal{Y} = \{y : 55 \leq y \leq 300\,\text{mg/dL}\}, \forall k$. The control action, that is, the available basal insulin injection, varies such that $u_2(k) \in \mathcal{U} = \{u : 0 \leq u \leq 500\,\text{pmol}\}, \forall k$.

Since we assume here that a physiological model for T1D patients is not available, the open-loop prediction of the MPC control problem are computed exploiting the CHoKI predictor (7). To guarantee the MPC robustness to possible model-plant mismatches, the employed strategy is to restrict the output constraints according to the future propagation of a certain error, representing the effect of uncertainty in the predictions based on data. This way, the system in closed loop with the proposed controller is proved to be Input-to-State Stable (ISS) (Manzano et al., 2021, Theorem 3).

The set of restricted output constraints is given by

$$\mathcal{Y}_j = \mathcal{Y}_{j-1} \ominus \mathcal{R}_j, \tag{10}$$

along the prediction horizon, $j = 1, ..., N$. $\mathcal{R}_j$ are the reachability sets that account for the possible errors in the nominal predictions and $\mathcal{Y}_0 = \mathcal{Y}$. To compute $\mathcal{R}_j$, the starting point is to consider $\mu \in \mathbb{R}^{n_y}$, which is the maximum absolute error obtained in the validation phase, such that $|y(k+1) - \hat{y}(1|k)| \leq \mu$. The set $\mathcal{R}_j$ is defined as $\mathcal{R}_j = \{y : |y| \in \mathcal{M}_j\}$ for all $j \in \mathbb{I}_1^N$, where $\mathcal{M}_j$ is calculated from the equations $\mathcal{M}_j = \mathcal{B}(\mathfrak{d}_{\mathcal{L}}^{\mathcal{P}}(\mathcal{G}_{j-1}))$ and $\mathcal{G}_j = \mathcal{M}_j \times \cdots \times \mathcal{M}_{\sigma(j)} \times \{0\} \times \cdots \times \{0\}$, with $\sigma(j) = \max(1, j - n_a)$, and $\mathcal{M}_1 = \mathcal{B}(\mu)$. In Manzano et al. (2021) it is also shown that $c_j \in \mathbb{R}^{n_y}$ and $d_j \in \mathbb{R}^{n_w}$ are such that $\mathcal{M}_j = \mathcal{B}(c_j)$ and $\mathcal{G}_j = \mathcal{B}(d_j)$. Then, the sets $\mathcal{M}_j$ and $\mathcal{G}_j$ can be calculated using the recursion $c_j = \mathfrak{d}_{\mathcal{L}}^{\mathcal{P}}(d_{j-1})$ and $d_j = (c_j, \ldots, c_{\sigma(j)}, 0, \ldots, 0)$, with $c_1 = \mu$, and then, $\mathcal{R}_j = \mathbb{B}(c_j)$.

In our specific control problem, an *a posteriori* analysis highlighted that the extreme values of the possible deviation of the nominal prediction are very unlikely to occur. Then, the value representing the 95% (or 90%) percentile of the probability distribution is used as μ instead of the maximum error (see Table 1). To counteract possible infeasibilities due to some realizations outside the 95% (or 90%) range, some slack variables $\boldsymbol{\delta} = \{\delta_{\min}, \delta_{\max}\}$ are added in the optimization problem; thus $\hat{y}(j|k) \in \mathcal{Y}_{j,\boldsymbol{\delta}}$, $\forall j \in \mathbb{I}_1^N$, where

$$\mathcal{Y}_{j,\boldsymbol{\delta}} = \{y : y_{\min}(j) - \delta_{\min}(j) \leq y \leq y_{\max}(j) + \delta_{\max}(j)\}, \tag{11}$$

where $y_{\min}$ and $y_{\max}$ are the extreme values of $\mathcal{Y}_j$ from (10) and $\delta_{\min}, \delta_{\max}$ are optimization variables.

3.1 Terminal ingredients computation

The tightened values of the constraints are computed just once and offline. Then, the control horizon is chosen as the maximum possible value that allows to have a reasonable and non-empty set of constraints. To increase the domain of attraction and the predictive ability of the controller, a prediction horizon (N_p) longer than the control horizon (N_c) is considered, i.e. $N_p > N_c$. To employ this strategy, we need to define a local control law for the predictions going from N_c to N_p. In this work we will use a control law of the form

$$u = K(\overline{x} - x) + \overline{u}, \tag{12}$$

where $K \in \mathbb{R}^{n_u \times n_x}$ is the control gain of a linear quadratic regulator (LQR) and $(\overline{x}, \overline{u})$ is an equilibrium point around which the system $\hat{F}(x, u)$, with $u = (u_1, u_2)$, is linearized. In particular, $\overline{x}$ is constructed as per (2), using $\overline{y} = 120\,\text{mg/dL}$ of glucose, and $\overline{u} = (0, u_{\text{ref}})$. Matrices $A \in \mathbb{R}^{n_x \times n_x}$ and $B \in \mathbb{R}^{n_x \times n_u}$ of the linearized model $x(k+1) = Ax(k) + Bu(k)$, are calculated numerically from the

Table 1. MPC settings

Subject	u_{ref} (pmol)	$N_{\mathcal{D}}$	L (LACKI)	$[L_a; L_b; L_c]$ (CHoKI)	μ (95%) (mg/dL)	μ (90%) (mg/dL)	N_c (95%)	N_c (90%)	ϵ	Q
Adult 1	122.379	4775	3.46	[0.736; 5.457; 0.293]	20.37	14.83	2	2	10	1
Adult 2	134.888	4950	3.277	[4.886; 3.960; 0.09]	15.5	10.19	1	2	20	1
Adult 3	149.97	4990	3.076	[0.709; 5.45; 0.09]	15.99	9.29	2	3	10	1
Adult 5	91.8273	4156	6.563	[0.837; 5.518; 0.444]	21.13	13.91	2	2	5	1
Adult 6	190.219	5339	3.405	[4.717; 3.520; 0.09]	16.8	11.27	1	1	1	1
Adult 8	105.825	4703	2.582	[1.084; 5.840; 0.096]	11.13	7.8	2	3	1	100
Adult 9	94.586	3976	3.72	[1.127; 4.089; 0.09]	16.91	11.63	2	2	1	100
Adult 10	124.855	4966	3.294	[3; 2; 0.09]	16.02	10.1	1	1	20	1

input-output data using the CHoKI model. In this way, each element $A(j,i)$ is given by considering that

$$A(j,i) = \frac{\partial \hat{F}_j}{\partial x_i} = \frac{\hat{F}_j(\overline{x_i}+\epsilon) - \hat{F}_j(\overline{x_i}-\epsilon)}{2\epsilon}, \qquad (13)$$

where ϵ is different for each subject (see Table 1). Notice that $A(1,1) = \frac{\partial y_{k+1}}{\partial y_k}$.

3.2 CHoKI-based MPC implementation

The MPC optimization problem is set as follows:

$$\min_{u_2, y_a, \delta_{\text{hyper}}, \delta_{\text{hypo}}, \delta_{\min}, \delta_{\max}} V_N(\hat{x}, u; \Theta, \mathcal{D}) \qquad (14a)$$

$$\text{s.t. } \hat{x}(0|k) = x(k) \qquad (14b)$$

$$\hat{x}(j+1|k) = \hat{F}(\hat{x}(j|k), u_1(j), u_2(j)),\ j \in \mathbb{I}_0^{N_c-1} \qquad (14c)$$

$$\hat{x}(j+1|k) = \hat{F}(\hat{x}(j|k), K(\bar{x} - x(j)) + \bar{u}), j \in \mathbb{I}_{N_c}^{N_p-1} \qquad (14d)$$

$$\hat{y}(j|k) = M\hat{x}(j|k),\ u_2(j) \in \mathcal{U},\ j \in \mathbb{I}_0^{N_p-1} \qquad (14e)$$

$$\hat{y}(j|k) \in \mathcal{Y}_{j,\boldsymbol{\delta}}, \quad j \in \mathbb{I}_0^{N_c-1} \qquad (14f)$$

$$\hat{y}(j|k) \in \mathcal{Y}_{N_c,\boldsymbol{\delta}},\ j \in \mathbb{I}_{N_c}^{N_p-1} \qquad (14g)$$

$$u_1(j) = 0,\ j \in \mathbb{I}_1^{N_p-1} \qquad (14h)$$

$$70 - \delta_{\text{hypo}} \le y_a \le 140 + \delta_{\text{hyper}} \qquad (14i)$$

$$\delta_{\text{hyper}} \ge 0,\ \delta_{\text{hypo}} \ge 0 \qquad (14j)$$

$$\delta_{\min}(j) \ge 0,\ \delta_{\max}(j) \ge 0 \qquad (14k)$$

where (14h) is used since the meals are not predictable and $\mathcal{Y}_{j,\boldsymbol{\delta}}$ comes from (11). The tightened constraints are computed as explained in the previous section, for all the subjects. This tightening implicitly defines the length of the control horizon N_c, which may be different for each virtual patient (divided for the 95% and 90% cases, see Table 1). As for the prediction horizon, it is set to $N_p = 12$ for all subjects, determining 60 minutes of predictions.
The cost functional is constructed as the sum of different cost functions,

$$V_N(\hat{x}, u; \Theta, \mathcal{D}) = V_{N_c} + V_{N_p} + V_s + \lambda V_P + V_\delta,$$

which are now briefly detailed.
The first term V_{N_c} is given by the summation of the stage cost along the control horizon N_c:

$$V_{N_c} = \sum_{j=0}^{N_c-1} \|\hat{y}(j|k) - y_a\|_Q^2 + \|u_2(j) - u_{\text{ref}}\|_R^2 \qquad (15)$$

where the insulin reference value u_{ref} is the constant basal insulin value for the chosen virtual patient of the UVA/Padova simulator. The set-point y_a is given by an auxiliary optimization variable, constrained to belong to the interval $[70, 140]$ and necessary for the implementation of the MPC in a zone control fashion. In addition some slack variables δ_{hypo} and δ_{hyper} are added to the previous constraint, leading to the stationary cost given by

$$V_s = p_{\text{hyper}}\delta_{\text{hyper}}^2 + p_{\text{hypo}}\delta_{\text{hypo}}^2. \qquad (16)$$

Such a cost is built in an asymmetric fashion taking the constants $p_{\text{hypo}} > p_{\text{hyper}}$, representing the fact that hypoglycemia is more dangerous than hyperglycemia (Abuin et al., 2020).
The cost from N_c to the prediction horizon $N_p - 1$ is

$$V_{N_p} = \textstyle\sum_{j=N_c}^{N_p-1} \|\hat{y}(j|k) - y_a\|_Q^2 \qquad (17)$$

The terminal cost V_P is used to guarantee the MPC stability and to penalize the difference between the last state $\hat{x}(N_p|k)$ and the reference state. It is weighted by a factor $\lambda > 0$, since no terminal constraint is considered. It is defined as follows:

$$V_P = \|\hat{x}(N_p|k) - x_{ref}\|_P^2 \qquad (18)$$

where P is the solution to the Riccati equation, given the LQR control gain K, the reference state x_{ref} contains the set point y_a, no meals and u_{ref}.
The cost V_δ is added, to penalize the slack optimization variables $\delta_{\min}$ and $\delta_{\max}$, added in the constraints (11):

$$V_\delta = \textstyle\sum_{j=1}^{N_P} \left(\delta_{\min}(j)^2 p_{\min} + \delta_{\max}(j)^2 p_{\max}\right) \qquad (19)$$

The chosen weights are: $R = 10$, $p_{\text{hypo}} = 1{\cdot}10^7$, $p_{\text{hyper}} = 1{\cdot}10^6$, $p_{\min} = 1{\cdot}10^7$, $p_{\max} = 1{\cdot}10^6$, $\lambda = 10$ and P comes from the solution of the LQR for the linearized system around the reference point, to guarantee stability. Q are reported in Table 1, in the cases of R greater than Q, it means to have a more conservative controller.

4. SIMULATIONS

The proposal is tested on the UVA/Padova simulator. The controller is customized for each virtual patient of the data collection phase. Different three days simulations were performed, with three meals a day (40 g of carbohydrates at 06:00am, 100 g at 12:00pm and 60 g at 07:00pm, with 15 min duration) and the relative boluses (whose amount is computed by the simulator) given 20 minutes after the meal starts. All the devices have the same noise setting as in the data collection phase.
The results of the simulations of the analyzed virtual patients are displayed in Figure 1. In particular, in the upper and middle graphs the BG trends are represented, for the 95% and 90% cases respectively, which are caused by the insulin injections shown in the lower graph, that varies according to the patients' model and situation. The BG values are mainly inside the euglycemic range (i.e. 70-180 mg/dL), except for some peaks caused by the glucose

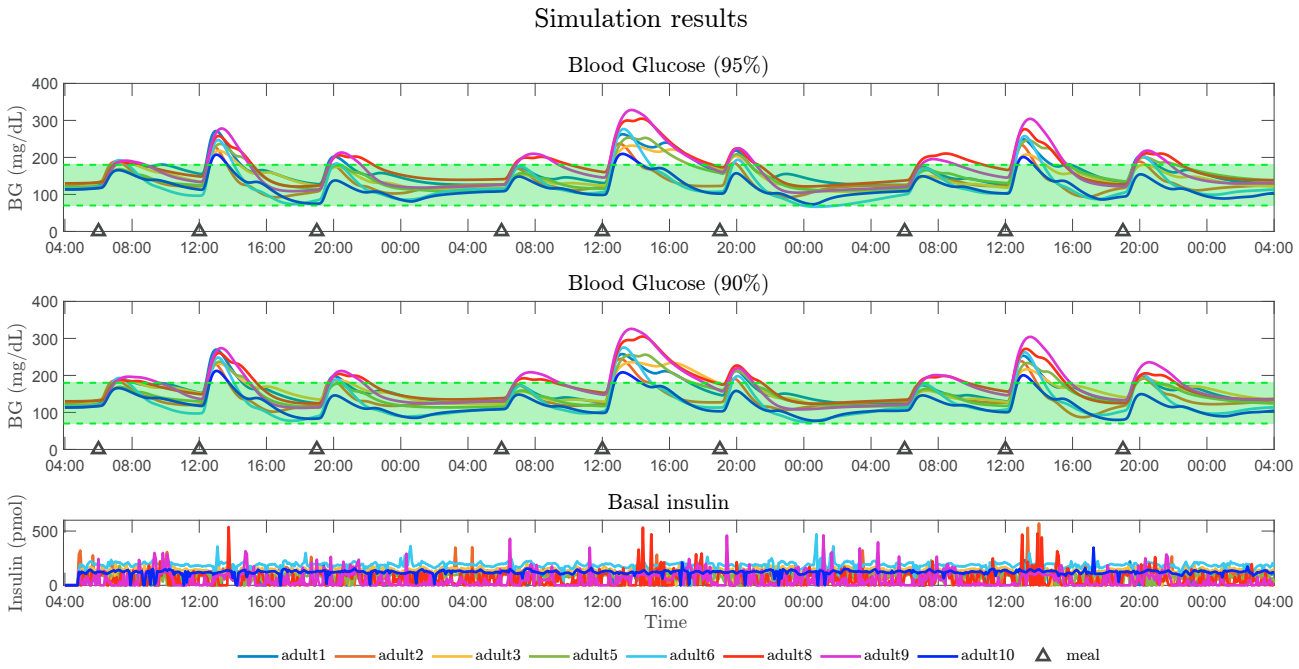

Fig. 1. Upper plot: BG trends of all patients, in the 95% case. The green zone represents the safe range. Middle plot: BG trends in the 90% case. Lower plot: basal insulin injections computed by the proposed MPC.

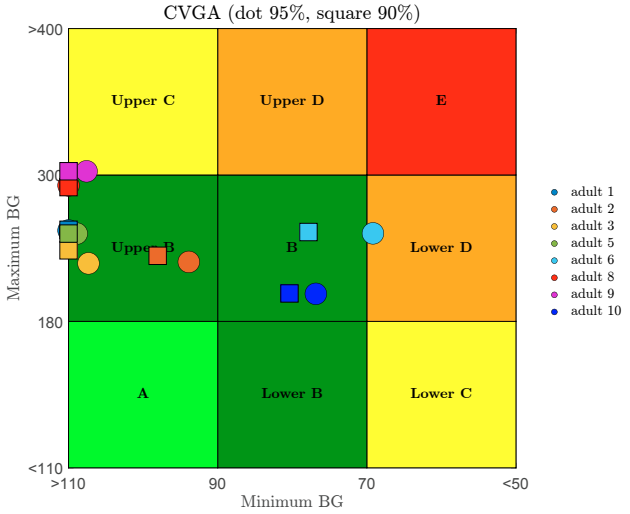

Fig. 2. CVGA result with BG measurements. Dots: 95% case. Squares: 90% case.

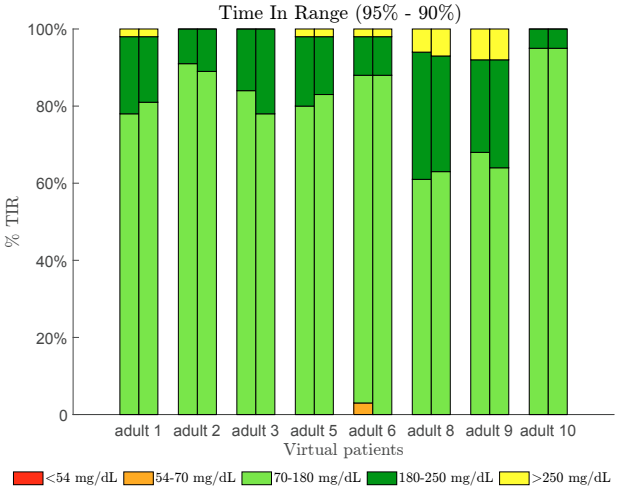

Fig. 3. TIR results of the analysed virtual patients. Left columns: 95% case. Right columns: 90% case.

increase due to the carbohydrates ingestion. The main goal is to reduce the hypoglycemic events, due to their dangerousness in a short time period, and it can be seen that such a result is achieved.

An important tool to evaluate AP performance is the Control-Variability Grid Analysis (CVGA) (Magni et al., 2008), which is a graphical representation that gives both visual and numerical information about the quality of the glucose management. In Figure 2, each dot on the graph describes a specific subject in the 95% case, while the squares are for the 90% case, with the minimum BG value as x-coordinate and the maximum BG value as y-coordinate. These worst cases are all into the safe zones (except for the adult 6 in the 95% case, which is in the Lower D zone).

Finally, the Time In Range (TIR), which shows the percentage of time a patient spends in each specific BG range, can also be assessed. In particular, according to the American Diabetes Association requirements, the TIR goals are: $< 5\%$ of time with BG higher than 250 mg/dL, $< 25\%$ between 180-250 mg/dL, $> 70\%$ between 70-180 mg/dL, $< 4\%$ between 55-70 mg/dL and $< 1\%$ for BG lower than 55 mg/dL. With the proposed controller, the TIR requirements are mostly satisfied, since the subjects never enter into the hypoglycemic ranges (except for the virtual adult 6 in the 95% case, but still satisfying the TIR specifications) and they generally stay between 70-180 mg/dL for more than 70% of the simulation time. A slight exception occurs for adults number 8 and 9, who are a bit under 70% and thus also a bit higher in the two hyperglycemia ranges. The results are displayed in Figure 3, where, for each subject, the column on the left is for the 95% case, while the one on the right for the 90% case.

The obtained results are promising, especially if compared to the ones obtained through the standard therapy pro-

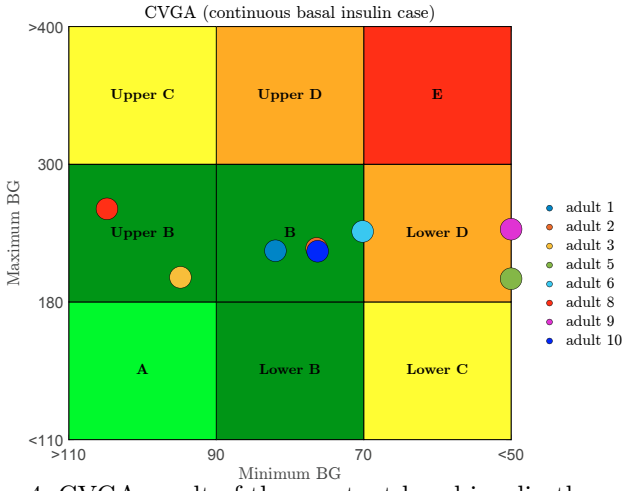

Fig. 4. CVGA result of the constant basal insulin therapy provided by the simulator, where each dot represents a specific virtual patient.

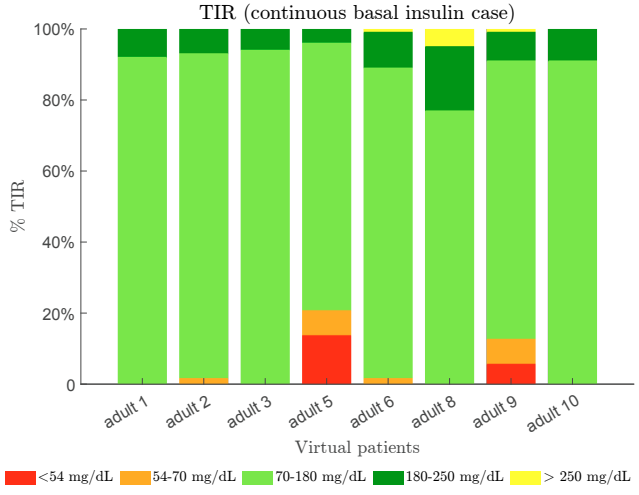

Fig. 5. TIR result of the constant basal insulin therapy provided by the simulator, for each subjects.

vided by the simulator, with constant basal insulin injection (u_{ref}) and with the same simulation settings. This is visible looking at the CVGA represented in Figure 4, where, for example, adults 5 and 9 are in the Lower D zone, while with the MPC CHoKI-based controller the same subjects are in the Upper B zone and on the border between Upper B and Upper C zones (Figure 2), respectively. The same improvements can be seen also in the TIR results, displayed in Figure 5. The outcomes for the 95% and 90% cases are quite similar, but considering the less conservative case with the 90% error percentile, it allows to increase a bit the prediction horizon N_c.

5. CONCLUSION

A new CHoKI-based MPC algorithm has been proposed to be used in the AP to manage the basal insulin in T1D patients. The entire system is tested on the UVA/Padova simulator. The main outcome is that the proposed controller reduces the (more dangerous) hypoglycemic events, maintaining the patients into the euglycemic zone most of the time. The results seem promising.

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