The application of Model Predictive Control to normalize glycemia of critically ill patients.

Tom Van Herpe, Niels Haverbeke, Bert Pluymers, Greet Van den Berghe, and Bart De Moor

Abstract— In this paper we propose a Model based Predictive Controller (MPC) to be used for glycemia control in critically ill patients. A model, that is particularly developed for describing the glucose and the insulin dynamics of these patients, is estimated for each individual patient and re-estimated as new measurements are obtained. Both a quantitative and a qualitative analysis are performed with respect to a real-life dataset from 19 critically ill patients. In the first analysis the robustness of the MPC is tested assuming a once per hour or a once per four hours insulin adaptation frequency is imposed. The second analysis is characterized by a comparison between the MPC insulin infusion sequence and the insulin flows (determined by the nurse) that were effectively administered to the patient. The contribution of this paper is the development of an MPC for glycemia control in the Intensive Care Unit (ICU). The penalty index, which is a specific concept for quantitative analysis of glycemia control in the ICU, is also proposed. The results of the developed MPC are satisfactory both in terms of control behavior (reference tracking and the suppression of unknown disturbance factors) and clinical acceptability.

Keywords: Control applications, Predictive control, Physical models, Parameter estimation, Kalman filters.

I. INTRODUCTION

Hyperglycemia (i.e., an increased glucose concentration in the blood) and insulin resistance (i.e., the resistance of the glucose utilizing tissues to insulin) are common in critically ill patients (even if they have not had diabetes before) and are associated with adverse outcomes. Tight glycemic control (between 80 and 110 mg/dl = target range) by applying intensive insulin therapy in patients admitted to the medical and the surgical intensive care unit (ICU) results in a spectacular reduction in mortality and morbidity [15], [18].

Currently, ICU patients are treated through a manual and rigorous administration of insulin [17]. In the available literature several physical models that describe the glucose dynamics and the insulin kinetics of healthy and diabetic subjects are used for glycemia control simulations in 'mathematical' diabetic (type I) patients (e.g., Hovorka et al. [8], Parker et al. [11], [12], among others). Analogously,

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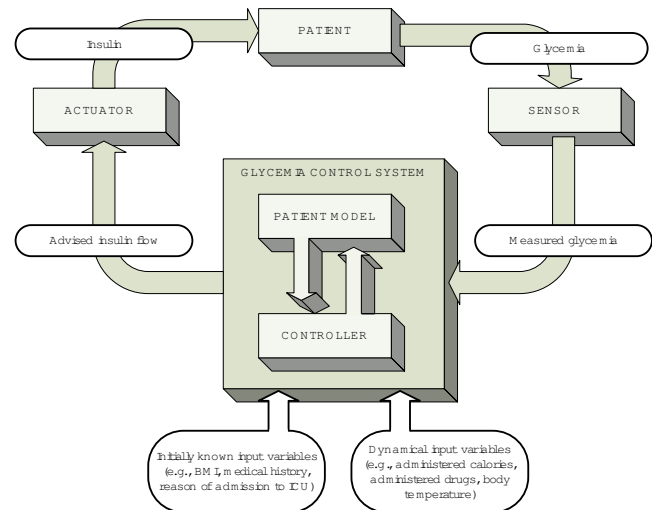
Fig. 1. Presentation of the (semi-)automated control system. The glycemia signal and other (initially known and/or dynamical) input variables (i.e., the disturbance factors) are denoted as inputs to the control system. At each time step (e.g., every hour), this system determines the insulin rate to be intravenously administered in order to normalize glycemia. After confirmation of a nurse, this advised insulin flow is delivered to the patient by means of a pump (actuator). This figure is taken from [19].

we want to design a semi-automatated control system for glycemia control in the ICU. This (future) system is illustrated in Figure 1. It may reduce the workload for medical staff and may also introduce the glycemia normalization concept in hospitals that are currently *not* making use of the manual intensive insulin protocol [17], world-wide leading to a potential further reduction of mortality and morbidity [19].

In this paper we present a model based predictive controller (MPC) that can be used to normalize glycemia in critically ill patients. Since patients who are admitted to the ICU significantly differ from diabetic patients with regards to clinical behavior [19] a model specifically developed for describing the glucose and the insulin dynamics of ICU patients is estimated and re-estimated as new measurements are obtained. An evaluation strategy typical of glycemia control in the ICU is presented. The paper is structured as follows. The ICU dataset, the model, the design of the MPC, and the evaluation strategy are described in Section 2 followed by a discussion about the simulation results and the comparison between MPC and the nurse-driven control behavior in Section 3.

II. MATERIALS AND METHODS

In this section the clinical ICU dataset that is used for the design and evaluation of the control system is described. Next, the considered model structure is introduced, followed by a description of the control strategy under study and the evaluation procedure.

A. ICU Dataset

In our setting, the Glucoday system (A. Menarini Diagnostics, Florence, Italy), a portable instrument provided with a micro-pump and a biosensor, coupled to a microdialysis system, was used to measure the glucose concentration. After informed consent from the next of kin, we implanted a microfibre in 19 ventilated adult patients who were admitted to the surgical ICU of the University Hospital K.U. Leuven (Belgium) for a variety of reasons (see Table I). After implantation of the fibre in the peri-umbilical subcutaneous tissue, we recorded near-continuous subcutaneous glucose levels during 48 hours. Every 3 minutes the mean value of the last 3 minutes was exported. During the first 24 hours, arterial blood glucose was measured concomitantly every hour using the ABL machine (Radiometer, Copenhagen, Denmark); during the next 24 hours, arterial blood glucose was measured every 4 hours. A 2-point retrospective calibration was executed at 12 and 20 hours. The administered flows of carbohydrate calories and insulin were also stored. There must be stressed that this near-continuous glucose sensor device was only used for this study. In current ICU practice, the used protocol [17] requires blood glucose levels to be measured every four hours (or more frequently, especially in the initial phase or after complications). However, the use of near-continuous glucose sensor devices will undoubtedly be *standard* in the future [3]. In this paper the observed near-continuous glucose test data are only used for estimating the model (see II-B) and for comparing the proposed MPC insulin infusion scheme with the control behavior of the nurse (see II-C.2).

B. ICU Minimal Model (ICU-MM)

The presented model structure originates from the known *minimal* model that is developed by Bergman et al. [1]. In [20] the original minimal model was extended to the ICU minimal model (ICU-MM) by taking into consideration some features typical of ICU patients. The new model was also validated on a real-life clinical ICU dataset. The ICU-MM is presented as follows:

$$\frac{dG(t)}{dt} = (P_1 - X(t))G(t) - P_1 G_b + \frac{F_G}{V_G}, \tag{1a}$$

$$\frac{dX(t)}{dt} = P_2 X(t) + P_3 (I_1(t) - I_b), \tag{1b}$$

$$\frac{dI_1(t)}{dt} = \alpha \ \max(0, I_2) - n(I_1(t) - I_b) + \frac{F_I}{V_I}, \tag{1c}$$

$$\frac{dI_2(t)}{dt} = \beta \ \gamma \ (G(t) - h) - n I_2(t), \tag{1d}$$

TABLE I

PATIENT POPULATION.

Variable	Value
Male sex - no (%)	13 (68.4)
Age - yr $(std - dev)$	61.7 (13.8)
Body-mass index - kg/m^2 $(std - dev)$	26.9 (4.7)
Reason for intensive care - no (%)	
Cardiac surgery	8 (42.1)
Noncardiac indication	11 (57.9)
Neurologic disease, cerebral trauma, or brain surgery	3 (15.8)
Abdominal surgery or peritonitis	3 (15.8)
Vascular surgery	2 (10.5)
Thoracic surgery, respiratory insufficiency, or both	2 (10.5)
Other	1 (5.3)
APACHE II score [1] (first 24 hr) $(std - dev)$	17.5 (5.6)
Mean glycemia - mg/dl $(std - dev)$	111 (26)
Minimal glycemia - mg/dl	50
Maximal glycemia - mg/dl	223

[1] The APACHE II score (Acute Physiology and Chronic Health Evaluation) is a score that determines the severity of illness.

where G and I_1 are the glucose and the insulin concentration in the blood plasma. The second insulin variable, I_2, is a purely mathematical manipulation such that I_2 does not have any direct clinical interpretation. The variable $X(t)$ describes the effect of insulin on net glucose disappearance and is proportional to insulin in the remote compartment. G_b and I_b are the basal value of plasma glucose and plasma insulin, respectively. The model consists of two input variables: the intravenously administered (exogenous) insulin flow (F_I) and the parenteral carbohydrate calories flow (F_G). The glucose distribution space and the insulin distribution volume are denoted as V_G and V_I, respectively.

The coefficient P_1 represents the glucose effectiveness (i.e., the fractional clearance of glucose) when insulin remains at the basal level; P_2 and P_3 are the fractional rates of net remote insulin disappearance and insulin dependent increase, respectively. The endogenous insulin is represented as the insulin flow that is released in proportion (by γ) to the degree by which glycemia exceeds a glucose threshold level h. The time constant for insulin disappearance is denoted as n. In case glycemia does not surpass the glucose threshold level h, the first part of 1c (that represents the endogenous insulin production) equals 0. In order to keep the correct units, an additional model coefficient, $\beta = 1$ min, was added. Finally, the coefficient α amplifies the mathematical second insulin variable I_2.

Due to the large inter and intra patient variability that exists in the ICU (e.g., patient specific initial and dynamical known input variables, reaction on medical treatment, time-varying insulin resistance, etc.), an individual and adaptive model strategy is selected [19] leading to the following modeling procedure.

First of all, the ICU-MM is used as a general template, which is estimated for each individual patient (based on the data belonging to the first 24 hours of each patient's dataset and leading to the 'initial' model for that patient) such that the model parameters P_1, P_2, P_3, n, α, and γ are patient-

specific. This is done by minimizing the (squared) errors between the simulated and observed glycemia trajectories (by using non-linear least squares). The simulated glycemia is obtained directly from the integration of the ICU-MM over the corresponding time span. In this way, an optimization problem is formulated in such a way that the optimal model parameters are found to be those that give the best possible simulation for the patient during the first 24 hours [20].

Secondly, the model is re-estimated at constant time instants. These re-estimations take place every hour or every four hours depending on the simulation setting (see II-C). In the re-estimation procedure the same non-linear estimation technique is applied. The re-estimation is based on a new *estimation* set that consists of two dataset parts. The first part is the first 24 hours data that were used to estimate the initial model. The second part starts after these 24 hours and ends at the current time instant. As initial values in these estimation processes the set of coefficients characteristic of the obese and low glucose tolerance patient group that is described in [1] is used. This patient group is mostly comparable to ICU patients with regards to insulin resistance. The units of all used variables and parameters and their initial coefficient values are represented in Table II.

TABLE II

VARIABLES, PATIENT FEATURES, AND COEFFICIENT VALUES
APPLICABLE IN THE ICU MINIMAL MODEL.

Variables	Units	Variables	Units
G	mg/dl	I_2	μU/ml
X	1/min	F_I	μU/min
I_1	μU/ml	F_G	mg/min
Patient features	Units	Value	
BM	kg	Body mass (weight)	
V_G	dl	BM*1.6 [8]	
V_I	ml	BM*120 [8]	
G_b	mg/dl	Basal glycemia	
I_b	μU/ml	Basal insulin	
Coefficients	Units	Value [1]	
P_1	1/min	-1.31 10^{-2} [1]	
P_2	1/min	-1.35 10^{-2} [1]	
P_3	ml/(min$^2\mu$U)	2.90 10^{-6} [1]	
h	mg/dl	136 [1]	
n	1/min	0.13 [1]	
α	1/min	3.11	
β	min	1	
γ	$\frac{\frac{\mu\text{U}}{\text{ml}} \frac{\text{dl}}{\text{mg}}}{\text{min}^2}$	5.36 10^{-3} [1]	

[1] As initial value for the model estimation process, the mean model coefficient values for the obese - low glucose tolerance patient group (described in [1]), are used.

C. Model based Predictive Controller (MPC)

The use of Model based Predictive Control to normalize glycemia in the ICU gives the advantage to consider the effect of current and future control moves (i.e., the insulin rates) on the future outputs (i.e, glycemia). It consists of solving a fixed-size optimal control problem at each time instant after which only the first control move (i.e., the insulin rate for the next time instant) of the optimal input

sequence is applied to the system (i.e., the patient). In this setting, only the delivered carbohydrate calories flow is a known disturbance input of the system. We assume this rate is known for the particular control horizon (i.e., 4 hours), which is a clinically feasible condition. As a result, this knowledge can be incorporated into the optimization problem leading to pro-active behavior.

The MPC methodology explicitly takes imposed constraints into account, which classical control algorithms [2], [6], [7] typically cannot. For medical reasons the maximum insulin infusion rate (i.e., the control input) is 50 U/hr. In addition, the administered insulin flow is obviously constrained to be positive.

The cost function that needs to be minimized in the optimization problem is described as follows:

$$
\min_{\mathbf{x},\mathbf{u}} \mathcal{J}_k(\mathbf{x},\mathbf{u}) =
$$
$$
\sum_{i=1}^{P} (x_{1,k+i} - x_{1,k+i}^{\text{ref}})^T Q (x_{1,k+i} - x_{1,k+i}^{\text{ref}}) \qquad (2)
$$
$$
+ \sum_{i=0}^{M-1} u_{k+i}^T R u_{k+i},
$$

where $\mathbf{x}$ and $\mathbf{u}$ denote vector sequences containing all states respectively inputs within the horizon. Every state vector x_k represents the four states of the ICU-MM: G, X, I_1, and I_2. The input vector u_k represents the variables F_G and F_I. The design parameters of the MPC are the weighting matrices Q and R, the control horizon M, and the prediction horizon P. The cost function comprises a trade-off between inputs and deviations from the desired glycemia level. The discrete time model used in the MPC is obtained implicitly via integration of its continuous time counterpart over piecewise constant inputs with a sampling time of $T_s = 1$ min. For reasons of computational complexity time steps of 10 minutes are considered in the optimization problem. The integrating method is a standard Matlab$^{\circledR}$ ODE (Ordinary Differential Equation) solver.

Numerically the optimization problem is solved in an SQP fashion (Sequential Quadratic Program) by means of local linearizations of the ICU-MM [10]. The gradients and the Hessians are computed by applying the forward Euler discretisation method. However, in the simulations the nonlinear format of the ICU-MM (as presented in II-B) is used. The initial value for insulin in each optimization problem is defined as the rate that is administered in the last time instant before the new optimization. A safety procedure is introduced to restrict hypoglycemic events by halving this initial value if a threshold glycemia value of 85 mg/dl is reached.

The assessment of the developed control system consists of a quantitative and a qualitative analysis:

1) Assessment 1: Quantitative analysis: In this part the performance of the MPC is evaluated by considering **two sets of simulations**. In each set of simulations the prediction and

the control horizon are both equal to 4 hours whereas the insulin flow adaptation frequency depends on the considered set of simulations.

The **first** set of simulations is characterized by an adaptation frequency of once per hour. This is further called the 'one-hour-period' simulations meaning that the most optimal insulin flow for the next 4 hours (i.e., the control horizon) is determined every hour, but that only the first insulin rate (that corresponds to the flow of the next hour) is effectively imposed to the ICU-MM. A new optimization problem is defined at the next time instant (i.e., one hour later) leading to an updated insulin infusion scheme for the following 4 hours. Again, only the first insulin flow is delivered to the ICU-MM.

In the **second** set of simulations the insulin infusion rate can only be adapted every 4 hours leading to solving the optimization problem only every 4 hours. This set of simulations is further defined as 'four-hours-period' simulations. The ICU-MM used in the simulations is updated every hour to incorporate the changing physical conditions of the patient.

The patient specific series of model coefficients that were gathered in the estimation process (see II-B) are considered in the simulations. The MPC simulations start after the first 24 hours (which were used to estimate the initial set of coefficients) and go on until the end of each patient's dataset (with a maximum simulation run of 24 hours). Some additional and non-modeled disturbance factors are added in this set of simulations in order to test the robustness of the developed MPC:

1) *Measurement error*: The *in-vitro* error, which is associated with glucose sampling, varies around 4% depending on the measurement device [13]. However, this percentage is lifted to 15% (gaussian noise) as a worst-case scenario for the *in-vivo* measurement error [21].

2) *Medication*: The administration of medication F_M (e.g., glucocorticoids) can disturb blood glucose levels. Although this disturbance factor is not included in the ICU-MM, it is also introduced as an additional disturbance factor in the simulations. After a first simulation period of 6 hours a (fictitious) continuous drug flow (leading to a glycemia increase of 2 mg/dl/min) is administered to the patient for 5 hours, followed by a continuous drug flow (that results in a glycemia increase of 1 mg/dl/min) for another 5 hours.

MPC is a practical method for the real-time application of optimal control theory that introduces the notion of feedback by using incoming measurements (i.e., the simulated glucose course in which 15% gaussian noise is added). In the MPC framework it is assumed that full state information is available. In our case only noisy measurements of glycemia are available and states need to be estimated. A nonlinear state estimator - in casu an extended Kalman filter - is employed for this purpose [9]. The tuning of the state

estimator is based on the auto-covariance of the addidative measurement noise. As discussed, to make the case more realistic an unknown input disturbance $\hat{d}_k$ is added to the ICU-MM. This disturbance could represent plant-model mismatch or could originate from administered medication. To account for these disturbances the extended Kalman filter equations are augmented. In the MPC it is assumed that the disturbances are constant over the future window: $\hat{d}_{k+i} = \hat{d}_k, i = 0 \ldots M - 1$. This approach proved to be effective for dealing with slowly varying input disturbances as encountered in this manuscript.

2) Assessment 2: Qualitative analysis: In this second assessment the performance of the MPC is compared with the nurse performance assuming the ICU-MM (that is estimated for each patient individually and re-estimated every hour to capture the patient's changing conditions) fully represents the particular patient (i.e., without any to the model unknown disturbance factors).

Since we do not know the exact glycemia evolution if a certain insulin infusion rate, other than the rate determined by the nurse, would have been administered to the patient, this analysis is purely qualitative. The near-continuous glucose values, that were measured by the Glucoday system, are submitted to the MPC and the optimization problem is defined every hour by using the one-hour model re-estimation sets. The adaptation frequency of the insulin rate is also once per hour and the prediction horizon equals 4 hours. The flow of carbohydrate calories that was effectively administered to the patient serves as (known) disturbance input variable of the system.

D. New evaluation procedure designed for the ICU quantitative analysis: Penalty index (PI)

In literature some assessment strategies for closed-loop glucose control in (virtual) type 1 diabetic patients have already been proposed [4], [5]. However, glycemia control in the ICU and in diabetic patients differ significantly. Typical of the glycemia normalization process in the ICU is the higher frequency of (arterial) glucose measurements (e.g., at 1-4 hour intervals [17] whereas only up to 4 measurements per day are supported for the treatment of type 1 diabetes). As a consequence, possible hypoglycemic events can be better controlled than with diabetic patients who are treated with insulin, leading to a lower hypoglycemic alarm level (40 mg/dl) in the ICU than with diabetic patients [14]. The direct relation between hyperglycemia and a higher mortality and morbidity rate is another feature typical of the ICU [15], [18]. As a result, it is stringently required to avoid hyperglycemic events. Therefore, the hyperglycemic alarm level is set to 200 mg/dl. Since (carbohydrate) calories are continuously administered to patients admitted to the ICU (i.e., the so-called 'parenteral' feeding process, present in particularly the first phase of their stay at the ICU) there is no need to distinct a grading system for *outside-meal* and *postprandial*

conditions as may be useful in the assessment of glycemia control in diabetic patients [5].

Table III gives an overview of the glycemic threshold values that are characteristic of the ICU. Each glycemic range is associated with a penalty. The glycemic target range in the ICU is defined as 80-110 mg/dl (with a penalty value equal to 0). Hypoglycemic and hyperglycemic events are amplified in relation to the magnitude of their deviation from the target range. The penalty index (PI) of the designed controller is calculated, for each patient, as follows:

$$PI = \frac{\sum_{i=1}^{t} PI_i}{t},\qquad(3)$$

where PI_i denotes the penalty index that corresponds to the glycemic range to which the simulated or clinically measured glycemia value at time instant i belongs (see Table III). The total simulation time or clinical validation time (for the considered patient) is represented by t. It must be stressed that PI can only be calculated per patient and not per *patient group* unless the simulation or clinical validation time for all patients is constant. Usually, the glycemia behavior is unstable particularly during the first days after admission to the ICU and gradually evolves to a more stable glucose course the longer a patient stays at the ICU. As a result, the calculated PI of a patient who stays at the ICU for a longer time (with a typically larger amount of normoglycemic values, consequently) is artificially lowered in comparison with a patient who stays for only a short time (characterized by the unstable glycemia behavior during these first days at the ICU). Therefore, PI should always be considered per patient and as a function of the length of stay at the ICU. An appropriate comparison between PIs also requires an equal glycemia sampling frequency (once per minute in these simulations) for each patient.

TABLE III

THRESHOLD VALUES AND PENALTY VALUES FOR THE EVALUATION OF GLYCEMIA CONTROL IN THE ICU.

Range No	Glycemic range (mg/dl)	Clinical description	Penalty	Reference
(1)	$40 > G$	Hypoglycemic alarm	3	[14]
(2)	$60 > G \geq 40$	Hypoglycemia	2	[14]
(3)	$80 > G \geq 60$	Slight hypoglycemia	1	[14]
(4)	$110 \geq G \geq 80$	Normoglycemia	0	[15], [18]
(5)	$150 \geq G > 110$	Slight hyperglycemia	1	[16]
(6)	$200 \geq G > 150$	Hyperglycemia	2	[16]
(7)	$G > 200$	Hyperglycemic alarm	3	[18]

III. RESULTS AND DISCUSSION

In this section the performance of the MPC is firstly discussed for both the 'one-hour-period' and the 'four-hours-period' simulations. In the next phase the performance of the MPC is compared with the control behavior from a qualitative point of view.

A. Assessment 1: Quantitative analysis

Figure 2 visualizes every patient specific PI as a function of the simulation time. Although some large disturbance

factors, which are unknown to the MPC, are included in the simulations the simulated glycemia values (to which a worst-case measurement error is included) are mostly situated between the normoglycemic borders (80-110 mg/dl) and the glycemic ranges close to them. Indeed, all the computed PIs (for both the 'one-hour-period' and the 'four-hours-period' simulations) are between 0 and 1 indicating that only a limited amount of time the normoglycemic borders are passed. In Table IV the relative number of times per glycemic range are presented. The relative time that is spent in the normoglycemic range (i.e., range no. 4) reaches 60% (when all patients are considered) in spite of the imposed disturbance factors and the short simulation period, which was restricted to 24 hours due to the characteristics of the available dataset.
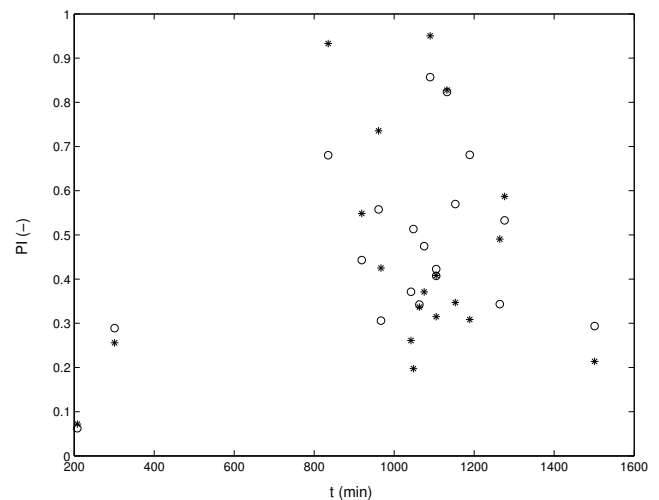

Fig. 2. The patient specific PI as a function of the simulation time (which is related to the length of stay at the ICU) for the one-hour-period and the four-hours-period simulations, that are represented by stars and circles, respectively. Each patient is denoted as a couple that consists of a star and a circle that lie on the same vertical line (corresponding to that patient's length of stay).

TABLE IV

RELATIVE NUMBER OF TIMES PER GLYCEMIC RANGE FOR THE 'ONE-HOUR-PERIOD' AND THE 'FOUR-HOURS-PERIOD' SIMULATIONS WHEN ALL PATIENTS ARE CONSIDERED.

Range No	Glycemic range (mg/dl)	One-hour-period (%)	Four-hours-period (%)
(1)	$40 > G$	0.1	0.2
(2)	$60 > G \geq 40$	0.7	2.2
(3)	$80 > G \geq 60$	9.7	15.9
(4)	$110 \geq G \geq 80$	58.6	55.8
(5)	$150 \geq G > 110$	26.6	23.2
(6)	$200 \geq G > 150$	4.2	2.6
(7)	$G > 200$	0.1	0.1

For the majority of the patients, the MPC with a once-per-hour insulin adaptation frequency outperforms the MPC in which the insulin infusion rate can be modified only once every four hours. This is also envisioned in Figure 2. The patient specific PIs obtained with the one-hour-period simulations are smaller than those that are generated with

the corresponding four-hours-period simulations for 60% of the patients. In Figure 3 the simulated glucose course of patient no. 11 that is generated with the one-hour-period and four-hours-period simulations and the delivered known and unknown input flows are illustrated.

Although the MPC is able to suppress the unknown medication disturbance factor in both approaches, the insulin flow is increased faster (at $t = 420$ min) when a once-per-hour insulin adaptation frequency is applied so that glycemia relatively fast re-enters the normoglycemic range in spite of the existing unknown disturbance factor. This prove of robustness is an important feature of the controller for possible use in a real-life ICU setting. It indicates its skill to take into consideration unknown disturbance factors that are abundantly present in the ICU by exploiting the extended Kalman filter.

Due to the ability to frequently adapt the insulin infusion rate with the one-hour-period MPC, glycemia values evolving to the hypoglycemic range can be better avoided. This is visualized in Figure 3 when the unknown medication disturbance factor is halved (at $t = 660$ min) and dropped (at $t = 960$ min). The simulated glycemia - in case of an adaptation frequency of once per hour - stays only for a limited amount of time in the slight hypoglycemic range. The observed (simulated) glycemic values, the future known disturbance factor (i.e., the administered carbohydrate calories) and the use of the extended Kalman filter (to estimate unknown disturbances) provide the appropriate information to the MPC for optimizing the insulin infusion sequence. The performance differences between the one- and four-hour(s)-period MPC are further mentioned in Table IV.

It is important to note that the (to the MPC unknown) disturbance factor is introduced at $t = 360$ min whereas the one-hour-period MPC and the four-hours-period MPC are only able to change the insulin rate after observing the disturbed glucose course (i.e., at $t = 420$ min and $t = 480$ min, respectively). If, however, the unknown disturbance factor would have been introduced earlier (e..g., $t = 240$ min), then the one-hour-period MPC would have changed the insulin flow again one hour later ($t = 300$ min), but the four-hour-period MPC would still have to keep the current insulin flow constant till $t = 480$ min since the insulin flow adaptation frequency is limited to once per four hours. This indicates that the controller performance difference between the one- and four-hours-period MPC would increase and explains the relatively small performance differences between the two approaches in the simulation setting that is presented in this manuscript (see Table IV).

In general, we can conclude that the performance of a controller will increase if the insulin infusion adaptation frequency is higher. Possible disturbed glucose courses can be captured more quickly so that, by properly modifying the insulin infusion rate, the reference glycemic value can be tracked. Still, it must be stressed that the PIs, that are obtained with the one-hour-period MPC simulations, from 7 patients are unexpectedly higher than the corresponding PIs obtained with the four-hours-prediction MPC. Five of

those patients belong to the cardiac surgery group. The latter patient group is typically characterized with shorter time periods at the ICU than patient groups with other pathologies. Future research is needed for differentiating the controller and/or the model parameters with respect to the reason for admission to the ICU (or other clinical features).
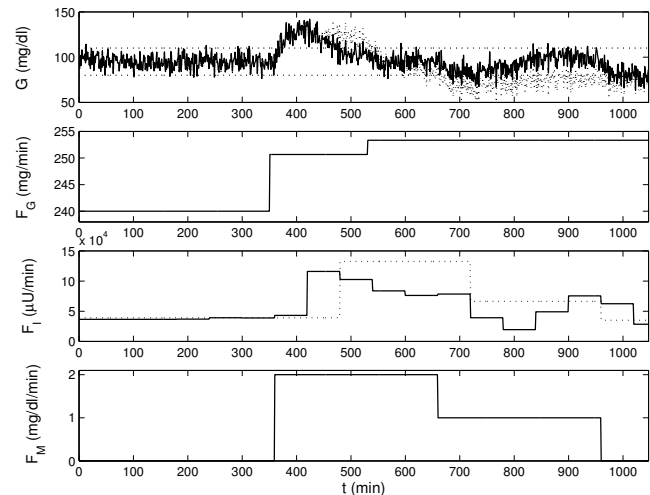

Fig. 3. The evolution of the simulated glycemia G (top panel) for the one-hour-period (solid line) and the four-hours-period (dotted line) simulations of patient no. 11. The flow of the carbohydrate calories F_G (second panel) is the known disturbance factor whereas the insulin rate F_I (third panel) is the insulin sequence that is proposed by the one-hour-period MPC (solid line) and the four-hours-period MPC (dotted line). A fictitious medication disturbance factor F_M (that is unknown to the MPC) is visualized in the bottom panel.

B. Assessment 2: Qualitative analysis

Figure 4 represents the real-life glucose course, measured with the Glucoday system (A. Menarini Diagnostics), of patient no. 4. These real glycemia values are delivered to the MPC in order to introduce the notion of feedback. However, we want to stress the infeasibility to quantitatively compare the insulin infusion rates proposed by the MPC with the flows that were delivered to the patient in real-life. Indeed, the evolution of the real glycemia when an insulin rate (determined by the MPC) other than the nurse-driven insulin flow would have been administrated cannot be known. Therefore, these second simulations are restricted to a qualitative analysis. It must also be noted that the nurses made use of the blood glucose values that were measured with the ABL machine (for determining the insulin flows) and *not* the Glucoday system since it was required to *retrospectively* calibrate the near-continuous glucose data (which were used for this paper) that were gathered from the latter.

The first three hours the MPC proposes to infuse a larger insulin rate than was administered in real-life. The increasing rate that is presented during these first hours is explained by the slight hyperglycemic event (top panel) and the fact that this insulin rise *seems* to be not enough to bring glycemia back to the reference signal (95 mg/dl). It can however

be assumed that glycemia would have been evolved to the reference signal if the initial higher insulin flow would have been delivered to the patient instead of the nurse-driven insulin flow.

The decrease in administered carbohydrate calories at time $t = 240$ min is known by the MPC in advance such that the proposed insulin flow is decreased as well. In reality, however, the nurse did not take into account this decreased calories flow. Because of the slight hyperglycemic event in the initial phase and the decreased food rate (while maintaining a constant insulin flow) glycemia evolved to the normoglycemic range.

At time $t = 480$ min the nurse increased the insulin flow leading to a slight hypoglycemic event two hours later. Since the cut-off glycemia value (85 mg/dl) is reached the initial insulin value is halved (in the MPC optimization problem) leading to a significant reduction of the proposed insulin flow that can be observed at time $t = 540$ min. Next, the nurse decreased the insulin rate (at time $t = 720$ min) leading to increased glycemia values. It is clearly illustrated that the MPC proposes to gradually increase the insulin flow to cover this glucose raising effect. The fluctuating glycemic values visualized in the last phase and the designed safety procedure cause the presented (fluctuating) insulin infusion sequence that corresponds to these last hours.
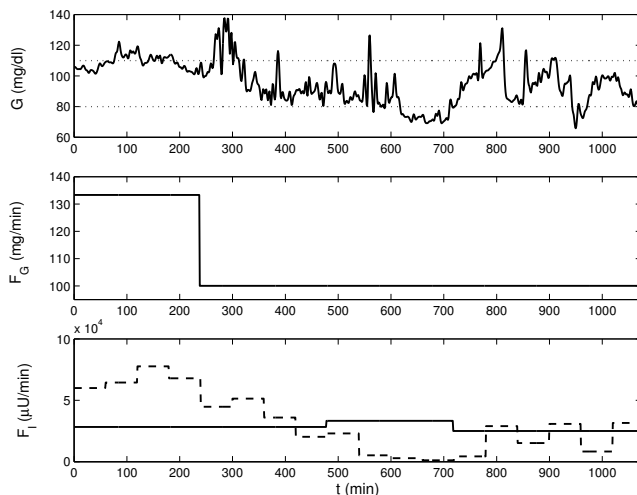

Fig. 4. The evolution of the real glycemia G (top panel), measured with the Glucoday system (A. Menarini Diagnostics), of patient no. 4 after administration of carbohydrate calories F_G (middle panel) and insulin F_I (bottom panel, solid line). The insulin infusion flow that is proposed by the MPC is presented in the bottom panel (dashed line) and can be qualitatively explained.

IV. CONCLUSIONS AND FUTURE WORKS

A. Conclusions

In this paper we present an MPC to be used for glycemia control in critically ill patients. A quantitative and a qualitative analysis approach are considered with respect to a real-life clinical ICU dataset. The computed patient specific PIs are all between 0 and 1 for both the one- and four-hour(s)-period simulations indicating that the simulated glycemic

values lie in the normoglycemic range for a large part. The robustness of both MPC approaches is improved by estimating states and unknown disturbance factors with an extended Kalman filter. In general, the MPC performance increases if the insulin infusion rate can be adapted every hour instead of every four hours. However, for the current simulation setting especially the cardiac surgery patients give the opposite result so that differentiation of the controller and/or the model parameters with respect to the reason for admission to the ICU may be necessary.

From a qualitative point of view, the developed MPC proposes clinically feasible insulin infusion sequences. When comparing the MPC insulin schemes to the nurse-driven insulin rates that were effectively administered to the patient, some hyperglycemic and hypoglycemic events (that are present in the current nurse-driven dataset) could have been avoided.

B. Future Works

Future work is conducted to the implementation of a moving horizon estimator (MHE) for the estimation of parameters, states and unknown input disturbances. This would allow to explicitly use the nonlinear dynamics of the model and to include constraints on states and disturbances thus leading to a further increase in performance of the closed-loop control scheme. Further research is also required to relate clinical features (e.g., the reason for admission to the ICU) to the controller and/or model parameters. Finally, the currently developed control system will soon be tested and validated in a real-life ICU setting on new patients.

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