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ADAPTIVE MODELING FOR CONTROL OF GLYCEMIA IN CRITICALLY ILL PATIENTS

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Abstract: In this paper we propose an optimized adaptive 'minimal' modeling approach for *predicting* glycemia of critically ill patients and a corresponding Model based Predictive Control (MPC) setting for *controlling* glycemia. Re-estimations of the model, based on a real-life dataset from 19 critically ill patients, are performed every hour or every four hours by only considering recently passed data. The contributions of this study are the determination of the best dataset size for the re-estimations and the proposed MPC design. The results are satisfactory both in terms of forecasting ability and in qualitative controller performance.

Keywords: Physical models, Parameter estimation, Model based Predictive Control, Control applications.

1. 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 (Van den Berghe *et al.*, 2006; Van den Berghe *et al.*, 2001).

Currently, ICU patients are treated through a manual and rigorous administration of insulin (Van den Berghe *et al.*, 2003). 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.*, 2004; Parker *et al.*, 1999), among others). Analogously, we want to design a semi-automated control system for glycemia control in the ICU. This system could reduce the workload for medical staff and could also introduce the glycemia normalization concept in hospitals that are currently *not* making use of the manual intensive insulin protocol (Van den Berghe *et al.*, 2003), world-wide leading to a possible further reduction of mortality and morbidity (Van Herpe *et al.*, 2006*b*).

In this study we present an adaptive 'minimal' modeling approach in a Model based Predictive Control (MPC) setting for normalizing glycemia in the ICU. Since patients who are admitted to the ICU significantly differ from diabetic patients with regards to clinical behavior (Van Herpe *et al.*, 2006*b*) a model specifically developed for de-

scribing the glucose and the insulin dynamics of ICU patients is estimated and re-estimated as new measurements are obtained. The design of the study is described in Section 2 followed by a discussion of the results in Section 3.

2. MATERIALS AND METHODS

In this section the clinical ICU dataset is described. Next, the considered model structure is introduced, followed by a description of the re-estimation strategy under study and the MPC approach.

2.1 ICU Dataset

We used the Glucoday system (A. Menarini Diagnostics, Italy), which is a portable instrument provided with a micro-pump and a biosensor coupled to a microdialysis system, 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 1). 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. It must be stressed that this near-continuous glucose sensor device was only used for this study. In current ICU practice, the used protocol (Van den Berghe *et al.*, 2003) 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 (Chase *et al.*, 2006). In this paper the observed near-continuous glucose test data are only used for (re-) estimating the model (see 3.1) and for comparing the proposed MPC insulin infusion scheme with the control behavior of the nurse (see 3.2).

Table 1. 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.

2.2 ICU Minimal Model (ICU-MM)

The presented model structure originates from the known *minimal* model that was developed by Bergman et al. (Bergman *et al.*, 1981). In (Van Herpe *et al.*, 2006*a*) 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 estimated in-sample by means of a real-life clinical ICU dataset. The ICU-MM is presented as follows:

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

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

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

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

where G and I_1 are the glucose and the insulin concentration in the blood plasma. The variable X describes the effect of insulin on net glucose disappearance and is proportional to insulin in the remote compartment. The variable I_2 has no direct clinical interpretation but is required for mathematical reasons. G_b and I_b are the basal value of plasma glucose and plasma insulin, respectively. The model consists of two input variables: the exogenous insulin flow (F_I) and the carbohydrate calories flow (F_G), both intravenously administered to the patient. 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, is added. Finally, the coefficient α amplifies the mathematical second insulin variable I_2.

2.3 Adaptive modeling approach

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.), it is required to re-estimate the ICU-MM at frequent time intervals to capture these dynamic features as much as possible (Van Herpe *et al.*, 2006*b*). The **first** contribution of the current study is the performance improvement of this re-estimation process. In general, the adaptive modeling approach can be described as follows:

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, Matlab®-function 'fminsearch'). 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 (i.e., 1440 minutes) (Van Herpe *et al.*, 2006*a*). To solve this problem the starting parameters are taken from the obese - low glucose tolerance patient group coming from (Bergman *et al.*, 1981) (see Table 2) whose patient characteristics are comparable to ICU patients.

Secondly, the model is re-estimated at certain time periods P for the rest of each patient's dataset. Two different settings are proposed: re-estimations every hour and every four hours. The number of recent data that are considered in each re-estimation process is called the Back-In-Time (BIT) number and may influence the performance of the model. Therefore, BIT is varied in each setting. In the re-estimation procedure the same non-linear estimation technique as described above is applied. The starting parameters in each optimization process are the end values of the previous period P. The model performance for each patient p is measured by computing the Mean Squared Error, $\text{MSE}_p = \frac{\sum_{t=1441}^{N}(G_{t,p}-\hat{G}_{t,p})^2}{N}$, and the Mean Percentage Error, $\text{MPE}_p = \frac{\sum_{t=1441}^{N}\frac{|G_{t,p}-\hat{G}_{t,p}|}{G_{t,p}}}{N}100\%$, where $G_{t,p}$ and $\hat{G}_{t,p}$ are the actual and simulated glycemia value for patient p. The size of each dataset is denoted as N.

The overall methodology for optimizing the re-estimation process is explained below:

(1) Estimate the 'initial' model (ICU-MM) based on the first dataset (first 24 hours, see above),
(2) For a re-estimation period $P = 1$ hour and $P = 4$ hours,
  (a) For $BIT = 20, 18, 16, 14, 12, 10, 8, 6, 5, 4, 3, 2, 1,$ and 0.5 hours,
    (i) Re-estimate the ICU-MM based on every last section (i.e., BIT) of the (moving) dataset with starting set of coefficients the values corresponding to the last period P (or the set of coefficients from the 'initial' model for the first re-estimation),
    (ii) Predict the glycemic course for the next period P (which is the validation set of the re-estimated model in this case),
    (iii) Compute the mean squared error (MSE) and mean percentage error (MPE) for all validation sets per patient,
  (b) Compare the MSEs and/or MPEs that are generated for the different BITs. The BIT that belongs to the smallest MSE and/or MPE is called 'optimal' and is ideally used in the re-estimation process,
(3) Compare the optimal BIT and the computed MSEs and MPEs for the $P = 1$ hour and $P = 4$ hours setting.

2.4 Model based Predictive Control (MPC)

The implementation of Model based Predictive Control to normalize glycemia in the ICU represents the **second** contribution of this study. MPC 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

Table 2. 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	
V_G	dl	BM*1.6	
V_I	ml	BM*120	
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	$\frac{\frac{\mu U}{ml}\frac{dl}{mg}}{min^2}$	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 (Bergman *et al.*, 1981)), are used.

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 (Doyle *et al.*, 1992) 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 optimization problem is described as follows:

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

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 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.

Numerically the optimization problem is solved in an SQP fashion (Sequential Quadratic Program) by means of local linearizations of the ICU-MM. However, in the simulations the nonlinear format of the ICU-MM (as presented in 2.2) 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 MPC control behavior 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 when 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 with the optimal BIT (see 2.3). 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.

3. RESULTS AND DISCUSSION

In this section the performance of the adaptive 'minimal' modeling approach is firstly discussed for both the 'one-hour-period' and the 'four-hours-period' simulations. This analysis is followed by a qualitative evaluation of the MPC.

3.1 Adaptive 'minimal' modeling performance

Figures 1 and 2 give an overview of the computed MSEs and MPEs as a function of BIT and P. As expected, the predictive performance of the model is higher when the model is re-estimated every hour ($P = 1$ hour) in comparison with model re-estimations every four hours. The optimal BIT is found to be 4 because of the smallest MSEs and MPEs in that case. This indicates that it is advised to incorporate only the data of the last four hours in the re-estimation process of the ICU-MM. The average MSE (std-dev) and average MPE (std-dev) that is obtained when applying this 'optimal' re-estimation strategy ($P =$ 1 hour, $BIT = 4$ hours) to the present data are

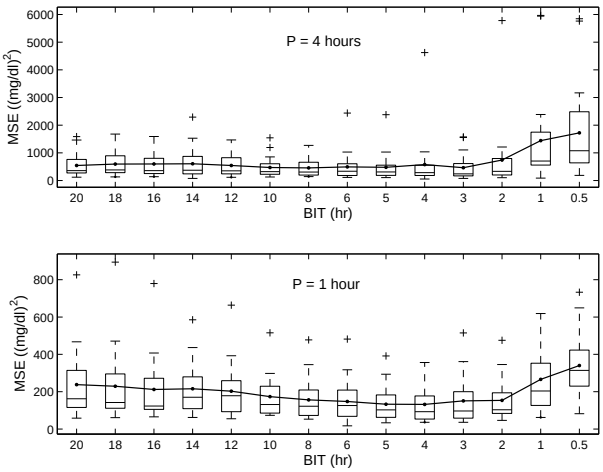

Fig. 1. Distribution of the MSEs (generated for each patient) as a function of BIT with re-estimations every four hours (top panel) or every hour (bottom panel). The line connects the averages of the MSEs. Re-estimations based on the last four hours dataset ($BIT = 4$) results in the smallest prediction errors.

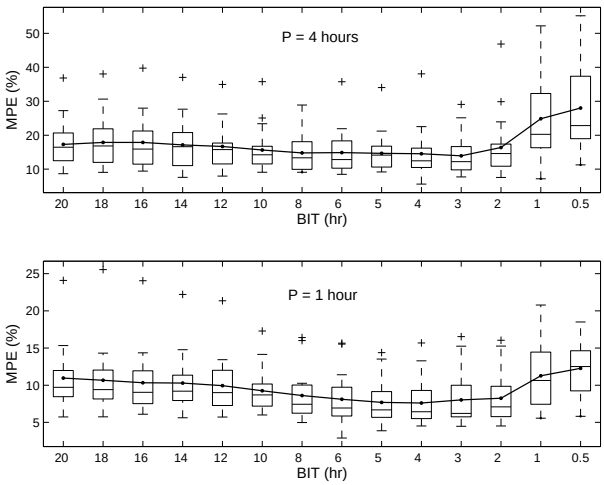

Fig. 2. Distribution of the MPEs (generated for each patient) as a function of BIT with re-estimations every four hours (top panel) or every hour (bottom panel). The line connects the averages of the MPEs. Re-estimations based on the last four hours dataset ($BIT = 4$) results again in the smallest prediction errors.

131.9 mg^2/dl^2 (99.9 mg^2/dl^2) and 7.6% (3.1%), respectively.

These clinically acceptable prediction errors indicate the potential use of the ICU-MM and its adaptive estimation strategy in the design of a predictive control system. Indeed, assuming the availability of an accurate continuous glucose sensor, the use of a model that predicts the glycemia signal of the next hour can potentially outperform the control behavior of non-predictive control systems (e.g., feedback control) and nurse-driven protocols (Van den Berghe *et al.*, 2003).

3.2 Controller performance

Figure 3 represents the real-life glucose course of patient no. 12, measured with the Glucoday system. These real glycemia values are submitted to the MPC in order to introduce the notion of feedback. However, we want to stress the fact that it is infeasible 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 signal when an insulin rate (determined by the MPC) other than the nurse-driven insulin flow would have been administrated cannot be known. Therefore, these 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 Glucoday data.

During the first three hours the MPC proposes to infuse a larger insulin rate than was administered in real-life. This proposed flow could have lead to normoglycemia instead of the hyperglycemic event that was obtained after administering the nurse-driven rate. At time $t = 240$ min the flow of carbohydrate calories is decreased to 0 mg/min for 2 hours (because of medical reasons). Since this input is known to the MPC, the proposed insulin infusion is significantly decreased as well. The safety procedure that is introduced to restrict hypoglycemic events is clearly shown in the next

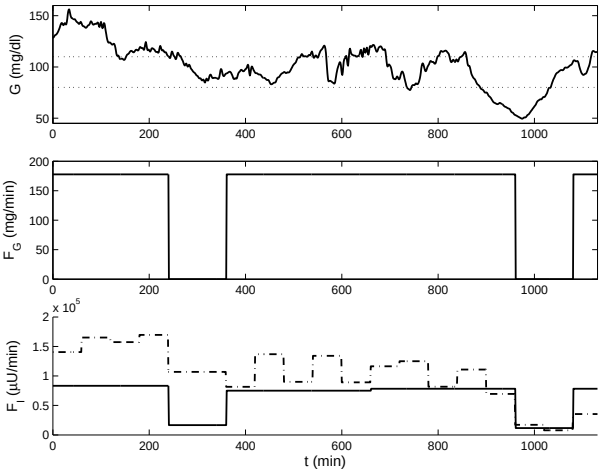

Fig. 3. The evolution of the real glycemia signal G (top panel) of patient no. 12, measured with the Glucoday system, after administration of carbohydrate calories F_G (middle panel) and insulin F_I (bottom panel, solid line). The insulin infusion flow that is proposed by the MPC is presented in the bottom panel (dashed line) and can be qualitatively explained.

phase. Each time the smoothed glycemia signal reaches the threshold glycemia value (85 mg/dl), the initial value in the optimization process is halved (e.g., at time $t = 480, 600,$ and 780 min). Since the real glycemia signal evolves to the hyperglycemic range in the time period that follows, the insulin rate is again increased each time. At time $t = 900$ and 960 min the decrease of the insulin flow is explained by the reaching of the threshold level and by the compensation for the known decrease in flow of administered carbohydrate calories.

4. CONCLUSIONS AND FUTURE WORK

In this paper we present an optimized adaptive 'minimal' modeling approach for *predicting* glycemia of critically ill patients and the design of an MPC for *controlling* glycemia. Simulations are performed with respect to a real-life clinical ICU dataset. Re-estimating the model every hour results in smaller prediction errors than re-estimations that take place every four hours. The optimal size of the dataset to be considered in each re-estimation process of the ICU-MM is found to be four hours. The use of the optimal adaptive model strategy (i.e., model re-estimations every hour based on the patient-specific data of the last four hours) in an MPC setting gives promising results. The MPC proposes clinically feasible insulin infusion sequences. Moreover, 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.

Future work is conducted to the quantitative analysis of the proposed control strategy and the implementation of a moving horizon estimator (MHE) for the estimation of 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 potentially leading to a further increase in performance of the closed-loop control scheme.

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