Artificial Pancreas: In Silico Study Shows No Need of Meal Announcement and Improved Time in Range of Glucose with Intraperitoneal vs Subcutaneous Insulin Delivery

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***Abstract*—Contemporary Artificial Pancreas (AP) consists of a subcutaneous (SC) glucose sensor, a SC insulin pump and a control algorithm. Even the most advanced systems are far from optimal, in particular due to the non-physiologic nature of SC route. While SC insulin delivery is convenient and minimally invasive, it introduces delays to insulin action that make tight control difficult, particularly during meals. In addition frequent patient interventions are needed, e.g. at mealtime. The intraperitoneal (IP) insulin delivery could address this major challenge since it exhibits a faster pharmacokinetics/pharmacodynamics, hence making easier to quickly respond to glycemic disturbances. A 1-day hospital closed-loop study has shown significant improvements of IP glucose control vs SC AP, and that meal announcement is not necessary. However, the IP AP has not been tested in more realistic everyday life conditions. In this work we have performed an *in silico* study of 14 days of an IP AP by using the UVA/Padova simulator which includes intra- and inter-day variability of insulin sensitivity and several real life scenarios. We show superiority of IP AP vs SC AP in terms of quality of glucose control (time in range 87% IP vs 80% SC) without the need of a meal announcement.**

***Index Terms*—Closed-loop glucose control, Model Predictive Control (MPC), Mathematical modeling, Simulation, Automated insulin delivery systems**

I. Introduction

Diabetes mellitus is a life-threatening disease and its global prevalence is dramatically increasing as a result of population ageing, urbanization and associated lifestyle changes [1], [2]. Between 1980 and 2017, the number of people with diabetes has more than doubled reaching 425 million people worldwide and it is projected to rise to 629 million by 2045 [3], [4]. In people with Type 1 Diabetes (T1D) - 10-15% of the diabetes population - the pancreas is no longer able to secrete insulin and T1D subjects face a lifelong challenging problem to reach near-normal glycemic control without increasing their risk of hypoglycemia [5]. The current T1D therapy requires the patient to compute and self-inject an appropriate amount of insulin, resulting in multiple daily procedures (including painful finger-pricking and frustrating computation) with a therapeutic effectiveness that strongly depends on the patient's skill. The standard insulin therapy for T1D patients is the so-called subcutaneous (SC) basal-bolus therapy: the combination of a piecewise constant insulin infusion, the basal (u_b), to supply to the insulin needs during fasting periods, and of impulse-like infusions, the insulin boluses (u_B), realising a feed-forward action performed to compensate perturbations, i.e. meals. As result the quality of glucose control is highly dependent on the chosen basal intervals and on the estimation by the T1D subject of the carbohydrate content of each meal. It has been estimated that only about half of the patients meet the targets recommended by the scientific societies clinical guidelines [6] despite the exorbitant number of therapeutic actions (100.000-500.000) in one patient's life. Not meeting the target recommendations has dramatic consequences: persistent hyperglycemia (Blood Glucose, BG, $>$ 180 mg/dl) can lead to eye, heart, kidney, and nerve injuries, whereas acute hyperglycemia (BG $>$ 250 mg/dl) can result in ketoacidosis, which is still the most frequent cause of death in people with T1D aged under 50 years [7]. On the other side of the glucose spectrum hypoglycemia (BG $<$ 70 mg/dl) may result in convulsions, coma and even death. Patients constantly fear hyperglycemia or forthcoming acute hypoglycemia. These and other disease associated burden triplicates depression in T1D subjects [8]. The economic burden of diabetes is remarkable: a diabetic subject cost is twice as much as for a non-diabetic subject, 560 billion €/year or 2600 €/year per patient in Western countries.

Some solutions to automatically manage insulin administration exist, but they are still far from being optimal. The forefront diabetes research in the EU and US consists of a SC wearable Automated Insulin Delivery systems (AID), often referred to as Artificial Pancreas (AP) [9] with three external-to-the-body devices: a SC glucose sensor, a SC insulin pump and a control algorithm implemented either on a tablet or directly on the pump. However, even the most advanced AP systems are far from optimal [10]–[15] due to the non-physiologic nature of SC route. While SC insulin delivery is convenient and minimally invasive, it introduces delays in insulin action and clearance [16] that make tight control difficult. The

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hurdles to glycemic control caused by these delays are very critical and frequent interventions are required by the patient, e.g. any time there is a meal or an exercise, to improve postprandial glucose control [17]–[19], thus rendering system full automation impossible. In summary, the SC insulin delivery route is the bottleneck of AP technology and the cause of the major limitations of this approach. Although improving glucose control with respect to manual insulin delivery, AP reaches an unsatisfactory glucose control, especially during meals and SC AP is still not able to avoid the acute complications of diabetes and reducing disease associated burdens.

The intraperitoneal (IP) site for insulin delivery could address this major challenge and is a promising alternative to the conventional SC route. Delivering insulin to the IP space results in faster pharmacokinetics/pharmacodynamics [20], [21] as shown in Fig. 1, hence it could be easier for an AP controller to quickly respond to glycemic disturbances. Preliminary studies of closed-loop control using implanted IP insulin technology in 1-day hospital studies, with a Proportional, Integral, Derivative (PID) controller [22] and a Model Predictive Controller (MPC) [23], have shown clinical feasibility and the potential to improve significantly glucose control with respect to SC AP. However, they have not been tested in the more realistic and challenging everyday life condition of outpatients. In addition to improved pharmacokinetics and pharmacodynamics, IP delivery also better mimics physiological insulin delivery by including a first liver pass and thus a higher insulin concentration in the portal system than in the peripheral system. This results in better insulin/glucagon balance and glycemic variability [24]. Some recent studies [25], [26] indicate that prolonged use of IP infusion does not adversely affect insulin-like growth-factor-1 (IGF-1) concentrations, as observed with prolonged SC use [27]. The use of IP insulin delivery also reduces frequency and severity of hypoglycemic episodes [28], [29].

Even if the advantages of the IP route is an accepted notion, its long-term usage is not widespread due to some major issues: the safety and the stability of the implant, the long-term power supply, the invasive refill procedure, the fluid leakage and contamination, and the frequency of catheter occlusions. Recently, several research groups have addressed these aspects to make the IP pumps a valuable alternative to SC ones. For example, Lee at al [30] designed a novel implantable insulin infusion system actuated by a magnetic pen. Peristaltic rotary pumps are also under study [31] since they can ensure low voltage actuation and low impact on fluid properties, solving the issue of the contact between fluids and pump mechanisms and thus avoiding leakages and fluid contaminations [32]. Catheter occlusions is an additional problem and active research is carried out. Less traumatic catheter tips and catheter components or coatings reducing inflammatory reactions at the catheter tip could provide solutions to minimize occlusions [33]. Recent studies reported catheter obstructions improvements moving from 8-57 to 4 occlusions per 100 patient-years [34]. Research on stable highly concentrated insulin analogues is also in progress.

On the market two IP insulin systems are available: the Medtronic implantable programmable system (model MMT-2007D; Medtronic Diabetes, Northridge, CA) and the DiaPort system by Roche (Second Generation, Roche Diagnostics, Mannheim, Germany), which is provided with a transcutaneous access allowing direct IP insulin delivery from an external portable device. However, new and more advanced systems are under study. For example, Iacovacci et al [35] developed a device equipped with a mechatronic system for noninvasive refilling that relieves the patient to periodically visit the hospital for pump refilling. The FET Proactive FORGETDIABETES EU funded project (n. 951933) aims at realising a fully-implanted IP sensor and IP pump system; in particular, the miniaturised IP pump has a noninvasive refill strategy and wireless battery recharging that is immuno-optimised and biocompatible in order to minimise adverse reactions and occlusions. Novel control algorithms using IP sensor and IP insulin delivery are being also developed within the project.

In this manuscript we propose a fully-automated IP MPC, i.e. unannounced meals, (MPC-IP-U) and compare it *in silico* to the SC hybrid MPC [36], i.e. with meal announcement, (MPC-SC-A) that was successfully employed in our long-period outpatient clinical trials [37]–[39]. In order to single out the improvements due to the new IP route, no further changes have been introduced in the MPC-IP-U with respect to the clinical validated MPC-SC-A. The glucose measurements are obtained using CGM (Continuous Glucose Monitoring) devices available on the market, which measure SC glucose. The delay due to this kind of measurements affect the AP performance in both cases (IP and SC). The MPC has been optimised for both IP with unannounced meals and SC with announced meals. The key point of the proposed IP approach is the possibility, thanks to the new technologies, to relieve the patient from counting the carbohydrate contents and announcing the meal. This is possible thanks to the fast IP route used for insulin delivery and the optimal action of the MPC-IP-U controller.

In addition, results obtained with the fully-automated SC MPC, i.e. no meal announcement (MPC-SC-U) have been reported for completeness and to understand the nature of the improvements obtained with the proposed method. The performance has been evaluated *in silico* on 100 virtual adult patients using using the most recent version of the FDA accepted UVA/Padova Type 1 Diabetes Simulator [40], [41]. that accounts for intra- and inter-patient variability of insulin sensitivity. All the results are based on the SC glucose sensor included in the simulator.

The paper is organised as follows. In Section II the fully-automated MPC algorithm is presented together with the hybrid MPC. In Section III the UVA/Padova simulator, the scenario, the controller parameters and the metrics used for the tests are presented. In Section IV the results achieved by both controllers are reported. In Section V results are discussed. In Section VI some conclusions are drawn.

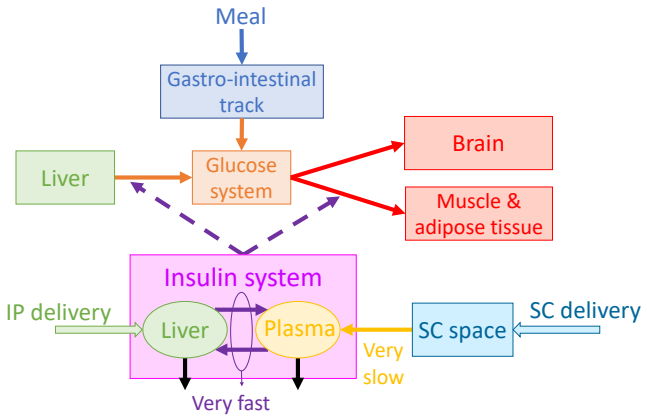

Fig. 1. Schematic diagram illustrating glucose metabolism and the two insulin delivery route: the state-of-art subcutaneous (SC) and the novel intraperitoneal (IP) route.

II. Fully-automated Intraperitoneal MPC artificial pancreas

In this Section, the proposed MPC algorithm designed to be used with an intraperitoneal insulin pump is introduced. The meal is not announced to the system allowing less interaction and stress for the patient, but requiring the use of a more invasive implanted pump. The model used in the MPC is a linearization of the average model of the UVA/Padova simulator [40], [41] and no constraints are considered in order to allow a closed-form solution easily implementable on the devices. Note that, as in [36] the model is a 13-states linear model obtained via linearisation from the metabolic nonlinear model [42]. The model is not personalised to the specific patient: the parameters are the ones of the average *in silico* patient. The personalisation is performed only via the tuning of the MPC aggressiveness, as described in Section II-C, and using the conventional basal-bolus therapy specific of each patient. The detailed design procedure is described in the following.

A. Design of the MPC-IP-U

The MPC-IP-U algorithm proposed in this work is a Linear Model Predictive Controller (LMPC) since it is based on the linear discrete time Model of the Average *in silico* Patient (MoAP) obtained from the linearization of the physiological model of the UVA/Padova simulator. The equilibrium point used for the linearisation is the one associated with the basal insulin (u_b) for the input and zero for the meal. This model can be written in the following form:

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

where

- $x(k) \in R^n$, is the vector of n states;
- $y(k) = CGM(k) - G_b$ (mg/dl), is the difference between the subcutaneous glucose (CGM) measured by a SC CGM device and the basal value (G_b);
- $u(k) = i(k) - u_b(k)$ (pmol/kg), is the difference between the injected insulin (i) and its basal value (u_b), typically a step-wise constant amount. The insulin is normalized by the patient weight.

Note that the meal contribution is not included in the model since no meal information is provided to the MPC-IP-U algorithm. The triplet (A, B, C) is both stabilizable and detectable for the considered MoAP. The predictions obtained through the MoAP are exploited to find the optimal insulin profile minimizing the following cost function:

$$\begin{aligned} J(x(k), u(\cdot), k) \quad = \quad & \textstyle\sum_{i=0}^{N-1} (q(y(k+i) - y_o(k+i))^2 \\ & + u(k+i)^2) + \|x(k+N)\|_P^2 \end{aligned} \tag{2}$$

where q is a positive scalar weight to be tuned and N is the prediction horizon. Parameter q represents the aggressiveness of the controller here proposed. The final cost term is $||x(k+N)||_P = x(k+N)'Px(k+N)$, where P is the unique nonnegative solution of the discrete time Riccati equation

$$P = A'PA + qC'C - A'PB\,(1 + B'PB)\,B'PA$$

and

- $y_o(k) = \tilde{y}(k) - G_b$ (mg/dl), is the difference between the reference value ($\tilde{y}$) of the subcutaneous glucose and the glucose basal value (G_b).

The proposed algorithm does not explicitly include constraints in order to avoid on-line optimization and the computational and memory burden of an explicit MPC for constrained systems. Hence, a closed form solution is available by exploiting the Lagrange formula. Defining:

$$\begin{aligned} Y(k) \quad &= \quad [y(k+1) \ \ldots \ y(k+N-1) \ x(k+N)]' \\ U(k) \quad &= \quad [u(k) \ \ldots \ u(k+N-2) \ u(k+N-1)]' \end{aligned}$$

the predicted vector $Y(k)$ can be written as a function of the initial state $x(k)$ and the vector of future insulin administrations $U(k)$ as follows:

$$Y(k) = \mathcal{A}_c x(k) + \mathcal{B}_c U(k) \tag{3}$$

where

$$\mathcal{A}_c = \begin{bmatrix} CA & \ldots & CA^{N-1} & A^N \end{bmatrix}'$$

$$\mathcal{B}_c = \begin{bmatrix} CB & 0 & \cdots & 0 \\ CAB & CB & \cdots & 0 \\ \cdots & \cdots & \cdots & \cdots \\ CA^{N-2}B & CA^{N-3}B & \cdots & 0 \\ A^{N-1}B & A^{N-2}B & \cdots & B \end{bmatrix}$$

Defining the reference vectors $Y_o \in R^{(N-1+n)\times 1}$

$$Y_o(k) \quad = \quad [y_o(k+1) \ \ldots \ y_o(k+N-1) \ 0]'$$

and setting the matrix:

$$\mathcal{Q} = \begin{bmatrix} q & 0 & \cdots & 0 & 0 \\ 0 & q & \cdots & 0 & 0 \\ \vdots & \vdots & \ddots & \vdots & \vdots \\ 0 & 0 & \cdots & q & 0 \\ 0 & 0 & \cdots & 0 & P \end{bmatrix} \tag{4}$$

the cost in (2) can be rewritten as

$$J(x(k), \quad u(\cdot), k) = (\mathcal{A}_c x(k) + \mathcal{B}_c U(k) - Y_o(k))' \mathcal{Q} \\ (\mathcal{A}_c x(k) + \mathcal{B}_c U(k) - Y_o(k)) + U(k)' U(k)$$

The terms that do not affect the solution of the optimization problem because they are not dependent on $u(k+j), j \geq 0$, i.e. $qy^2(k)$, have been dropped. Zeroing the gradient, the vector of future optimal inputs is

$$U^o(k) = (\mathcal{B}_c' \mathcal{Q} \mathcal{B}_c + \mathcal{R})^{-1} (-\mathcal{B}_c' \mathcal{Q} \mathcal{A}_c x(k) + \mathcal{B}_c' \mathcal{Q} Y_o(k)) \quad (5)$$

which depends on the state at sample time k, the output future reference. The future optimal inputs can be expressed in a compact form defining the following gain matrices:

$$\begin{aligned} K_x &= (\mathcal{B}_c' \mathcal{Q} \mathcal{B}_c + I)^{-1} \mathcal{B}_c' \mathcal{Q} \mathcal{A}_c \\ K_{Y_o} &= (\mathcal{B}_c' \mathcal{Q} \mathcal{B}_c + I)^{-1} \mathcal{B}_c' \mathcal{Q} \end{aligned}$$

so that

$$U^o(k) = (-K_x x(k) K_{Y_o} Y_o(k)) \quad (6)$$

and the time-invariant LMPC control law ($u^{\text{MPC-IP-U}}$) is obtained applying the receding horizon principle as:

$$\begin{aligned} u^{\text{MPC-IP-U}}(k) &= \begin{bmatrix} 1 & 0 & \cdots & 0 \end{bmatrix} \\ & (-K_x x(k) + K_{Y_o} Y_o(k)) \end{aligned} \quad (7)$$

Note that differently from [36] a posteriori constraints can be relaxed in view of the fast response to the IP delivery. Hence, only the pump physical minimum and maximum limitations are considered.

Usually the state $x(k)$ of the model is not measurable. In partcular, in the considered application it includes the internal state of the 13 compartments of the Padova model [42] that describe the metabolism of insulin and meal of a diabetes patient, not measurable by their nature.

The use of a non minimal state-space realization of the input-output model, whose state is made by past input and output values, was investigated in [43]. However, also in that case, closed-loop performance were affected by the not negligible sensor noise present in the output measurements. So, in this paper, we followed the approach presented in [44] using a Kalman Filter, to exploit the knowledge included in the model and the past injected insulin, in order to improve the quality of the state estimation provided to the LMPC algorithm.

B. Kalman Filter design

The noises affecting the system have to be considered in order to design the Kalman Filter (KF). So, the linear system description (1) is enriched with noises on the state (v_x) and on the output (v_y) as follows:

$$\begin{cases} x(k+1) = Ax(k) + Bu(k) + v_x(k) \\ y(k) = Cx(k) + v_y(k) \end{cases} \quad (8)$$

The vector $v = [v_x \; v_y]$ is a multivariate zero-mean white Gaussian noise with covariance matrix:

$$V = \begin{bmatrix} Q_{\text{KF}} & 0 \\ 0 & R_{\text{KF}} \end{bmatrix}, \; Q_{\text{KF}} > 0 \; R_{\text{KF}} > 0 \quad (9)$$

and the initial state $x_0 = x(0)$ is assumed to be a zero mean Gaussian random variable independent of v.

Under these assumption, the steady-state KF has the following equations:

$$\begin{aligned} \hat{x}(k+1|k) =& A\hat{x}(k|k) + Bu(k) \\ \hat{x}(k|k) =& \hat{x}(k|k-1) + L\left(y(k) - C\hat{x}(k|k-1)\right) \end{aligned} \quad (10)$$

where

$$L = P_{KF} C' \left[C P_{KF} C' + R_{\text{KF}}\right]^{-1} \quad (11)$$

with P_{KF} the unique positive definite solution of the Riccati equation

$$\begin{aligned} P_{KF} = \; & A P_{KF} A' + Q_{\text{KF}} \\ & - A P_{KF} C' \left[C P_{KF} C' + R_{KF}\right]^{-1} C P_{KF} A' \end{aligned}$$

According to the separation principle, the estimated state is plugged into the control law (7)

$$\begin{aligned} u^{\text{MPC-IP-U}}(k) &= \begin{bmatrix} 1 & 0 & \cdots & 0 \end{bmatrix} \\ & (-K_x \hat{x}(k) + K_{Y_o} Y_o(k)) \end{aligned} \quad (12)$$

The main advantage of using the Kalman filter is that, by properly tuning Q_{KF} and R_{KF}, the controller can be made less sensitive to sensor noise.

C. Calibration procedure for MPC individualisation

The significant inter-individual variability that affects the diabetes population calls for patient-tailored AP systems. The limited amount of information that can be collected and the limitation about the test feasible on each single subject in order to guarantee his/her safety make the individualization task not trivial. The less critical parameters of the algorithm are then kept fixed, while the personalization of the control action is obtained by tailoring the cost function (2). This choice is justified by the low correlation between parameters like the control horizon N or the KF weights with the single patients, since they are mainly related to the quality of the sensor and the model included in the filter. For this reason, in the algorithm proposed in this work the control horizon N is kept equal to 1 hour and the KF weights (Q_{KF}, R_{KF}) are set on the base of simulated and clinical insulin-meal glucose profiles as reported in [36]. These weights should be retuned if the quality of the model or the sensor changes significantly. Note that the use of the solution of the Riccati equation in the final cost term, as reported in equation (2), brings the tail of the cost function from N to ∞.

The elements that can be individualized in the cost function are the model and the aggressiveness of the control. Since a patient-tailored model is still not available for each patient - even if the authors are exploring different approaches with this aim [45]–[47] - the approach proposed in this work is based on the individualization of the scalar weight q that represents the aggressiveness of the controller. An appropriate trade-off between a too mild control and the risk of hypoglycemic episods induced by a too aggressive regulator is the final goal of the calibration procedure.

Exploiting the possibility to perform potentially dangerous test

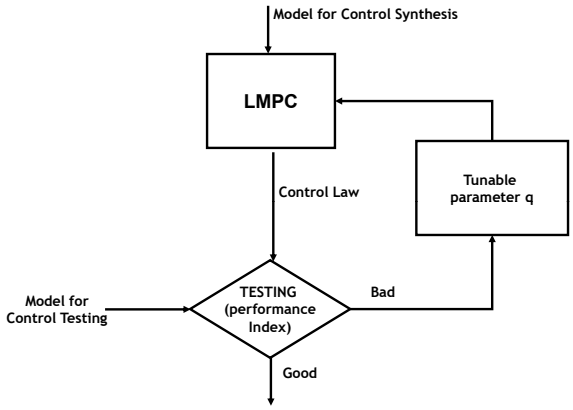

Fig. 2. Control Design Procedure

on the *in silico* patients of the UVA/Padova simulator, the tuning of q is done through the iterative procedure represented in Fig. 2 on the *in silico* population. Several simulation are performed using different values of q for each *in silico* subject, in order to find the optimal q^o for the specific individual. The performance is evaluated using the Control Variability Grid Analysis (CVGA) [44], where a single point represents the couple of 2.5 and 97.5 percentiles of BG values reached by the virtual patient during the considered week. As index we choose the distance between the point representing the subject under control and the optimal point on the bottom left corner of the grid where max(BG) = min(BG) = 110 mg/dl. The optimal weight can be formally describe as

$$q^o = \arg\min_q \left\| \begin{bmatrix} X_{CVGA} & Y_{CVGA} \end{bmatrix} \right\|_2 \tag{13}$$

At the end of this procedure, an optimal q^o is obtained for each *in silico* subject. Then, a linear regression function is identified in order to correlate the obtained optimal q values with some clinical well-known parameters of the *in silico* subjects. The linear tuning rule for the weight q is defined as

$$q^o(i) = \phi(i)'\theta + \epsilon(i), \quad i = 1, \ldots, 100 \tag{14}$$

where q^o is his/her optimal weight computed during the calibration procedure, $\phi(i)$ is the vector of clinical parameters for the $i-th$ patient, θ is the parameter vector to be estimated and $\epsilon(i)$ is an error term. Using a linear stepwise regression, the most correlated parameters of ϕ and the values of vector θ are derived. Then, the q^o for a real patient j can be estimated as

$$q^o(j) = \alpha\phi(j)'\theta \tag{15}$$

where $\alpha \in (0; 1]$ is a tunable parameter to increase the conservativeness of the controller. Both MPC-IP and MPC-SC have been calibrated using the simulators described in details in Section III-A. The MPC-SC design is reported in [36] with $\alpha = 0.85$, while in the MPC-IP version, the vector ϕ contains the body weight (BW) of the patient, and the optimal weight q^o is computed as $q^o_{\text{IP}} = e^{(-0.1315\ \text{BW}+19.0586)}$.

III. Simulations

A. The UVA/Padova Simulator with Intraperitoneal Insulin Delivery

The most recent version of the FDA-accepted UVA/Padova T1D simulator [40], [41] which includes a SC insulin delivery model was used to test the MPC with announced (MPC-SC-A) and unannounced (MPC-SC-U) meals. A novel T1D simulator was developed to account for IP insulin delivery. The metabolic core of the FDA-accepted UVA/Padova T1D simulator [40], [41] was retained and equipped with a novel IP insulin delivery module. Since the insulin subsystem of the simulator consists of two compartments, the liver and the plasma compartment, we have assumed that the insulin infusion predicted by the controller enters directly into the liver compartment [20]. New models of the intraperitoneal insulin kinetics are currently under study and will be taken into consideration for a future development of this work. All the metabolic features of the most recent version of the simulator including the possibility of implementing multiple-day scenarios with intra- and inter-day variability of insulin sensitivity and new distributions of carbohydrate-to-insulin ratio (CR) at breakfast, lunch and dinner are present. This novel IP simulator was used to test the MPC with unannounced meals (MPC-IP-U).

B. Scenario

All the algorithms considered in this work are tested on the 100 *in silico* adults of the simulators described in Section III-A. A 2-week realistic *in silico* scenario is considered where a constant random $\pm 50\%$ variation of the nominal insulin sensitivity is applied from the beginning and throughout the trial. For the announced algorithm this variation is applied together with a uncertainty of $\pm 30\%$ about the carbohydrate content announced at mealtime: 66% of the patients tends to underestimate the meal (consumed a +30% of carbohydrates with respect to the announced amount due to the fear of hypoglycaemia) while 34% to overestimate it (applying a -30% meal variation with respect to the announcement). The CGM sensor is affected by the error noise described in [36]. The patient diet involves three meals per day: breakfast at 7:30 am, lunch at 2:00 pm, and dinner at 8:30 pm containing 50 g, 60 g, and 70 g of CHO, respectively. These settings are chosen in order to mimic the habits occurring in real life, like those observed in [37]. In case of potentially dangerous low BG values (BG $<$ 65 mg/dl), the protocol prescribes a rescue carbohydrate dose of 16 g, the so called hypo-treatment (ht). Two ht are separated by at least 30 minutes.

C. Controller parameters

The model used in both the MPC-IP-U and MPC-SC-A is a 13-state ($n = 13$) model obtained by linearising the glucose-insulin model [42] around the equilibrium associated with the working point $[u_b, 0]$, where u_b is the basal insulin profile of the specific patient. The parameter G_b is the basal glucose of the patient, i.e. the ideal glucose value reached delivering u_b to the patient in fasting conditions. G_b is known for each patient

in real life. The references $\tilde{y}$, $\tilde{u}$ are set equal to 120 mg/dl and to the basal-bolus therapy, respectively. The prediction horizon N is equal to 1 hour. The KF matrices are set as in [36]: $R_{KF} = 0.0283$ and Q_{KF} is a diagonal matrix whose entries q_i are equal to 10 for $i = 4, 5$ and $q_i = 0.1$ otherwise.

D. Metrics and statistical analysis

The performance metrics used in this work has been selected following the consensus endpoints for AP trial described in [48], [49]. They consists in average BG (A), standard deviation (SD) and coefficient of variation (CV) of BG, percentage of time spent in euglycemic range [70-180] mg/dl (T_r), percentage of time spent in tight range [80-140] mg/dl (T_{tr}), percentage of time spent above 180 mg/dl (T_a), percentage of time spent below 70 mg/dl (T_b), Low Blood Glucose Index (LBGI) and High Blood Glucose Index (HBGI).
These metrics are computed during day & night (D&N), during night (N, 0:00 pm - 8:00 am), and as an average of all the Post-Prandial (PP) periods (4h) of the whole period.
Median $[25^{th}, 75^{th}]$ percentiles for non-Gaussian distributed data and mean ($\pm$ standard deviation) otherwise are reported for the various indices. The gaussianity and homoscedasticity of the data distributions are assessed by the Lilliefors test and two-sample F-test, respectively. In order to evaluate the significant differences, the more appropriated statistical test is selected based on the characteristics of the data distributions. If at least one distribution is non-Gaussian, the Wilcoxon rank sum test is used; if both distributions are Gaussian and homoscedastic, a two-sample t-test is performed; otherwise, if the homoscedasticity is not satisfied, the two-sample t-test with Satterthwaites approximation is used.
Finally, the daily mean glucose profiles of the 100 *in silico* patients for the MPC-IP-U vs MPC-SC-A configurations on the 2-week scenario are calculated.

IV. Results

The results of MPC-IP-U and MPC-SC-A are presented in Table I: even if the meal is unannounced, the MPC-IP-U algorithm is able to reduce the mean BG with respect to the MPC-SC-A overall, but also in the post-prandial period. Moreover, the standard deviation of the BG is reduced by 17%. The time in range and in tight range are improved (by 9% and 68%, respectively), reducing the time above 180 mg/dl by 48% without increasing hypoglycemia (the time below 70 mg/dl remains negligible). All these improvements are statistically significant (p-value$<$0.001).

The performance improvement obtained by MPC-IP-U with respect to MPC-SC-A can be also observed in Fig. 3: the mean daily glucose profiles of the the 100 *in silico* patients are represented in terms of median $[25^{th}, 75^{th}]$ percentiles. The superior performance of the intraperitoneal version of the MPC are evident. The SC approach is not able to properly compensate the meal effects due to the intrinsic delay of the SC route. In particular, it is interesting to note that BG is particularly high after midnight in the SC case: this is the effect of the poor glucose control of the dinner in the previous day.

The mean daily insulin profiles are not reported because, considering the high variability both from one day to the other (in terms of carbohydrate content) and from one patient to the other (in terms of insulin requirements), this comparison would not be significant.

V. Discussion

The results obtained with MPC-SC-A are in agreement with several AP studies, including the most recent state-of-art trial [50]. The comparison of our MPC-IP-U results with literature rely on the single paper [23]: the conclusion of superiority of IP vs SC insulin delivery route are in perfect agreement with [23], more difficult is to move to a comparison of the various metrics, in fact the study lasted 1 vs 14 days and the three meals differed in terms of carbohydrate content.
In order to evaluate the improvement obtained with the IP route, the performance of the fully-automated SC MPC (MPC-SC-U) are compared with the proposed MPC-IP-U in Table II. Again, the IP route demonstrated its power, improving all the indices. The LBGI slightly increases, but the T_b remains negligible. In this work, the absorption time of the insulin has been considered negligible due to the fast dynamics of the intraperitoneal route. A more detailed model based on new data is currently under development, but we do note expect a large change in the major conclusions of the simulation, i.e. meal announcement is not needed in contrast to SC insulin deliver.

VI. Conclusion

It is an accepted notion that the IP route for insulin delivery in T1D, being quasi-portal, is the most physiological since it recreates a pre-liver administration of insulin (Fig. 1). While intensive and successful research has been made on AP with SC insulin delivery with several contributions from several US and EU groups, only one study [23] has examined the role of IP delivery in AP. Albeit short in duration (1 day), the important finding was that the IP insulin delivery allows to avoid the meal announcement (the so-called hybrid AP) which is one of the bottleneck of hybrid AP. In this work, we have undertaken an *in silico* study of 14 days of an IP AP to confirm the 1 day clinical results and to extend them by using the UVA/Padova simulator which includes intra- and inter-day variability of insulin sensitivity and several real life scenario features. Our results support the notion that an IP AP does not necessitates the meal announcement, thus opens the way for a fully automated AP, i.e. not requiring the patient to announce the carbohydrate content of the meal. Further work in this context will be the use of an IP insulin kinetic model based on data [23] to include in the simulator in order to design a more refined IP MPC controller. Of interest will also be to explore the potential advantages of an IP vs SC glucose sensor.

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		D&N	N	PP
A (mg/dl)	MPC-IP-U	**141.32 [126.73, 161.61]**	**128.61 [116.37, 143.49]**	**156.43 [135.81, 182.78]**
	MPC-SC-A	**155.11^a [128.07, 193.94]**	**144.39^a [117.62, 169.75]**	**168.38^a [140.65, 213.37]**
SD (mg/dl)	MPC-IP-U	**28.72 [22.37, 36.02]**	**14.73 [11.81, 21.22]**	**30.39 ($\pm$ 11.03)**
	MPC-SC-A	**34.76^a [28.26, 41.10]**	**20.70^a [15.92, 27.87]**	**35.69^a ($\pm$ 11.19)**
CV (mg/dl)	MPC-IP-U	**0.20 ($\pm$ 0.06)**	**0.11 [0.09, 0.17]**	**0.18 [0.15, 0.22]**
	MPC-SC-A	**0.22^b ($\pm$ 0.07)**	**0.14^a [0.11, 0.20]**	**0.20^b [0.15, 0.26]**
T_r (%)	MPC-IP-U	**87.22 [72.37, 94.56]**	**99.28 [90.46, 100.00]**	**79.88 [52.38, 91.39]**
	MPC-SC-A	**80.32^a [43.75, 87.83]**	**87.18^a [69.83, 98.28]**	**69.89^a [18.24, 80.85]**
T_{tr} (%)	MPC-IP-U	**56.67 [26.13, 69.21]**	**73.77 [41.72, 89.18]**	**28.76 [9.34, 52.90]**
	MPC-SC-A	**33.68^a [3.53, 62.67]**	**34.40^a [5.07, 80.98]**	**14.08^a [2.19, 47.81]**
T_a (%)	MPC-IP-U	**9.15 [3.31, 26.06]**	**0.00 [0.00, 1.13]**	**17.93 [6.55, 47.62]**
	MPC-SC-A	**17.50^a [8.94, 56.25]**	**6.63^a [0.22, 29.27]**	**29.07^a [14.65, 81.76]**
T_b (%)	MPC-IP-U	0.00 [0.00, 1.26]	0.00 [0.00, 0.76]	0.00 [0.00, 0.66]
	MPC-SC-A	0.00 [0.00, 2.77]	0.00 [0.00, 0.61]	0.00 [0.00, 1.71]
LBGI	MPC-IP-U	0.03 [0.00, 0.39]	0.03 [0.00, 0.32]	0.01 [0.00, 0.24]
	MPC-SC-A	0.00 [0.00, 0.88]	0.00 [0.00, 0.45]	0.01 [0.00, 0.45]
HBGI	MPC-IP-U	**2.57 [1.45, 5.37]**	**0.97 [0.50, 2.31]**	**4.28 [2.47, 8.88]**
	MPC-SC-A	**4.81^a [2.26, 11.13]**	**2.86^a [0.71, 6.24]**	**6.13^a [3.52, 14.96]**

TABLE I

PERFORMANCE METRICS OF MPC-IP-U VERSUS MPC-SC-A ON THE 2-WEEK SCENARIO. ^{a} P-VALUE < 0.001, ^{b} P-VALUE < 0.01, ^{c} P-VALUE < 0.05. STATISTICALLY SIGNIFICANT RESULTS ARE HIGHLIGHTED IN BOLD.
D=DAY; N=NIGHT; PP=POSTPRANDIAL; A=AVERAGE BG; SD=STANDARD DEVIATION BG; CV=COEFFICIENT OF VARIATION BG; T_r=TIME IN RANGE; T_{tr}=TIME IN TIGHT RANGE; T_a=TIME ABOVE RANGE; T_b=TIME BELOW RANGE; LBGI=LOW BLOOD GLUCOSE INDEX; HBGI=HIGH BLOOD GLUCOSE INDEX. FOR A COMPLETE DESCRIPTION SEE SECTION III-D.

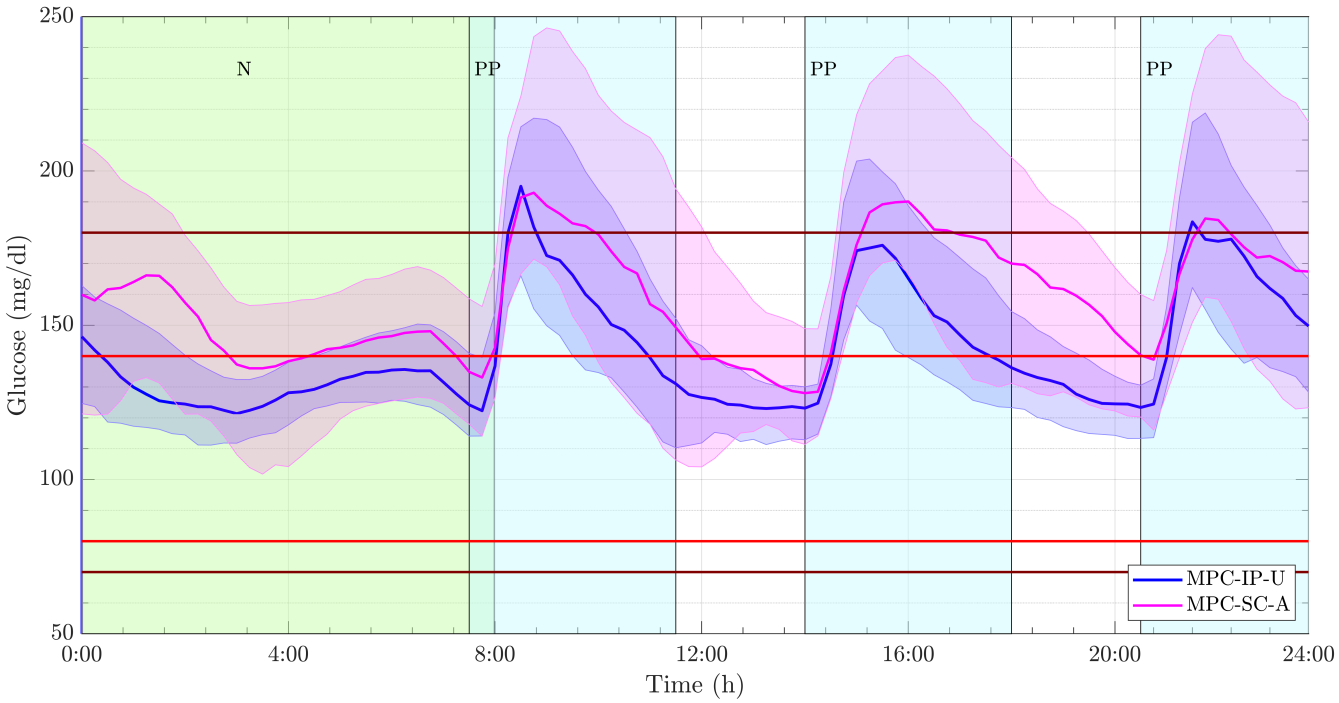

Fig. 3. Comparison of average glucose time courses with MPC-IP-U (blue) versus MPC-SC-A (magenta) on the 2-week scenario. Continuous lines are the median across patients, with [25th, 75th] percentiles as shading. Night (N) and Post-Prandial (PP) regions are highlighted in green and light blue, respectively.

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		D&N	N	PP
A (mg/dl)	MPC-IP-U	**141.32 [126.73, 161.61]**	**128.61 [116.37, 143.49]**	**156.43 [135.81, 182.78]**
	MPC-SC-U	**169.74**^{a} **[145.91, 209.55]**	**149.67**^{a} **[120.64, 179.90]**	**194.21**^{a} **[179.01, 237.27]**
SD (mg/dl)	MPC-IP-U	**28.72 [22.37, 36.02]**	**14.73 [11.81, 21.22]**	**30.39 (± 11.03)**
	MPC-SC-U	**46.19**^{a} **[33.38, 54.40]**	**24.84**^{a} **[19.52, 32.61]**	**40.97**^{a} **(± 14.93)**
CV (mg/dl)	MPC-IP-U	**0.20 (± 0.06)**	**0.11 [0.09, 0.17]**	**0.18 [0.15, 0.22]**
	MPC-SC-U	**0.25**^{a} **(± 0.09)**	**0.17**^{a} **[0.13, 0.21]**	**0.19**^{c} **[0.15, 0.23]**
T_r (%)	MPC-IP-U	**87.22 [72.37, 94.56]**	**99.28 [90.46, 100.00]**	**79.88 [52.38, 91.39]**
	MPC-SC-U	**59.52**^{a} **[38.56, 72.10]**	**80.96**^{a} **[62.97, 97.68]**	**31.48**^{a} **[13.42, 47.74]**
T_{tr} (%)	MPC-IP-U	**56.67 [26.13, 69.21]**	**73.77 [41.72, 89.18]**	**28.76 [9.34, 52.90]**
	MPC-SC-U	**25.88**^{a} **[2.65, 52.48]**	**30.88**^{a} **[3.57, 79.66]**	**10.69**^{a} **[1.22, 21.35]**
T_a (%)	MPC-IP-U	**9.15 [3.31, 26.06]**	**0.00 [0.00, 1.13]**	**17.93 [6.55, 47.62]**
	MPC-SC-U	**39.88**^{a} **[26.07, 61.44]**	**12.28**^{a} **[0.99, 36.30]**	**68.52**^{a} **[51.96, 86.58]**
T_b (%)	MPC-IP-U	0.00 [0.00, 1.26]	0.00 [0.00, 0.76]	**0.00 [0.00, 0.66]**
	MPC-SC-U	0.00 [0.00, 0.99]	0.00 [0.00, 0.00]	**0.00**^{a} **[0.00, 0.00]**
LBGI	MPC-IP-U	**0.03 [0.00, 0.39]**	**0.03 [0.00, 0.32]**	**0.01 [0.00, 0.24]**
	MPC-SC-U	**0.00**^{c} **[0.00, 0.40]**	**0.00**^{b} **[0.00, 0.43]**	**0.00**^{a} **[0.00, 0.04]**
HBGI	MPC-IP-U	**2.57 [1.45, 5.37]**	**0.97 [0.50, 2.31]**	**4.28 [2.47, 8.88]**
	MPC-SC-U	**7.10**^{a} **[4.81, 14.32]**	**3.29**^{a} **[0.80, 8.15]**	**11.63**^{a} **[8.84, 20.28]**

TABLE II

PERFORMANCE METRICS OF MPC-IP-U VERSUS MPC-SC-U ON THE 2-WEEK SCENARIO. ^{a} P-VALUE < 0.001, ^{b} P-VALUE < 0.01, ^{c} P-VALUE < 0.05. STATISTICALLY SIGNIFICANT RESULTS ARE HIGHLIGHTED IN BOLD.CHR

D=DAY; N=NIGHT; PP=POSTPRANDIAL; A=AVERAGE BG; SD=STANDARD DEVIATION BG; CV=COEFFICIENT OF VARIATION BG; T_r=TIME IN RANGE; T_{tr}=TIME IN TIGHT RANGE; T_a=TIME ABOVE RANGE; T_b=TIME BELOW RANGE; LBGI=LOW BLOOD GLUCOSE INDEX; HBGI=HIGH BLOOD GLUCOSE INDEX. FOR A COMPLETE DESCRIPTION SEE SECTION III-D.

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