Available online at www.sciencedirect.com

ScienceDirect

IFAC Papers Online CONFERENCE PAPER ARCHIVE

IFAC PapersOnLine 50-1 (2017) 7737–7742

Artificial Pancreas: from Control-to-Range to Control-to-Target ⋆

Gian Paolo Incremona * **Mirko Messori** * **Chiara Toffanin** * **Claudio Cobelli** *** **Lalo Magni** **

* *Department of Industrial and Information Engineering, University of Pavia, 27100, Italy.*
** *Department of Civil Engineering and Architecture, University of Pavia, 27100, Italy.*
*** *Department of Information Engineering, University of Padova, 35131, Italy.*

Abstract: In the last decade, control algorithms designed for Artificial Pancreas (AP) systems were characterized by significant progresses. In particular, the Control-to-Range Model Predictive Control (MPC) showed its effectiveness and safety in several real life studies. Recent studies on model individualization and the enhanced quality of glucose sensors further improved the efficacy of MPC, thus allowing moving from a Control-to-Range to a Control-to-Target approach. In this study, an integral action in the MPC approach (IMPC) is proposed. This ensures beneficial effects in terms of regulation to the target in presence of disturbances such as delays, pump limitation and model uncertainties. The integral action is even more important when model individualization is performed since, during the identification phase, it allows to focus on the identification of the dynamical part of the model rather than to the static gain. The patient models considered in this contribution have been identified through a constrained optimization approach. A procedure for tuning the IMPC aggressiveness by considering both the glucose control performance and the integral of the error with respect to the target is described. Finally, in silico experiments are presented to assess the effectiveness of the proposed IMPC.

Keywords: Biomedical control, biomedical systems, predictive control, integral action, system identification.

1. INTRODUCTION

Type 1 diabetes mellitus (T1DM) is an important health problem in the world, affecting people during the teenage years, adults, and also very young children. T1DM is an autoimmune disease that leads to the irreversible destruction of the pancreatic beta cells, which are in charge of producing and releasing insulin. Since the pancreas is no longer able to produce this hormone, which regulates the glucose level in the blood (glycemia), the subject can experience chronic hyperglycemia, with an increasing risk of life-threatening events and severe long-term complications.

Self-monitoring of glycemia is extremely important for individuals with T1DM, which have to maintain the blood glucose concentration inside the euglycemic range, spanning from 70 to 140 mg/dl. If on one hand external insulin supplies are needed to avoid hyperglycemia phenomena, on the other hand hypoglycemia can be caused by possible erroneous insulin overestimation. T1DM patients usually provide the needed insulin through the conventional therapy, which is composed of basal insulin, used to maintain a stable glycemia during fasting periods, and insulin boluses used to compensate the glucose rise caused by meals intake.

Insulin administration can be performed through subcutaneous insulin pumps that can be programmed with a patient-specific conventional therapy, and are in charge of continually infusing insulin micro-boluses. The subcutaneous glucose concentration is measured through continuous glucose monitor (CGM) devices, which allow to perform measurements up to 5 minutes per sample. The combination of subcutaneous pump and CGM defines the sensor augmented pump (SAP) therapy, which assists the patient in maintaining the glucose concentration within the euglycemic range. SAP therapy, however, needs manual interventions on the pump to properly adjust the insulin administrations, and the evaluation of possible critical hypo- and hyperglycemia phenomena are demanded to the patient. The automation of insulin infusions based on automated glycemia readings has been investigated since the seventies, when the first concept of artificial pancreas (AP) appeared in the literature [Cobelli et al., 2011]. The AP system aims to a complete automatic closed-loop glucose control and, thanks to the latest technological and methodological developments, the system has become

⋆ Corresponding author: Gian Paolo Incremona, Dipartimento di Ingegneria Industriale e dell'Informazione, University of Pavia, Via Ferrata 5, 27100 Pavia, Italy
e-mail: gianpaolo.incremona01@universitadipavia.it

10.1016/j.ifacol.2017.08.1152

wearable and minimally invasive [Thabit and Hovorka, 2016].

One of the most recent AP architectures is composed of a control algorithm that communicates with a CGM and with a subcutaneous pump through wireless connections [Messori et al., 2015]. This architecture is the results of several clinical studies promoted by the Juvenile Diabetes Research Foundation, the European Commission, and the National Institutes of Health [Bequette, 2012; Cobelli et al., 2009; Breton et al., 2012; Doyle et al., 2014; Russell et al., 2014; Del Favero et al., 2015; Thabit et al., 2014; Kropff et al., 2015].

The core of the AP system is the control algorithm, which is in charge of estimating the proper quantity of insulin to infuse during fasting, meal, and postprandial periods. This task is particularly challenging because of the system architecture, which uses a subcutaneous route both for insulin infusion and glucose sensing. Indeed, subcutaneous pumps are affected by inherent delays due to the insulin absorption dynamics, whereas subcutaneous glucose measurements are normally affected by CGM sensor noise. Among the possible control strategies, which include classical Proportional-Integral-Derivative (PID) control or Fuzzy Logic (FL), Model Predictive Control (MPC) resulted to be a very effective and promising solution [Hovorka et al., 2004; Magni et al., 2007; Wilinska et al., 2009; Grosman et al., 2010; Doyle et al., 2014].

The MPC considered in this study is described in [Toffanin et al., 2013], and has been successfully used in an outpatient clinical study in 2013. Subsequently, it has been used in the first randomized crossover clinical trial performed in free-living conditions [Kropff et al., 2015] later followed by an additional extension study [Renard et al., 2016]. Although the good glucose control performance, the MPC described in [Toffanin et al., 2013] is synthesized by considering a non-individualized linear model. Thus, since diabetic patients are affected by significant inter-subject variability, further improvements could be achieved by considering patient-individualized models. To this aim, two novel identification approaches that can be used for individualizing linear glucose-insulin models have been introduced in [Messori et al., 2016].

In this study, an individualized integral MPC (IMPC) is proposed. The individualized models are identified through the constrained optimization (CO) procedure described in [Messori et al., 2016]. This procedure may result in individualized models that could be affected by steady-state errors, an effect that was not predominant in the non-individualized linear model. Thus, the integral action is added to increase the glucose control robustness with respect to model uncertainties, moving from a Control-to-Range (CTR) to a Control-to-Target (CTT) approach. Moreover, the presence of the integral action eases the identification process, since the control designer can focus on the identification of the dynamic part of the individualized model rather than to the static gain.

Since different patients are usually characterized by different insulin sensitivity, a procedure for tuning the IMPC aggressiveness is also presented.

2. INTEGRAL MODEL PREDICTIVE CONTROL

In this section the CTT IMPC is discussed. The main ingredients to design the IMPC are the definition of an augmented system (which takes into account the integral action), a cost function, a model-based optimization problem, and the so-called Receding Horizon (RH) criterion.

2.1 Glucose-Insulin Model

MPC algorithms are intrinsically based on the knowledge of a model describing the dynamics of the system under control. In this paper, the proposed IMPC is synthesized on a linear time-invariant model, the structure of which is obtained from the linearization around a suitable working point of the more complex nonlinear model described in [Dalla Man et al., 2014]. In particular, the model considered in the controller has the following form:

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

where x and y are the differential states and output (i.e. subcutaneous glucose) with respect to their steady-state values, respectively, u represents the differential insulin with respect to the basal insulin i_b, and d represents the amount of carbohydrates (CHO) associated to the meals announced to the controller. The model (1) is identified through the CO approach described in [Messori et al., 2016], which is a grey-box identification approach able to identify linear time-invariant models having a pre-defined parametric structure.

2.2 Augmented system

In order to introduce the integral action in the controller, it has to be synthesized on the enlarged system composed of both the process and the integrator. The integrator can be described in state variables by the following system

$$\begin{aligned} v(k+1) &= v(k) + e(k) \\ e(k) &= y_{sp}(k) - Cx(k)\,. \end{aligned} \tag{2}$$

Then, the enlarged system including process and integrator, with inputs u and d and outputs y and v, is

$$\begin{cases} \bar{x}(k+1) = \overline{A}\bar{x}(k) + \overline{B}u(k) + \overline{M}d(k) + \overline{B}_{sp}y_{sp}(k) \\ \bar{y}(k) = \overline{C}\bar{x}(k) \end{cases} \tag{3}$$

where $\bar{x} = [x(k)\ v(k)]^T \in \mathbb{R}^{n+1}$ is the augmented state, $\bar{y} = [y(k)\, v(k)]^T \in \mathbb{R}^2$ is the output, and where the augmented matrices are

$$\begin{aligned} &\overline{A} = \begin{bmatrix} A & 0 \\ -C & 1 \end{bmatrix} \in \mathbb{R}^{(n+1)\times(n+1)},\ \overline{B} = \begin{bmatrix} B \\ 0 \end{bmatrix} \in \mathbb{R}^{(n+1)}, \\ &\overline{M} = \begin{bmatrix} M \\ 0 \end{bmatrix}, \in \mathbb{R}^{(n+1)}\ \overline{B}_{sp} = \begin{bmatrix} 0 \\ 1 \end{bmatrix} \in \mathbb{R}^{(n+1)}, \\ &\overline{C} = \begin{bmatrix} C & 0 \\ 0 & 1 \end{bmatrix} \in \mathbb{R}^{2\times(n+1)} \end{aligned} \tag{4}$$

with n denoting the number of states of the original model (1).

2.3 Cost function

Assuming that the triplet $(\overline{A}, \overline{B}, \overline{C})$ is both stabilizable and detectable, the IMPC control action is the result of

an optimization procedure that consists of minimizing the following quadratic cost function:

$$J(\hat{x}(k|k), v(k|k), u(\cdot), k) = \sum_{i=0}^{N-1} \big(q_y(y(k+i) - y_{sp}(k+i))^2 + q_v v^2(k+i) + + (u(k+i) - u^0(k+i))^2\big) + \|\bar{x}(k+N)\|_P^2 \quad (5)$$

subject to

$$\begin{aligned} x(k) &= \hat{x}(k|k) \\ v(k) &= v(k|k) \\ \bar{x}(k+i+1) &= \overline{A}\bar{x}(k+i) + \overline{B}u(k+i) + \\ &\quad + \overline{M}d(k+i) + \overline{B}_{sp}y_{sp}(k+i) \\ \bar{y}(k+i+1) &= \overline{C}\bar{x}(k+i+1) \\ u^0(k+i) &= u^{OL}(k+i) - i_b(k+i) \end{aligned}$$

where $q_y > 0$ is the weight associated to the first output, $q_v \geq 0$ is the weight associated to the integral of the error e, y is the subcutaneous glucose concentration, v is the output of the integrator, $y_{sp} = 120$ (mg/dl) is the constant glucose set-point, u^{OL} is the insulin that would be injected by the open-loop therapy, which is taken as input reference, and $\hat{x}(k|k)$ is provided by a Kalman Filter, as discussed in [Toffanin et al., 2013]. Moreover, N is the prediction horizon, $\|\cdot\|_p$ denotes the p-norm, and P is the unique non-negative solution of the discrete-time Riccati equation for the corresponding Linear Quadratic Regulator (LQR) problem with infinite horizon.

2.4 Closed-form of the IMPC law

The closed-form of the IMPC law can be achieved by relying on the Lagrange formula. The model output and state predictions within the horizon N can be obtained through the following formula

$$Y(k) = \mathcal{A}_c\hat{\bar{x}}(k) + \mathcal{B}_c U(k) + \mathcal{M}_c D(k) + \mathcal{B}_{sp,c}Y_0(k) \quad (6)$$

where $\hat{\bar{x}}(k) = [\hat{x}(k|k) \;\; v(k)]^T$ is the augmented linear model state at time k, with the state prediction $\hat{x}(k|k)$. As for the other terms, one has that the output is $Y(k) = [\bar{y}(k+1), \bar{y}(k+2), \cdots, \bar{y}(k+N-1), \bar{x}(k+N)]^T$, while $Y_0(k) = [y_{sp}(k), y_{sp}(k+1), \cdots, y_{sp}(k+N-1)]^T$, and inputs $D(k) = [d(k), d(k+1), \cdots, d(k+N-1)]^T$ and $U(k) = [u(k), u(k+1), \cdots, u(k+N-1)]^T$. Instead, $\mathcal{A}_c$, $\mathcal{B}_c$, $\mathcal{M}_c$, $\mathcal{B}_{sp,c}$ are matrices properly defined according to the discrete-time Lagrange formula. Note that, according to the cost function (5), the last element of $Y(k)$ represents the model state prediction and the integrator state, $\bar{x}(k+N)$, at the end of the horizon. The predicted trajectory $Y(k)$ depends on the applied input trajectory $U(k)$, which is obtained after an optimization procedure consisting of minimizing the cost (5). By defining the weight matrix $\mathcal{Q}$ as

$$\mathcal{Q} = \begin{bmatrix} Q & 0 & \cdots & 0 \\ 0 & \ddots & \ddots & 0 \\ \vdots & \ddots & Q & \vdots \\ 0 & \cdots & 0 & P \end{bmatrix} \in \mathbb{R}^{(2(N-1)+n+1)\times(2(N-1)+n+1)} \quad (7)$$

with $Q = \mathrm{diag}(q_y, q_v)$, the controller cost function can be rewritten as follows:

$$\begin{aligned} &J(\hat{\bar{x}}(k), u(\cdot), k) = \\ &\Big(\mathcal{A}_c\hat{\bar{x}}(k) + \mathcal{B}_c U(k) + \mathcal{M}_c D(k) + \\ &+\mathcal{B}_{sp,c}Y_0(k) - Y_{sp}(k)\Big)^T \mathcal{Q}\Big(\mathcal{A}_c\hat{\bar{x}}(k) + \mathcal{B}_c U(k) + \\ &+\mathcal{M}_c D(k) + \mathcal{B}_{sp,c}Y_0(k) - Y_{sp}(k)\Big) + \\ &+\Big(U(k) - U^0(k)\Big)^T\Big(U(k) - U^0(k)\Big) \end{aligned} \quad (8)$$

where Y_{sp} and U^0 are defined as $Y_{sp}(k) = [y_{sp}(k+1), 0, y_{sp}(k+2), 0, \cdots, y_{sp}(k+N-1), 0, \; 0, \cdots, 0]^T$ and $U^0(k) = [u^0(k), u^0(k+1), \cdots, \; u^0(k+N-1)]^T$, respectively. By zeroing the gradient with respect to U, the vector U^o containing the optimal input trajectory is achieved in the following closed-form:

$$\begin{aligned} U^o(k) = \; &\big(\mathcal{B}_c^T\mathcal{Q}\mathcal{B}_c + I\big)^{-1}\big(- \mathcal{B}_c^T\mathcal{Q}\mathcal{A}_c\hat{\bar{x}}(k) + \\ &-\mathcal{B}_c^T\mathcal{Q}\mathcal{M}_c D(k) - \mathcal{B}_c^T\mathcal{Q}\mathcal{B}_{sp,c}Y_0(k) + \\ &+\mathcal{B}_c^T\mathcal{Q}Y_{sp}(k) + U^0(k)\big) \end{aligned} \quad (9)$$

where I is an identity matrix with proper dimensions. Hence, according to the RH criterion, the time-invariant IMPC control law is given by

$$\begin{aligned} u^{MPC}(k) = \; &\begin{bmatrix}1 & 0 & \cdots & 0\end{bmatrix}\big(- K_{\bar{x}}\hat{\bar{x}}(k) - K_d D(k) + \\ &-K_{Y_0}Y_0(k) + K_{Y_{sp}}Y_{sp}(k) + K_{U^0}U^0(k)\big) \end{aligned} \quad (10)$$

where the gain matrices $K_{\bar{x}}$, K_d, K_{Y_0}, $K_{Y_{sp}}$, and K_{U^0} are defined as

$$\begin{aligned} K_{\bar{x}} &= \big(\mathcal{B}_c^T\mathcal{Q}\mathcal{B}_c + I\big)^{-1}\mathcal{B}_c^T\mathcal{Q}\mathcal{A}_c \\ K_d &= \big(\mathcal{B}_c^T\mathcal{Q}\mathcal{B}_c + I\big)^{-1}\mathcal{B}_c^T\mathcal{Q}\mathcal{M}_c \\ K_{Y_0} &= \big(\mathcal{B}_c^T\mathcal{Q}\mathcal{B}_c + I\big)^{-1}\mathcal{B}_c^T\mathcal{Q}\mathcal{B}_{sp,c} \\ K_{Y_{sp}} &= \big(\mathcal{B}_c^T\mathcal{Q}\mathcal{B}_c + I\big)^{-1}\mathcal{B}_c^T\mathcal{Q} \\ K_{U^0} &= \big(\mathcal{B}_c^T\mathcal{Q}\mathcal{B}_c + I\big)^{-1}\;. \end{aligned} \quad (11)$$

Note that, due to the unconstrained nature of the IMPC, as discussed in [Toffanin et al., 2013] for an MPC without integral action, the control action in (10), obtained by applying the RH criterion, includes some *a posteriori* saturations and constraints on the insulin delivery.

As for the choice of q_y and q_v, these values must be set on the basis of the estimated insulin sensitivity of the patient. The tuning of these weights is performed in two different steps. The first step is the calibration of the value q_y by a trial and error procedure as discussed in [Soru et al., 2012], by posing $q_v = 0$. The second step consists in the definition of a constant value q_v. Note that, in this preliminary study, a constant value of q_v has been considered for all the patients and has been tuned by a trial and error approach.

2.5 In Silico Scenario

The simulations are carried out on 100 virtual adult patients of the UVA/PADOVA simulator presented in [Dalla Man et al., 2014; Kovatchev et al., 2009]. The constant insulin sensitivity of each virtual patient is randomly varied by a ±25 % factor, and the controller is blind to these variations. Moreover, the simulated CGM measurements are affected by the error model described in [Toffanin et al., 2013]. The simulation scenario consists of five meals: the first is compensated in open-loop through the conventional therapy, while the remaining meals are compensated in closed-loop. The simulation scenario starts at 6:00 and lasts 34 hours, and the loop is closed at 8:00, within the

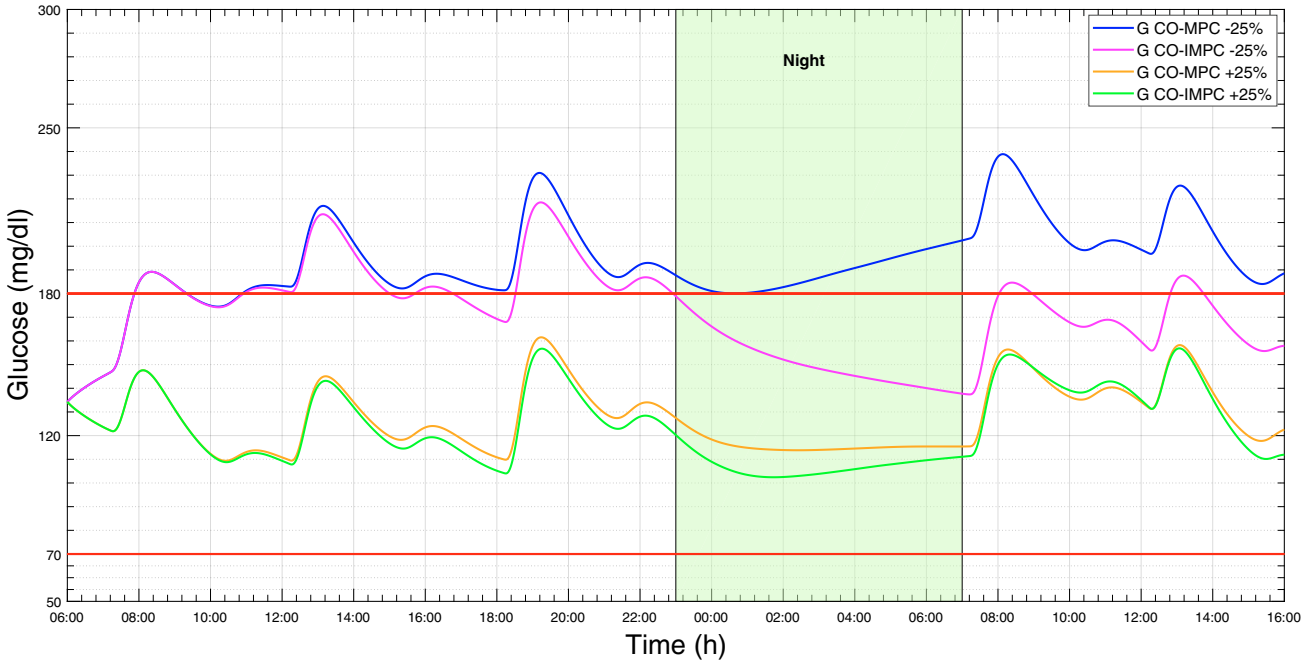

Fig. 1. Blood glucose profiles achieved through CO-MPC and CO-IMPC in the simulation scenario for patient #95. The perturbed cases with insulin sensitivity varied by a ±25% factor are shown.

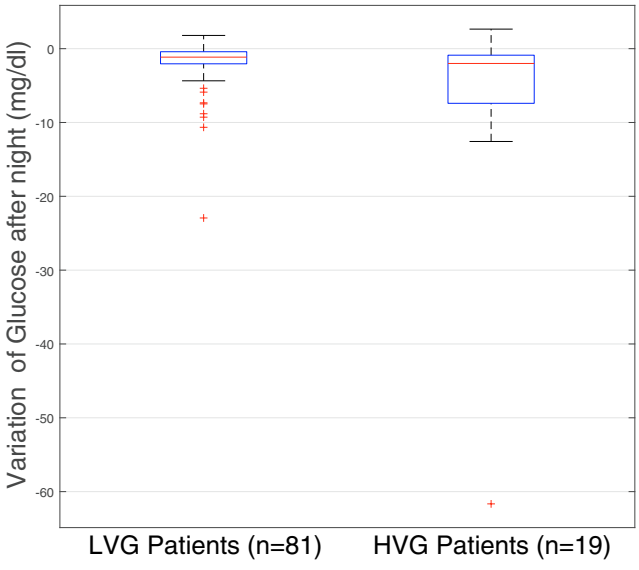

Fig. 2. Distribution of the differences of the glucose level at the end of night between CO-IMPC and CO-MPC for patients controlled via CO-MPC with glucose level inside the range 105-135 mg/dl (LVG) and out of the range 105-135 mg/dl (HVG) at end of the night (from 6:00 to 7:00), respectively.

postprandial period of the open-loop compensated meal. This contributes to increase the variability associated with the closed-loop starting conditions. Meal amounts are 50 g CHO for the first breakfast, 60 g CHO for the second one (both at 7:00), 60 g for the two lunches (at 12:00) and 80 g CHO for the dinner (at 18:00). Postprandial periods are defined as 4-hour time intervals starting from each meal time. Night period starts at 23:00 and lasts eight hours.

Table 1. Results obtained by simulating the strategies CO-MPC and CO-IMPC both for LVG and HVG patients. p-value (p) significance levels are: $a := p < 0.05$, $b := p < 0.01$, $c := p < 0.001$

		LVG	HVG
A (mg/dl)	CO-MPC	**117.05 (± 7.41)**	**134.07 (± 31.74)**
	CO-IMPC	**115.16^a (± 6.81)**	**127.17^c (± 24.36)**
SD (mg/dl)	CO-MPC	0.61 [0.43, 1.16]	0.68 [0.38, 1.07]
	CO-IMPC	0.64 [0.37, 1.19]	0.61 [0.31, 1.19]
Ttt (%)	CO-MPC	100.00 [100.00, 100.00]	100.00 [13.98, 100.00]
	CO-IMPC	100.00 [100.00, 100.00]	100.00 [98.73, 100.00]
Tb (%)	CO-MPC	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]
	CO-IMPC	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]

2.6 Outcome metrics

In order to assess the performance of the individualized IMPC, standard indices in evaluating AP clinical trials [Maahs et al., 2016] have been considered: average glucose (A), glucose standard deviation (SD), time in tight target or percentage of time spent within 70-140 mg/dl (Ttt), and time below target or percentage of time spent below 70 mg/dl (Tb).

3. SIMULATION RESULTS

The beneficial effects of the integral action are more evident by scrutinizing the individuals of the population. For instance, in Figure 1, the glucose profiles achieved through CO-MPC and CO-IMPC are shown for patient #95 with insulin sensitivity varied by a ±25 % factor. In particular, one can observe that the glucose at the end of the night (where the patient is supposed to be

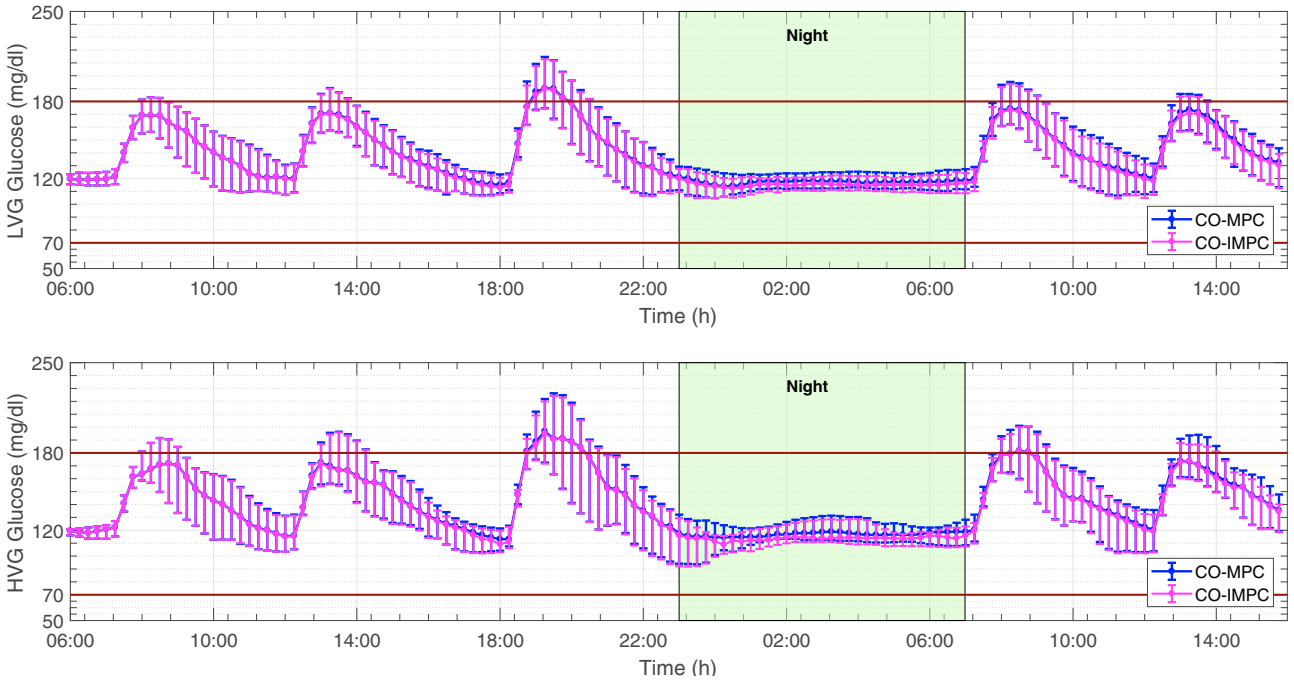

Fig. 3. Blood glucose profiles achieved through CO-MPC and CO-IMPC in the simulation scenario both for LVG (top) and HVG (bottom) patients. Glucose profiles are shown in terms of median (solid lines) surrounded by colored regions representing the glucose 25-th and 75-th percentiles.

in a quasi-steady state condition) is evidently closer to the target when the integral action is applied in case of insulin sensitivity varied by a -25 %. Furthermore, it is worth noticing that, even when the insulin sensitivity is varied by a +25 %, the performance are not deteriorated by the integral action, but the glucose level is similar for both CO-MPC and CO-IMPC.

Figure 2 shows the distribution of glucose differences at the end of the night between CO-IMPC and CO-MPC, distinguishing among patients with glucose level inside the range 105-135 mg/dl (LVG) and out of the range 105-135 mg/dl (HVG) at end of the night (from 6:00 to 7:00), respectively, when CO-MPC (i.e., without integral action), is used. Note that CO-IMPC allows to decrease the glucose level of HVG patients (n=19) without worsening glucose level of the remaining LVG patients (n=81).

Table 1 shows the outcome indices achieved by the individualized MPC and IMPC based on the models identified through constrained optimization (CO-MPC and CO-IMPC, respectively). Each index is evaluated at the end of night (from 6:00 to 7:00). Normal data are shown as mean (standard deviation) while non-normal data are shown as median [25-th, 75-th percentiles]. Data normality is evaluated through the Lilliefors test. The clinical relevance on the indices differences is evaluated through statistical comparisons performed through the paired t-test for normal data, and through the Wilcoxon signed-rank test for non-normal data. CO-IMPC improves the control performance in terms of average glucose with respect to CO-MPC for both LVG and HVG patients.

In Figure 3, the glucose profiles are illustrated in terms of median surrounded by vertical bars representing the glucose 25-th and 75-th percentiles for LVG (top) and HVG (bottom) patients. As expected, CO-IMPC allows to reach the glucose set-point more precisely, as shown by the lower nighttime median glucose.

4. CONCLUSIONS

An AP MPC strategy with integral action aimed at moving from a CTR to a CTT glucose regulation has been proposed. IMPC has shown good properties in terms of regulation to the target in presence of disturbances and model uncertainties. Moreover, it has improved the performance achievable with an individualized MPC for some critical patients, without worsening the overall performance. Beneficial effects of the MPC integral action are present even during the identification phase driven by the CO procedure, allowing to focus on the identification of the dynamical part of the model rather than to the static gain.

REFERENCES

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

Breton, M., Farret, A., Bruttomesso, D., Anderson, S., Magni, L., Patek, S., Dalla Man, C., Place, J., Demartini, S., Del Favero, S., Toffanin, C., Hughes-Karvetski, C., Dassau, E., Zisser, H., Doyle III, F.J., De Nicolao, G., Avogaro, A., Cobelli, C., Renard, E., and Kovatchev, on behalf of The International Artificial Pancreas (iAP) Study Group, B. (2012). Fully integrated artificial pancreas in type 1 diabetes: modular closed-loop glucose control maintains near normoglycemia. *Diabetes*, 61(9), 2230–2237.

Cobelli, C., Dalla Man, C., Sparacino, G., Magni, L., De Nicolao, G., and Kovatchev, B.P. (2009). Diabetes: models, signals, and control. *IEEE Rev. Biomed. Eng.*, 2, 54–96.

Cobelli, C., Renard, E., and Kovatchev, B.P. (2011). Artificial pancreas: past, present, future. *Diabetes*, 60(11), 2672–2682.

Dalla Man, C., Micheletto, F., Lv, D., Breton, M., Kovatchev, B., and Cobelli, C. (2014). The uva/padova type 1 diabetes simulator: New features. *J Diabetes Sci. Technol.*, 8(1), 26–34.

Del Favero, S., Place, J., Kropff, J., Messori, M., Keith-Hynes, P., Visentin, R., Munaro, M., Bruttomesso, D., Galasso, S., Boscari, F., Toffanin, C., Di Palma, F., Lanzola, G., Scarpellini, S., Ferret, A., Kovatchev, B., Magni, L., Avogaro, A., DeVries, J.H., Cobelli, C., and Renard on behalf of the AP@home Consortium, E. (2015). Multicentre outpatient dinner/overnight reduction of hypoglycemia and increased time of glucose in target with a wearable artificial pancreas using multimodular model predictive control algorithm in adults with type 1 diabetes. *Diabetes Obes. Metab.*, 17(5), 468–476.

Doyle, F.J., Huyett, L.M., Lee, J.B., Zisser, H.C., and Dassau, E. (2014). Closed-loop artificial pancreas systems: engineering the algorithms. *Diabetes Care*, 37(5), 1191–1197.

Grosman, B., Dassau, E., Zisser, H.C., Jovanovič, L., and Doyle III, F.J. (2010). Zone model predictive control: a strategy to minimize hyper- and hypoglycemic events. *J. Diabetes Sci. Technol.*, 4(4), 961–975.

Hovorka, R., Canonico, V., Chassin, L.J., Haueter, U., Massi-Benedetti, M., Orsini Federici, M., Pieber, T.R., Schaller, H.C., Schaupp, L., Vering, T., and Wilinska, M.E. (2004). Nonlinear model predictive control of glucose concentration in subjects with type 1 diabetes. *Physiol. Meas.*, 25(4), 905–920.

Kovatchev, B.P., Breton, M.D., Dalla Man, C., and Cobelli, C. (2009). In silico preclinical trials: a proof of concept in closed-loop control of type 1 diabetes. *J. Diabetes Sci. Technol.*, 3(1), 44–55.

Kropff, J., Del Favero, S., Place, J., Toffanin, C., Visentin, R., Monaro, M., Messori, M., Di Palma, F., Lanzola, G., Farret, A., Boscari, F., Galasso, S., Magni, P., Avogaro, A., Keith-Hynes, P., Kovatchev, B.P., Bruttomesso, D., Cobelli, C., DeVries, J.H., Renard, E., and Magni for the AP@home consortium, L. (2015). 2 month evening and night closed-loop glucose control in patients with type 1 diabetes under free-living conditions: a randomised crossover trial. *Lancet Diabetes Endocrinol.*, 3(12), 939–947.

Maahs, D.M., Buckingham, B.A., Castle, J.R., Cinar, A., Damiano, E.R., Dassau, E., DeVries, J.H., Doyle III, F.J., Griffen, S.C., Haidar, A., Heinemann, L., Hovorka, R., Jones, T.W., Kollman, C., Kovatchev, B., Levy, B.L., Nimri, R., O'Neal, D.N., Philip, M., Renard, E., Russell, S.J., Weinzimer, S.A., Zisser, H., and Lum, J.W. (2016). Outcome measures for artificial pancreas clinical trials: a consensus report. *Diabetes Care*, 39(7), 1175–1179.

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

Messori, M., Cobelli, C., and Magni, L. (2015). Artificial pancreas: from in-silico to in-vivo. In *IFAC 9th Int. Symp. on Adv. Control of Chem. Proc.*, 1301–1309. Whistler, British Columbia, Canada.

Messori, M., Toffanin, C., Del Favero, S., De Nicolao, G., Cobelli, C., and Magni, L. (2016). Model individualization for artificial pancreas. *Comput. Meth. Prog. Bio.*, -(-), –.

Renard, E., Farret, A., Kropff, J., Bruttomesso, D., Messori, M., Place, J., Visentin, R., Calore, R., Toffanin, C., Di Palma, F., Lanzola, G., Magni, P., Boscari, F., Galasso, S., Avogaro, A., Keith-Hynes, P., Kovatchev, B., Del Favero, S., Cobelli, C., Magni, L., and DeVries for the AP@home Consortium, J.H. (2016). Day and night closed-loop glucose control in patients with type 1 diabetes under free-living conditions: results of a single-arm 1-month experience compared with a previously reported feasibility study of evening and night at home. *Diabetes Care*, 39(7), 1151–1160.

Russell, S.J., El-Khatib, F.H., Sinha, M., Magyar, K.L., McKeon, K., Goergen, L.G., Balliro, C., Hillard, M.A., Nathan, D.M., and Damiano, E.R. (2014). Outpatient glycemic control with a bionic pancreas in type 1 diabetes. *N. Engl. J. Med.*, 371, 313–325.

Soru, P., De Nicolao, G., Toffanin, C., Dalla Man, C., Cobelli, C., and Magni on behalf of the AP@home consortium, L. (2012). MPC based artificial pancreas: strategies for individualization and meal compensation. *Annu. Rev. Control.*, 36(1), 118–128.

Thabit, H., Lubina-Solomon, A., Stadler, M., Leelarathna, L., Walkinshaw, E., Pernet, A., Allen, J.M., Iqbal, A., Choudhary, P., Kumareswaran, K., Nodale, M., Nisbet, C., Wilinska, M.E., Barnard, K.D., Dunger, D.B., Heller, S.R., Amiel, S.A., Evans, M.L., and Hovorka, R. (2014). Home use of closed-loop insulin delivery for overnight glucose control in adults with type 1 diabetes: a 4-week, multicentre, randomised crossover study. *Lancet Diabetes Endocrinol.*, 2(9), 701–709.

Thabit, H. and Hovorka, R. (2016). Coming of age: the artificial pancreas for type 1 diabetes. *Diabetologia*, 59(9), 1795–1805. doi:10.1007/s00125-016-4022-4.

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

Wilinska, M.E., Budiman, E.S., Taub, M.B., Elleri, D., Allen, J.M., Acerini, C.L., Dunger, D.B., and Hovorka, R. (2009). Overnight closed-loop insulin delivery with model predictive control: assessment of hypoglycemia and hyperglycemia risk using simulation studies. *J. Diabetes Sci. Technol.*, 3(5), 1109–1120.