Preprints of the 19th World Congress
The International Federation of Automatic Control
Cape Town, South Africa. August 24-29, 2014

A Constrained Model Predictive Controller for an Artificial Pancreas ⋆

Mirko Messori * **Enrico Fornasiero** * **Chiara Toffanin** *
Claudio Cobelli ** **Lalo Magni** *

* *Department of Civil Engineering and Architecture, University of Pavia, Pavia, Italy.*
** *Department of Information Engineering, University of Padova, Padova, Italy.*

Abstract: A Constrained Model Predictive Control (CMPC) approach for regulating blood-glucose levels in people with type 1 Diabetes is proposed. The controller uses the past suggested insulin, the subcutaneous glucose level, and an estimation of the carbohydrate amount of the future meals provided by the patient as inputs to decide the quantity of insulin to inject by a subcutaneous pump. This strategy achieves good control performance by keeping into account a series of bounds which allow the control law to be as conservative as possible to avoid hypoglycemia phenomena without increasing the risk of hyperglycemia. The constraints definition is based on the knowledge of *in-vivo* clinical trials performed with an unconstrained MPC. In order to avoid the solution of the constrained optimization problem, a saturated MPC (SMPC), where all the constraints are applied as saturations, is also considered. The controller performance is evaluated in an *in-silico* study on 100 virtual patients of the UVA/Padova simulator. In order to underline the robustness of CMPC and SMPC in presence of model uncertainties, the simulations are performed both in nominal and in perturbed scenarios.

Keywords: Control of physiological and clinical variables; Chronic care and/or diabetes; Artificial pancreas or organs.

1. INTRODUCTION

Individuals with Type 1 Diabetes Mellitus (T1DM) require external insulin injections to maintain the blood glucose (BG) level within an optimal range. If the BG concentration reaches too low levels (e.g. below 50 mg/dl), the patient may enter into a hypoglycemic state with very near-term dangerous consequences. If the BG level stays high over long periods (e.g. above 200 mg/dl), long-term consequences may arise.
The Artificial Pancreas (AP) is a system resulting from the integration of subcutaneous (sc) glucose sensors, sc insulin pumps, and a control algorithm. Since 1999, when the first commercial Continuous Glucose Monitoring (CGM) system was introduced, several research projects on AP were stimulated and founded by the Juvenile Diabetes Research Foundation, the European Commission, and the National Institutes of Health (see Weinzimer et al. [2008], Cobelli et al. [2009], Hovorka et al. [2010], El-Khatib et al. [2010], Kovatchev et al. [2010], Bequette [2012], and Luijf et al. [2013]). Designing a sc-to-sc glucose-insulin system is challenging because the system is characterized by significant inter-individual variability, time varying dynamics, nonlinear phenomena, and time delays due to the absorption of the insulin from the sc level to the blood and, in reverse, of the glucose from the blood to the sc level. In the literature, several algorithms have been presented (see Cobelli et al. [2009], and Bequette [2012]).
The aim of this work is to design a controller for regulating BG levels in people with T1DM by a Constrained Model Predictive Control (CMPC) strategy. This approach achieves to define a control law able to consider different objectives with the formulation of a Finite Horizon Optimal Control Problem (FHOCP) that involves specific control bounds. The control bounds definition is based on the knowledge obtained using previous MPC versions (see Magni et al. [2007], Magni et al. [2009], and Patek et al. [2012]) *in-silico* and *in-vivo* (see Luijf et al. [2013]). These bounds are designed to avoid dangerous situations for the patients like e.g. hypoglycemia or hyperglycemia phenomena, too aggressive controller reactions on glucose level rising, and ketone bodies formation.
CMPC performance is evaluated on an *in-silico* study on 100 virtual patients of the UVA/Padova simulator described in Dalla Man et al. [2014]. The FHOCP of CMPC is converted into a QP problem and it is solved through the Matlab® *quadprog* function. CMPC performance is compared with the performance obtained by using an unconstrained (UMPC) and a saturated (SMPC) versions of MPC where the constraints defined in the CMPC optimization problem are added to the solution of UMPC as saturations.
In order to account for the model uncertainties, the simulations are performed in nominal and in perturbed scenarios.

⋆ This work was supported by ICT FP7-247138 Bringing the Artificial Pancreas at Home (AP@home) project and the Fondo per gli Investimenti della Ricerca di Base project Artificial Pancreas: In Silico Development and In Vivo Validation of Algorithms for Blood Glucose Control funded by Italian Ministero dell'Istruzione, dell'Università e della Ricerca.

Particularly, the latter is characterized by random insulin sensitivity variations used to simulate a non optimal insulin therapy or an unexpected response of the patient to the insulin injections.
The paper is organized as follows. In Section 2 the CMPC controller designed in this work is entirely defined. In Section 3 the CMPC implementation is presented. In Section 4 the results of the performed simulations both in nominal and in perturbed scenarios are analyzed.

2. CONSTRAINED MPC DESIGN

In this section the CMPC designed for an AP is presented. The model considered to synthesize the controller is the linearization around the nominal basal equilibrium of the average Dalla Man et al. [2014] glucose-insulin system, which can be written as follows:

$$\begin{cases} x(k+1) = Ax(k) + Bu(k) + Md(k) \\ y(k) = Cx(k) \end{cases} \tag{1}$$

where $x(k) \in \mathbb{R}^n$ $(n = 13)$ is the state vector, $u(k) \in \mathbb{R}$ is the difference between the injected insulin and its basal value $u_b(k)$, $y(k) \in \mathbb{R}$ is the difference between the sc glucose and its basal value G_b, and $d(k) \in \mathbb{R}$ represents the carbohydrates intake. The basal value G_b is not individualized because it is unknown for a real patient while the insulin basal value $u_b(k)$ is the one used in real life by each patient.

2.1 Constraints Design

The input constraints design is a very critical issue that must be based on a solid clinical evidence. In fact, a too high insulin delivery may lead the patient into a hypoglycemic state with the possibility to restore a correct glucose level only through an administration of external carbohydrates. On the other hand, leaving the patient without insulin for long periods may lead to high glucose levels especially after a meal assumption. In order to avoid these situations, a series of input constraints have been designed.

Pump Constraint The sc insulin pump is characterized by physical limitations. The injected insulin cannot be removed from the patient and this fact is translated into a low insulin constraint that specifies the minimum quantity of insulin that can be suggested by the controller. On the other hand, the pump is characterized by a high saturation that is hardware dependent. In order to obtain a safer controller, a tighter low constraint is imposed on the future inputs so that, even in the presence of model uncertainties, hypo phenomena can be avoided in a better way. In fact, it is expected that if the controller must inject a higher quantity of insulin in the future, the current suggestion will result more conservative. To avoid a controller over-reaction (in particular just after a meal where a significant error on the meal absorption model is unavoidable due to different meals compositions), a constraint on the maximum injected insulin in a specific time window is introduced. The pump constraint can be expressed as

$$\begin{cases} u(k+i) \leq \min\{I(k) - \sum_{j=1}^{N_H} u(k+i-j), \overline{u}_{k+i}\} \\ u(k+i) \geq (\beta(i)-1)u_b(k+i) \end{cases} \tag{2}$$

with

$$\beta(i) = \begin{cases} 0 & \forall i \in \{0, N_\beta, N_\beta+1, \ldots, N\} \\ \overline{\beta} & \forall i \in \{1, \ldots, N_\beta - 1\} \end{cases}$$

and with $i = 0, \ldots, N-1$, $\overline{\beta} \in [0,1]$, $N_\beta \leq N$, $\overline{u}_k = \overline{u} - u_b(k)$ where $\overline{u}$ is the maximum insulin deliverable by the pump in a sample time k. N represents the *prediction horizon* while N_H specifies the time interval in which the past insulin is considered.

$$I(k) = \alpha \max(last_{ibolus}, \frac{y(k) - y_{th}}{CF})$$

where $\alpha > 0$ is a suitable parameter, $last_{ibolus}$ is the last insulin meal bolus, y_{th} is a defined glucose threshold, and CF is the *Correction Factor* and it is a patient's clinical parameter.

Maximum Variation Constraint This constraint is added to obtain a smoother control law by limiting the maximum variation between the controller suggestion at time k and the previous suggestion at time $k-1$ and it is defined as

$$u(k) - u(k-1) \leq \zeta \cdot u_b(k) \tag{3}$$

where $\zeta > 0$ is a suitable parameter. The constraint is inactive when an insulin bolus must be delivered for a meal compensation.

Ketone Bodies Constraint If the patient reaches high glucose levels and is left without insulin for long periods, there is the possibility to encounter the ketone bodies formation. This constraint is used to guarantee a minimum quantity of delivered insulin when the patient's glucose level exceeds a specific security threshold. Thus, it is imposed

$$u(k) \geq \gamma \cdot u_b(k) \qquad \text{if } y(k) \geq \overline{G}$$

where $\overline{G}$ is the chosen security threshold and $\gamma > 0$ is a suitable parameter. Since the UVA/Padova simulator does not include the ketone bodies formation, the tuning of this constraint is entirely based on data coming from real *in-vivo* experiments.

2.2 Optimization Problem Formulation

The FHOCP is defined as

$$u^o(k) = arg\min_{u(k)} J(x(k), u(\cdot), k) \tag{4}$$

such that the dynamics described by (1) and the constraints (2) and (3) are satisfied, and where $u^o(k)$ is the computed optimal control vector and $J(x(k), u(\cdot), k)$ represents the cost function. The latter is given by

$$\begin{aligned} J(x(k), u(\cdot), k) = \sum_{i=0}^{N-1} (\|y(k+i) - y_0(k+i)\|_q^2 \\ + \|u(k+i) - u_0(k+i)\|_r^2) + \|x(k+N)\|_P^2 \end{aligned} \tag{5}$$

where $y_0(k)$ is the reference output vector and it is the difference between the reference value of the sc glucose and G_b, $u_0(k)$ is the reference input obtained through the open loop therapy, N is the prediction horizon, $q > 0$ represents the output weight, $r > 0$ represents the input weight, and $P \geq 0$ is a positive semidefinite matrix that represents the states weights at the end of the horizon. In view of the reachability of the pair (A, B), the P matrix is set equal

to the unique non-negative solution of the discrete time Riccati equation

$$P = qC'C + A'PA - A'PB(r + B'PB)^{-1}B'PA \ .$$

According to the *Receding Horizon* criterion, only the first element of the optimal control vector defined in (4) is kept and applied to the system. Thus, the FHOCP must be solved at each sample time k.

3. CONSTRAINED MPC IMPLEMENTATION

The FHOCP defined in (4) has been converted in a QP problem and CMPC has been *in-silico* tested by exploiting the Matlab® *quadprog* function.

3.1 QP Optimization Problem

Defining the matrices $\mathcal{A}_c$, $\mathcal{B}_c$, and $\mathcal{M}_c$ as described in Soru et al. [2012], and the vectors

$$\begin{aligned} Y(k) &= [\, y(k+1) \ \cdots \ y(k+N-1) \ x(k+N) \,]' \\ U(k) &= [\, u(k) \ u(k+1) \ \cdots \ u(k+N-1) \,]' \\ D(k) &= [\, d(k) \ d(k+1) \ \cdots \ d(k+N-1) \,]' \end{aligned}$$

with $Y(k) \in \mathbb{R}^{N-1+n}$, $U(k) \in \mathbb{R}^N$, and $D(k) \in \mathbb{R}^N$, it is proved that

$$Y(k) = \mathcal{A}_c x(k) + \mathcal{B}_c U(k) + \mathcal{M}_c D(k)$$

and by defining the weight matrices

$$\mathcal{Q} = \begin{bmatrix} q & 0 & \cdots & 0 \\ 0 & \ddots & \ddots & 0 \\ \vdots & \ddots & q & \vdots \\ 0 & \cdots & 0 & P \end{bmatrix} \quad \mathcal{R} = \begin{bmatrix} r & 0 & \cdots & 0 \\ 0 & \ddots & \ddots & \vdots \\ \vdots & \ddots & r & 0 \\ 0 & \cdots & 0 & r \end{bmatrix}$$

where $\mathcal{Q} \in \mathbb{R}^{(N-1+n)\times(N-1+n)}$ and $\mathcal{R} \in \mathbb{R}^{N\times N}$, and the reference vectors

$$\begin{aligned} Y_0(k) &= [\, y_0(k+1) \ y_0(k+2) \ \cdots \ y_0(k+N-1) \ 0 \,]' \\ U_0(k) &= [\, u_0(k) \ u_0(k+1) \ \cdots \ u_0(k+N-1) \,]' \end{aligned}$$

with $Y_0(k) \in \mathbb{R}^{N-1+n}$ and $U_0(k) \in \mathbb{R}^N$, the controller cost function (5) can be rewritten as

$$\begin{aligned} J(x(k), u(\cdot), k) = \frac{1}{2}U'(k)(\mathcal{B}_c'\mathcal{Q}\mathcal{B}_c + \mathcal{R})U(k) \\ +((\mathcal{A}_c'x(k) + \mathcal{M}_c D - Y_0(k))'\mathcal{Q}\mathcal{B}_c - U_0(k)'\mathcal{R})U(k) \end{aligned} \tag{6}$$

where only the terms depending from $U(k)$ have been kept. As described in Toffanin et al. [2013], the system states vector $x(k) \in \mathbb{R}^n$ is estimated by a Kalman Filter.
In order to have only one parameter to tune in the cost function (5), it is imposed $r = 1$. The tuning of the q parameter is obtained with the calibration procedure described in Soru et al. [2012] that leads to have a regression model that depends from the Body Weight (BW) and the Carbo-to-Ratio (CR) of the diabetic patient. Thus, once the calibration procedure is performed on half virtual population, the q parameter can be adapted to a specific patient with the formula

$$q = e^{BW \cdot R_1 + CR \cdot R_2 + k_r} \tag{7}$$

where BW and CR are the only two considered clinical parameters, and R_1 and R_2 are their related regressors. The FHOCP (4) can be converted in the QP problem

$$\begin{aligned} U^o(k) = arg\min_{U(k)} \frac{1}{2}U'(k)\mathcal{H}U(k) + \mathcal{F}'U(k) \\ \mathcal{A}U(k) \leq \mathcal{B} \\ \Theta \leq U(k) \leq \Omega \end{aligned} \tag{8}$$

where

$$\begin{aligned} \mathcal{H} &= (\mathcal{B}_c'\mathcal{Q}\mathcal{B}_c + \mathcal{R}) \\ \mathcal{F} &= ((\mathcal{A}_c x(k) + \mathcal{M}_c D - X_0(k))'\mathcal{Q}\mathcal{B}_c - U_0(k)'\mathcal{R})' \end{aligned}$$

and where $\mathcal{A} = [A_{HL} \ A_{MV}]'$, and $\mathcal{B} = [B_{HL} \ B_{MV}]'$.

3.2 Constraints

The *Pump Constraint* is implemented by imposing the matrices $\Theta \in \mathcal{R}^{N\times 1}$ and $\Omega \in \mathcal{R}^{N\times 1}$ defined in (8) as

$$\Theta = \begin{bmatrix} -u_b(k) \\ (\overline{\beta} - 1)u_b(k+1) \\ \vdots \\ (\overline{\beta} - 1)u_b(k+N_\beta - 1) \\ -u_b(k+N_\beta) \\ \vdots \\ -u_b(k+N-1) \end{bmatrix} \quad \Omega = \begin{bmatrix} \overline{u}_k \\ \overline{u}_{k+1} \\ \vdots \\ \overline{u}_{k+N-1} \end{bmatrix} .$$

and by imposing

$$A_{HL} = \begin{bmatrix} 1 & 0 & 0 & \cdots & \cdots & 0 \\ \vdots & 1 & 0 & \ddots & \ddots & \vdots \\ 1 & \ddots & \ddots & \ddots & \ddots & \vdots \\ 0 & \ddots & \ddots & \ddots & 0 & 0 \\ \vdots & \ddots & \ddots & \ddots & 1 & 0 \\ 0 & \cdots & 0 & 1 & \cdots & 1 \end{bmatrix} \quad B_{HL} = \begin{bmatrix} I(k) - \tilde{u}_{N_H} \\ I(k) - \tilde{u}_{N_H - 1} \\ \vdots \\ I(k) - \tilde{u}_1 \\ I(k) \\ \vdots \\ I(k) \end{bmatrix}$$

where $\tilde{u}_j = \sum_{i=1}^{j} u(k-i)$, $A_{HL} \in \mathbb{R}^{N\times N}$ has a number of ones diagonals equal to N_H, and $B_{HL} \in \mathbb{R}^{N\times 1}$.
The *Maximum Variation* constraint is implemented by imposing

$$A_{MV} = \begin{bmatrix} 1 & 0 & \cdots & \cdots & 0 \\ -1 & 1 & \ddots & \ddots & 0 \\ 0 & -1 & \ddots & \ddots & \vdots \\ \vdots & \ddots & \ddots & \ddots & 0 \\ 0 & \cdots & 0 & -1 & 1 \end{bmatrix} \quad B_{MV} = \begin{bmatrix} \zeta u_b(k) - \tilde{u}_1 \\ \zeta u_b(k) \\ \vdots \\ \zeta u_b(k) \end{bmatrix}$$

where $A_{MV} \in \mathbb{R}^{N\times N}$, $B_{MV} \in \mathbb{R}^{N\times 1}$.

In order to avoid a *Mixed Integer* implementation, the *Keton Bodies* constraint is applied as a saturation downstream the controller suggestions as follows:

$$u^{CMPC}(k) = \begin{cases} u^o(k), & if \ y(k) < \overline{G} \\ \max(u^o(k), \gamma \cdot u_b(k)) & otherwise \end{cases}$$

where $u^o(k)$ is the first element of the $U^o(k)$ vector in (8), and $u^{CMPC}(k)$ is the final CMPC suggestion.

4. RESULTS

The control performance of CMPC is compared with the performance obtained by UMPC and SMPC. The first uses the closed form control law obtained without considering input constraints in the QP problem defined in (8). The second is obtained by applying the input constraints as equivalent saturations downstream the UMPC suggestions. The three MPC are evaluated on an *in-silico* study on 100 virtual patients of the UVA/Padova simulator. The simulation scenarios start at 6:00 and last 34 hours. Five meals are assumed by the patients: 2 breakfasts at 7:00

Table 1. Abbreviations used in Table 2 and Table 3.

Abbreviation	Meaning
O	Overall
N	Night
PP	Mean of postprandial periods
M	BG mean
SD	BG standard deviation
Tt	% of time spent in euglycemic range $(70-180\ mg/dl)$
Ta	% of time spent above 180 mg/dl
Tb	% of time spent below 70 mg/dl
Th	% of time spent below 50 mg/dl
# HT	Total number of hypo treatments
^{a}	p-value $< .001$
^{b}	p-value $< .01$
^{c}	p-value $< .05$

of the first and second day, 2 lunches at noon of the first and second day, and dinner at 18:00. The carbohydrates amounts are equal to $50g$ for the first breakfast, $60g$ for the lunches and for the second breakfast, and $80g$ for the dinner. Since the loop is closed at 8:00 of the first day, the first breakfast is treated in open loop. Thus, perturbed closed loop initial conditions are obtained for each patient. The night is defined from 23:00 to 7:00 of the next morning and a postprandial period is defined as a 3 hours time interval after a meal. The sample time of the system is equal to 15 min.

The simulated CGM sensor is affected by an error noise whose model is described in Toffanin et al. [2013]. The sensor is re-calibrated half hour before each meal and at night start. A perturbed scenario is considered in which a random $\pm 25\%$ variation factor is applied to the insulin sensitivity (VSENS) of the virtual patient. This leads to have simulated non optimal basal/bolus insulin.

If the glycaemia falls below 65 mg/dl, the protocol imposes 16 g of carbohydrates administration, called Hypo Treatment (HT). Two consecutive HT are separated from at least $30min$.

The outcome indices used to evaluate the control performance are shown in Tables 2, and 3, where the meaning of the abbreviations are described in Table 1. The p-values are referred to the comparisons between CMPC and UMPC and between CMPC and SMPC.

An improved version of the Control Variability Grid Analysis (CVGA) defined in Magni et al. [2008] is also used to evaluate the control performance. This improved version was introduced in Soru et al. [2012] by allowing the classic CVGA nine square zones to become concentric rings zones ranging from A to D. A single point on the CVGA represents the couple of minimum and maximum BG values reached by the virtual patient during a closed loop simulation.

4.1 Nominal Scenario

The outcome indices of the three MPC strategies reported in Table 2 show that CMPC is able to obtain an acceptable mean glucose and time spent in target range with a statistically significant lower number of occurred hypo treatments and time spent in hypoglycemia with respect to UMPC. This fact is also confirmed by Figure 1, where the UMPC global trend is affected by obvious undershoots after each meal, and by the CVGA in Figure 2, where

Table 2. Simulations results obtained on Nominal scenario.

		O	N	PP
M (mg/dl)	UMPC	131.46^a	113.25	149.64^b
	SMPC	139.55^a	115.93	158.95
	CMPC	136.50	114.38	156.46
SD (mg/dl)	UMPC	26.94^c	8.63	24.46
	SMPC	27.40	9.32	24.12
	CMPC	27.18	8.86	24.12
Tt (%)	UMPC	91.12^a	99.87	82.54
	SMPC	87.66^b	99.82	76.05
	CMPC	90.01	99.86	78.80
Ta (%)	UMPC	7.99^a	0.13	16.92
	SMPC	12.29^b	0.18	23.95
	CMPC	9.92	0.14	21.17
Tb (%)	UMPC	0.87^a	0.00	0.54
	SMPC	0.05	0.00	0.00
	CMPC	0.07	0.00	0.03
Th (%)	UMPC	0.15^c	0.00	0.10
	SMPC	0.00	0.00	0.00
	CMPC	0.01	0.00	0.00
# HT	UMPC	52^a	0	19^c
	SMPC	2	0	0
	CMPC	5	0	0

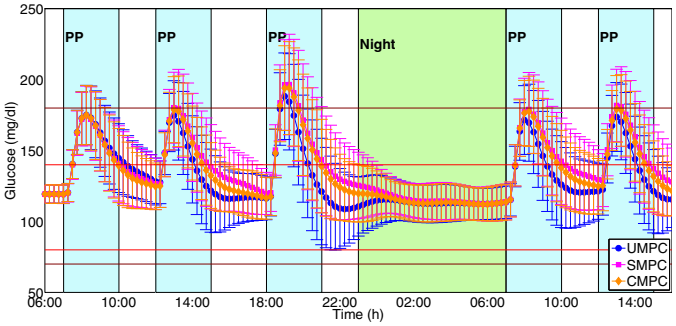

Fig. 1. Glucose profiles for UMPC (blue, circles), SMPC (magenta, squares), and CMPC (orange, diamonds) with mean $\pm$ standard deviation obtained in 100 virtual patients on nominal scenario. OL, open loop; PP, postprandial period.

points in C and D zones are increased by UMPC.

SMPC has a global trend that is closer to the CMPC one (Figure 1) and also the CVGA differences are minimal (Figure 2). Table 2 shows that SMPC is able to obtain good control performance without increasing the number of occurred hypo treatments and it could be considered as a good approximation of CMPC.

An example of glucose and injected insulin trends obtained in nominal scenario is shown in Figure 3. The UMPC injects a higher quantity of insulin (especially just after the dinner) bringing the virtual patient into a hypoglycemic state in which five HT are needed in order to recover a safe glycaemia. SMPC and CMPC have similar and safer behaviors and glucose trends, as expected.

4.2 Perturbed Scenario

CMPC is able to obtain statistically significant lower number of occurred hypo treatments and time spent in hypoglycemia with respect to UMPC also on VSENS scenario. In this case there is no significant difference on the time spent in target, as shown in Table 3. Moreover,

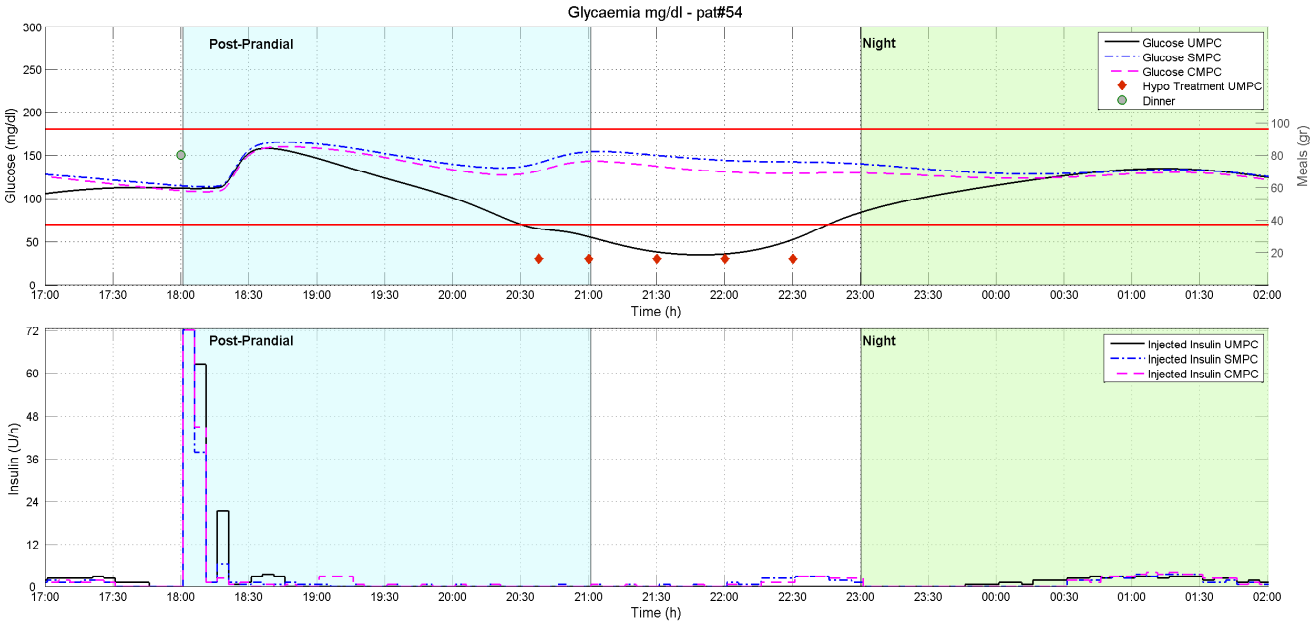

Fig. 3. Glucose (upper panel) and injections (lower panel) trends of the virtual patient #54 obtained by UMPC (solid black), SMPC (dot dashed blue), and CMPC (dashed magenta) on nominal scenario.

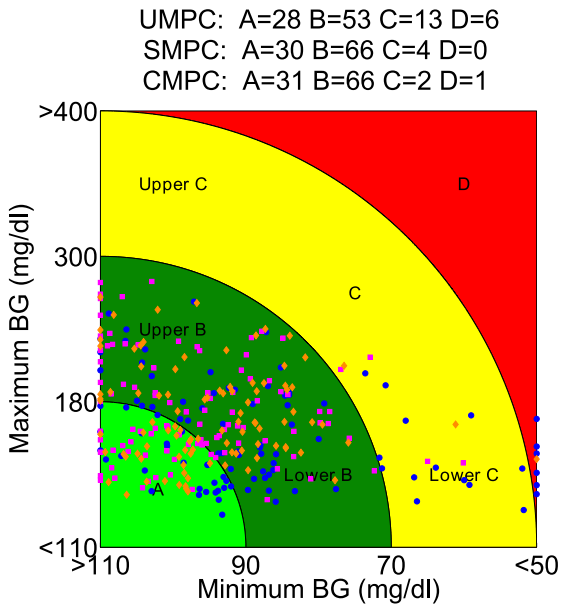

Fig. 2. CVGA representing the results obtained using UMPC (blue, circles), SMPC (magenta, squares), and CMPC (orange, diamonds) on nominal scenario.

UMPC experiences more pronounced undershoots on the global glucose trends after each meal treated in closed loop (Figure 4), and an evident increase of the number of CVGA points that fall in C and D zones (Figure 5).
Albeit SMPC obtains a higher BG mean and lower time in target with respect to CMPC, there are no significant differences for what regards the times spent in hypoglycemia and the number of occurred hypo treatments (Table 3). SMPC and CMPC have also similar global glucose trends (Figure 4) and similar CVGA (Figure 5), demonstrating once again that SMPC could be considered as a good approximation of CMPC.

Table 3. Simulations results obtained on VSENS scenario.

		O	N	PP
M (mg/dl)	UMPC	134.54[a]	116.14	152.50
	SMPC	142.36[a]	118.46	161.84
	CMPC	139.20	116.82	159.16
SD (mg/dl)	UMPC	28.21	9.51	25.22
	SMPC	28.62	10.25	24.89
	CMPC	28.26	9.64	24.72
Tt (%)	UMPC	84.33	98.19	74.02
	SMPC	83.06[a]	98.69	70.23
	CMPC	84.97	98.92	72.29
Ta (%)	UMPC	11.79[a]	0.22	23.06
	SMPC	15.55[a]	0.53	28.99
	CMPC	13.66	0.30	26.94
Tb (%)	UMPC	3.88[a]	1.59	2.92
	SMPC	1.39	0.78	0.79
	CMPC	1.37	0.78	0.77
Th (%)	UMPC	1.66[a]	0.13	1.60[c]
	SMPC	0.41	0.09	0.24
	CMPC	0.35	0.00	0.24
# HT	UMPC	256[a]	18	106
	SMPC	86	9	28
	CMPC	86	9	26

5. CONCLUSION

CMPC presented in this work shows that the inclusion of well designed input constraints can significantly improve the performance of an unconstrained MPC. The constraints considered in the control variable have been derived from clinical evidences achieved from *in-vivo* clinical trials and they have been implemented directly into the controller cost function. Despite its good control performance, CMPC has still not been implemented in AP due to the need of an online optimizer. Thus, SMPC has been formulated with a closed form control law and with equivalent constraints implemented as saturations. The results show that SMPC can be considered as a good approximation of CMPC and it is actually used in outpatients trials.

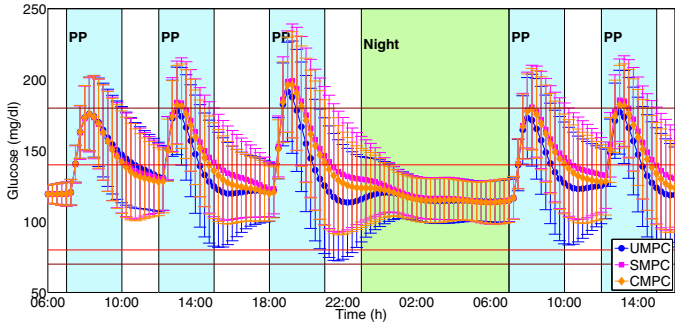

Fig. 4. Glucose profiles for UMPC (blue, circles), SMPC (magenta, squares), and CMPC (orange, diamonds) with mean ± standard deviation obtained in 100 virtual patients on VSENS scenario. OL, open loop; PP, postprandial period.

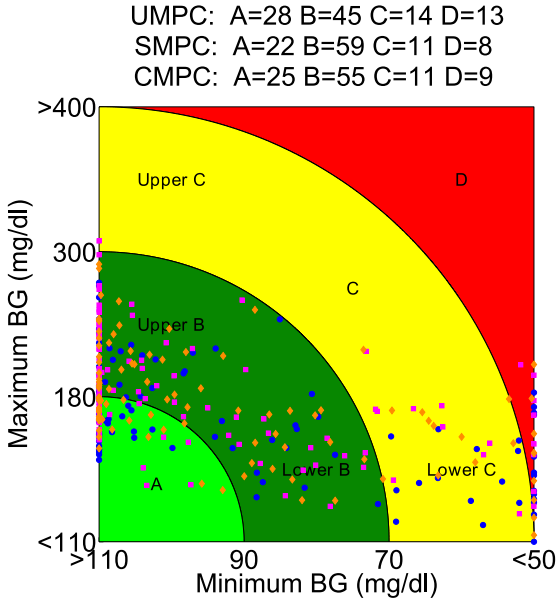

Fig. 5. CVGA representing the results obtained using UMPC (blue, circles), SMPC (magenta, squares), and CMPC (orange, diamonds) on VSENS scenario.

Possible future improvements of the glucose control could be obtained by considering constraints also in the system states, with the possibility to further increase the global control performance.

REFERENCES

B.W. Bequette. Challenges and recent progress in the development of a closed-loop artificial pancreas. *Annual Review in control*, 36(2):255–266, 2012.

C. Cobelli, C. Dalla Man, G. Sparacino, L. Magni, G. De Nicolao, and B.P. Kovatchev. Diabetes: models, signals, and control. *IEEE Reviews in Biomedical Engineering*, 2:54–96, 2009.

C. Dalla Man, F. Micheletto, D. Lv, M. Breton, B.P. Kovatchev, and C. Cobelli. The UVA/Padova Type 1 Diabetes Simulator: New Features. *J Diabetes Sci Technol*, 8(1):26–34, 2014.

F.H. El-Khatib, S.J. Russell, D.M. Nathan, R.G. Sutherlin, and E.R. Damiano. A bihormonal closed-loop artificial pancreas for type 1 diabetes. *Science Translational Medicine*, 2:27ra27, 2010.

R. Hovorka, J.M. Allen, D. Elleri, L.J. Chassin, J. Harris, D. Xing, C. Kollman, T. Hovorka, A.M.F. Larsen, M. Nodale, A. De Palma, M.E. Wilinska, C.L. Acerini, and D.B. Dunger. Manual closed-loop insulin delivery in children and adolescent with type 1 diabetes: a phase 2 randomised crossover trial. *Lancet*, 375:743–751, 2010.

B. Kovatchev, C. Cobelli, E. Renard, S. Anderson, M. Breton, S. Patek, W. Clarke, D. Bruttomesso, A. Maran, S. Costa, A. Avogaro, C. Dalla Man, A. Facchinetti, L. Magni, G. De Nicolao, J. Place, and A. Farret. Multinational study of subcutaneous model-predictive closed-loop control in type 1 diabetes mellitus: summary of results. *J Diabetes Sci Technol*, 4:1374–1381, 2010.

Y. M. Luijf, J. H. DeVries, K. Zwinderman, L. Leelarathna, M. Nodale, K. Caldwell, K. Kumareswaran, D. Elleri, J. M. Allen, M. E. Wilinska, M. L. Evans, R. Hovorka, W. Doll, M. Ellmerer, J. K. Mader, E. Renard, J. Place, A. Farret, C. Cobelli, S. Del Favero, C. Dalla Man, A. Avogaro, D. Bruttomesso, A. Filippi, R. Scotton, L. Magni, G. Lanzola, F. Di Palma, P. Soru, C. Toffanin, G. De Nicolao, S. Arnolds, C. Benesch, and L. Heinemann. Day and night Closed-Loop control in adults with Type 1 Diabetes Mellitus: A comparison of two closed-loop algorithms driving continuous subcutaneous insulin infusion versus patient self-management. *Diabetes Care*, 36:3882–3887, 2013.

L. Magni, D.M. Raimondo, L. Bossi, C. Dalla Man, G. De Nicolao, B. Kovatchev, and C. Cobelli. Model predictive control of type 1 diabetes: an in silico trial. *Journal of Diabetes Science and Technology*, 1(6):804-812, 2007.

L. Magni, D.M. Raimondo, C. Dalla Man, M. Breton, S. Patek, G. De Nicolao, C. Cobelli, B.P. Kovatchev. Evaluating the efficacy of closed-loop glucose regulation via control-variability grid analysis. *J Diabetes Sci Technol*, 2(4):630–635, 2008.

L. Magni, D.M. Raimondo, C. Dalla Man, G. De Nicolao, B.P. Kovatchev, and C. Cobelli. Model predictive control of glucose concentration in type I diabetec patients: an in silico trial. *Biomedical Signal Processing and Control*, 4:338–346, 2009.

S.D. Patek, L. Magni, E. Dassau, C.S. Hughes, C. Toffanin, G. De Nicolao, M. Breton, C. Dalla Man, E. Renard, H. Zisser, F.J. Doyle III, C. Cobelli, and B.P. Kovatchev. Modular closed-loop control of diabetes. *IEEE Transactions on Biomedical Engeneering*, 59(11):2986–2999, 2012.

P. Soru, G. De Nicolao, C. Toffanin, C. Dalla Man, C. Cobelli, L. Magni, and on behalf of the AP@home consortium. MPC based Artificial Pancreas: strategies for individualization and meal compensation. *Annual Review in Control*, 36:118–128, 2012.

C. Toffanin, M. Messori, F. Di Palma, G. De Nicolao, C. Cobelli, and L. Magni. Artificial Pancreas: MPC design from clinical experience. *J Diabetes Sci Technol*, 7(6): 1470–1483, 2013.

S.A. Weinzimer, G.M. Steil, K.L. Swan, J. Dziura, N. Kurtz, and W.V. Tamborlane. Fully-automated closed-loop insulin delivery versus semi-automated hybrid control in pediatric patients with type 1 diabetes using an artificial pancreas. *Diabetes Care*, 31(5):934–939, 2008.