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An adaptive input–output modeling approach for predicting the glycemia of critically ill patients

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Abstract

In this paper we apply system identification techniques in order to build a model suitable for the prediction of glycemia levels of critically ill patients admitted to the intensive care unit. These patients typically show increased glycemia levels, and it has been shown that glycemia control by means of insulin therapy significantly reduces morbidity and mortality. Based on a real-life dataset from 15 critically ill patients, an *initial* input–output model is estimated which captures the insulin effect on glycemia under different settings. To incorporate patient-specific features, an *adaptive* modeling strategy is also proposed in which the model is re-estimated at each time step (i.e., every hour). Both one-hour-ahead predictions and four-hours-ahead simulations are executed. The optimized adaptive modeling technique outperforms the general initial model. To avoid data selection bias, 500 permutations, in which the patients are randomly selected, are considered. The results are satisfactory both in terms of forecasting ability and in the clinical interpretation of the estimated coefficients.

Keywords: intensive care unit, glycemia, medical systems and applications, system identification, autoregressive models, parameter identification

1. Introduction

In general, critically ill patients (who are typically admitted to the intensive care unit (ICU)) show hyperglycemia and insulin resistance resulting in adverse outcomes (Mizock 1995,

McCowen *et al* 2001, Capes *et al* 2000, Cely *et al* 2004). In two previous randomized, controlled studies (in a surgical and a medical ICU), strict blood glucose control (between 80 and 110 mg dl^{-1}) resulted in an important reduction in mortality and morbidity. As an example, in a surgical ICU the mortality of patients who required intensive care for more than 5 days was reduced from 20.2% to 10.6% (Van den Berghe *et al* 2001, 2003, Mesotten and Van den Berghe 2003). In a recently published article concerning the medical ICU, the in-hospital mortality of patients who stayed in the ICU for 3 or more days was reduced from 52.5% to 43.0% (Van den Berghe *et al* 2006). However, normalization of glycemia requires a rigorous administration of insulin by means of a very time-demanding empirical protocol (Van den Berghe *et al* 2003) in which expertise from nurses and doctors is necessary. The protocol requires blood glucose levels to be measured every 4 h (or more frequently, especially in the initial phase or after complications). The flow of the continuous insulin infusion is then adjusted by using a certain schedule. The effectiveness of this protocol (i.e., obtaining and maintaining normoglycemia) is hindered by the following complicating factors:

- Caloric intake (number of calories, class (proportion of carbohydrates, proteins and fat) and daily interruption of caloric intake) has a profound impact on insulin requirements.
- Switch from intravenous glucose infusion to total parenteral feeding (also given intravenously) and finally to enteral feeding can profoundly change the dynamics of the process inputs (e.g., administration of insulin) and output (i.e., glycemia).
- Administration of drugs (e.g., glucocorticoids) can disturb blood glucose levels.
- Finally, it is also known that the constitution or profile of the patient (e.g., body mass index (BMI)[3], APACHE II score[4], medical history) can influence the reaction to insulin administration.

In this paper, we develop an empirical model for predicting the blood glucose levels of critically ill patients (admitted to a *surgical* ICU). A predictive system for glycemia levels can ideally be used in the development of a (semi-)automated control system consisting of a model (to predict glycemia) and a controller (to calculate the most optimal exogenous insulin flow). Such a control system is an important factor to reduce the workload for the medical staff and to 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), worldwide. Consequently, an ICU glycemia normalization control system also has the potential to (further) reduce mortality and morbidity. The general concept of the (semi-)automated control system is summarized in figure 1.

Until recently, the glycemia normalization problem was particularly known in diabetic patients. A closed-loop control system may drastically improve the life of (type I) diabetic patients. Typically, physical compartmental model theory (Bailey and Haddad 2005) is used for this application resulting in basic models that describe the glucose and insulin kinetics of a diabetic patient (Furler *et al* 1985, Lehmann and Deutsch 1998, Parker *et al* 1999, 2000, Hovorka *et al* 2004, Ruiz-Velázquez *et al* 2004). However, until now, none of these models are used in clinical practice due to possibly unacceptable accuracy levels (Lehmann and Deutsch 1998, Parker *et al* 2001, Steil *et al* 2005). Unprecise glycemia predictions can result in inaccurate insulin flow calculations by the controller. This can possibly cause (severe) hypo- or hyperglycemia in the patient.

Other reasons that indicate the potential difficulties encountered when using (diabetes type I) models in an ICU (semi-)automated control system are the different physiological

[3] The body mass index is the weight in kilograms divided by the square of the height in meters.

[4] The APACHE (Acute Physiology and Chronic Health Evaluation) II score is a score that determines the severity of illness. Each day this score is calculated based on parameters, such as body temperature, arterial pH, breathing frequency, etc.

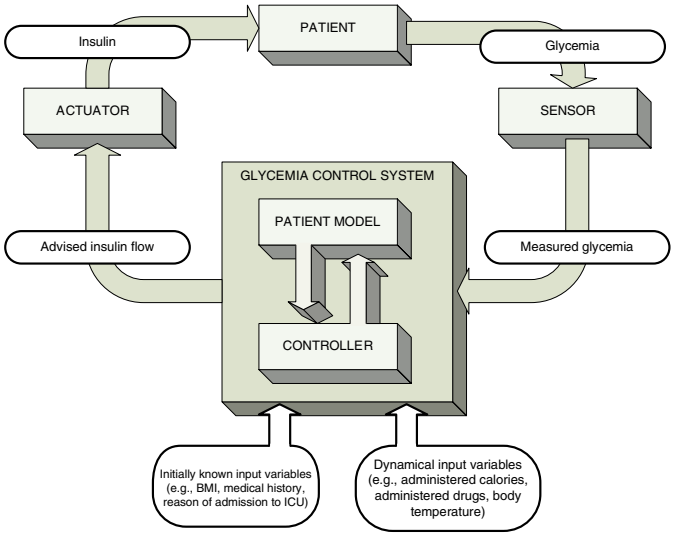

Figure 1. Presentation of the (semi-)automated control system. Undiluted arterial blood glucose (i.e., glycemia) is measured every 4 h or more frequently in the case of complications. Glycemia values and other (initially known and/or dynamical) input variables (i.e., the disturbance factors) are denoted as inputs to the control system. At each time step (e.g., every hour), the latter determines the insulin rate that is required to normalize glycemia of critically ill patients. After confirmation of a nurse, this advised insulin flow is delivered to the patient by means of a pump (actuator).

characteristics of both ICU and diabetes patient groups (e.g., particular ICU hormonal fluctuations), an increased and time-varying resistance of the glucose utilizing tissues to insulin (or 'insulin resistance') (Wolfe *et al* 1979, 1987, Shangraw *et al* 1989) that is typical of ICU patients (Van den Berghe *et al* 2001, 2006), the specific medical treatment for these patients (e.g., administration of different drugs, specific nutritional patterns), etc.

In this paper, we present an initial and adaptive black-box input–output model (instead of a physical compartmental model) based on real-life clinical ICU data. The paper is structured as follows. The data and the modeling-validation strategy are described in section 2 followed by the evaluation in section 3. A discussion of the obtained results is presented in section 4.

2. Materials and methods

2.1. Patient data

The dataset originates from 15 patients admitted to the ICU division of the University Hospital K U Leuven (Belgium) in 2005. All of them had a specific clinical history and particular evolution during their stay at ICU. Table 1 gives an overview of the study population with some important clinical characteristics.

Whole-blood glucose in undiluted arterial blood (i.e., glycemia) was measured *every hour* by means of a glucose analyzer (ABL700 Radiometer Medical, Copenhagen). In the protocol described above (Van den Berghe *et al* 2003), glycemia is advised to be measured every 4 h or more frequently in the initial phase or in the case of complications in order to control glycemia between narrow limits (80–110 mg dl^{-1}). However, since frequent measurements are necessary to obtain an accurate prediction model, this 1 h glycemia sample time was imposed. Because

Table 1. Patient population.

Variable	Value
Male sex (no (%))	9 (65.0)
Age (years (standard deviation))	70.0 (12.6)
Body mass index (kg m^{-2} (standard deviation))	25.6 (5.8)
Reason for intensive care (no (%))	
Cardiac surgery	10 (66.7)
Abdominal surgery or peritonitis	5 (33.3)
APACHE II score (first 24 h) (no (standard deviation))	18 (4)
Mean glycemia (mg dl^{-1} (standard deviation))	101 (23)
Minimal glycemia (mg dl^{-1})	37
Maximal glycemia (mg dl^{-1})	214

Table 2. Overview of the known input variables that influence glycemia.

Initial input variables	Dynamical input variables
BMI	Total carbohydrate calories (parenteral and enteral infusion)
APACHE II score	Total fat calories (parenteral and enteral infusion)
History of diabetes	Body temperature
Pathology	Drugs (e.g., glucocorticoids, noradrenaline, dobutamine, dopamine, β-blockers)

of the significantly increased workload for doctors and nurses, this even more intensified protocol was only applied during the first 2 days after admission. Consequently, only the data belonging to these first 2 days of each patient are considered in this paper.

Many disturbance factors (the so-called *input* variables) can influence glycemia. Table 2 gives an overview of the known input variables. They consist of initially known (i.e., when a patient enters ICU) and dynamical variables. The latter's flow was adapted with a maximum frequency of once every hour. As a result, the number of data points per patient and per variable is restricted to 48.

2.2. Introduction to the model structure used

Depending on the number of data and the complexity of the system, different modeling methodologies can be applied. The current setting is rather complex due to the varying patient behavior which is caused by a large inter- and intra-patient variability. There is an abundance of factors that result in a high variance among patients. On the one hand, there is the *inter*-patient variability that is caused by the reason why a patient is admitted to the ICU, the medical history, the medical treatment (e.g., type and dose of administered farmaca, type and amount of calories that are delivered), etc. The *intra*-patient variability, on the other hand, can be caused by the time-varying insulin resistance, the hormonal behavior, the (possible) recovery process of the patient and other sometimes unmeasurable or unknown parameters related to the patient.

In previous work (Van Herpe *et al* 2006), a first model to predict glycemia of critically ill patients was proposed. In this work, we applied system identification techniques (Ljung 1999) to identify the dynamic relation between the glycemia evolution (i.e., the *output* of the system) and the (known) *input* variables (i.e., the disturbance factors described above). The input–output data of 41 patients admitted to a surgical ICU were considered. The arterial glucose

Table 3. Overview of the output and input variables that were used in model (1) observed at time t.

Variable	Symbol	Unit
Glycemia	y_t	mg dl^{-1}
Insulin	$u_{1,t}$	U h^{-1}
Insulin $\times$ dummy fever	$u_{1,t} D_{\mathrm{F},t}$	U h^{-1}
Total carbohydrate calories	$u_{3,t}$	kcal h^{-1}
Body temperature	T_t	$^\circ$C
Dopamine	$u_{4,t}$	γ [a]

[a] The unit γ is used in the ICU to symbolize the amount of the considered catecholamine drug (μg) per kg body weight and per minute.

Table 4. Effect of insulin (to predict the glycemia value at $t + 1$) in the case of fever or no fever.

	Effect of insulin	Clinical assessment
No fever ($T_t \leqslant 37.5\,^\circ$C, $D_{\mathrm{F},t} = 0$)	b_1	$b_1 < 0$
Fever ($T_t > 37.5\,^\circ$C, $D_{\mathrm{F},t} = 1$)	$b_1 + b_2$	$b_2 > 0$
		$b_1 + b_2 < 0$

concentration was measured at 1–4 h intervals depending on the physical condition of the patient. In spite of the complex behavior that is described above, we selected a parsimonious model structure (ARX, which is an autoregressive model with exogenous input variables) because the number of available input–output ICU data was rather limited. In this way, the complexity of the model could be restricted (Sjöberg *et al* 1995, Ljung 1999). The optimal order of the ARX structure was determined by computing the performance (mean squared prediction error (MSE)) on a test dataset that was randomized over 500 permutations. Each permutation consisted of an estimation dataset (30 patients) and a test dataset (11 patients). The optimal order q, which was found to be $q = 2$, was selected such that it gave the best performance averaged over those 500 permutations. Furthermore, an input selection was performed on the existing dataset. Only those dynamical input variables (presented in table 2) statistically different from zero (using t-tests) were selected. This was an iterative process in which one variable was removed at a time and in which the model was re-estimated until all variables were found to be statistically significant (at a 95% level).

The presented model is given by

$$\hat{y}_{t+1} = \hat{a}_1 y_t + \hat{a}_2 y_{t-1} + \hat{b}_1 u_{1,t} + \hat{b}_2 u_{1,t} D_{\mathrm{F},t} + \hat{b}_3 u_{3,t} + \hat{b}_4 u_{4,t}, \tag{1}$$

where y_t and $\hat{y}_t$ are the observed and predicted glycemia levels at time t, respectively, $u_{1,t}$ is the insulin flow at t, $D_{\mathrm{F},t}$ is a dummy variable that is 1 if the body temperature is above 37.5 $^\circ$C and zero otherwise, $u_{3,t}$ is the flow of total carbohydrate calories and $u_{4,t}$ is the exogenous dopamine flow (i.e., a catecholamine drug). The symbols $\hat{a}_1, \hat{a}_2, \hat{b}_1, \hat{b}_2, \hat{b}_3$ and $\hat{b}_4$ denote the corresponding model coefficients that are estimated. Table 3 presents the output and input variables that are considered in model equation (1) and their respective units.

It is known that increased insulin resistance is typical of critically ill patients (Van den Berghe *et al* 2001, 2006). In the case of fever (i.e., the body temperature surpasses 37.5 $^\circ$C), extra stress is present in the majority of critically ill patients resulting in a higher insulin resistance than without fever. Since insulin resistance significantly influences the effect of insulin on glycemia, we parameterized the insulin effect as a combination of a base effect and a possible additional effect due to fever in the model described above. This is further explained in table 4. When the body temperature of the patient is below or equal to 37.5 $^\circ$C (no

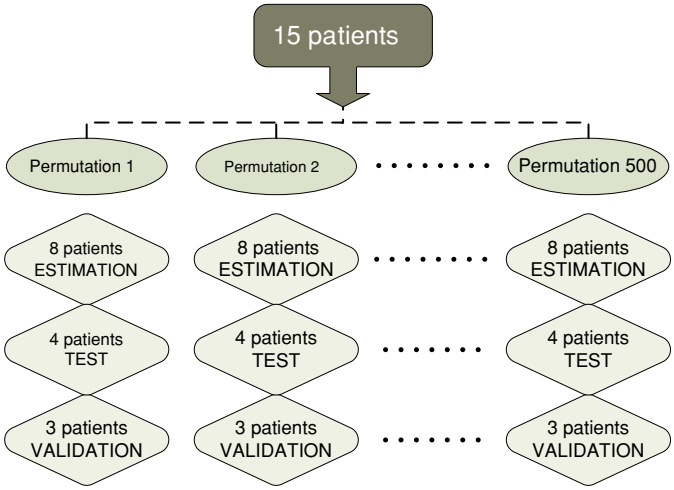

Figure 2. Different sets of patients were used for estimating, testing and validating the developed models. This randomized process is repeated 500 times to avoid data selection bias.

fever, $D_{\mathrm{F},t} = 0$), the effect of insulin is captured by b_1, which is expected to be negative since insulin is a protein that decreases glycemia. In the case of fever ($D_{\mathrm{F},t} = 1$), the insulin activity is captured by the total contribution of ($b_1 + b_2$), which is assumed to be negative as well. However, the (positive) coefficient b_2 is expected to cause a reduction of the insulin activity. Similarly, the model coefficient values for administered calories are expected to be positive. Although the glycemia reactions on administered drugs are patient specific, a positive value for dopamine can also be expected.

2.3. Modeling strategy

In this paper, an *adaptive* modeling strategy that is based on the previously developed model (equation (1)) is presented. We apply an initial and an adaptive modeling strategy on a new surgical ICU dataset in which a glycemia sample time of 1 h was imposed for this purpose. Both initial and adaptive modeling techniques are evaluated by applying a one-hour-ahead prediction and a four-hours-ahead simulation process. To avoid data selection bias, the models are estimated using different randomizations on the available data.

2.3.1. Patient selection procedure. In order to enforce independence on the patient selection, the available dataset (15 patients) is divided into an estimation, a test and a validation set in a random way 500 successive times leading to 500 randomized estimation–test–validation partitions or permutations. Each permutation consists of an estimation set (eight patients), a test set (another four patients) and a validation set (the remaining three patients). For all permutations, the *estimation* set is used to estimate the initial model giving 500 initial model coefficients (see section 2.3.2). Next, the optimal weighting factor is detected by applying the adaptive modeling strategy on the selected *test* sets for different weighting factors (see section 2.3.3). Finally, the implementation of the found optimal weighting factor in the adaptive modeling strategy is validated on the remaining *validation* set for each particular data partition and compared with the model performance (MSE) when no adaptive modeling strategy is applied (see section 2.3.3). In figure 2, the patient selection procedure is visualized.

2.3.2. Initial model. For each permutation, an initial model is estimated based on the data of eight randomly selected patients by applying ordinary least squares (OLS) (Maddala 2001) such that the squared error (i.e., the squared difference between the predicted and the observed value) is minimized. This can be presented as follows:

$$\min_{\beta,e} \quad e^t e, \qquad \text{s.t.} \quad Y = X\beta + e, \tag{2}$$

where the $n \times 1$ vector Y denotes the output variable, the $n \times m$ matrix X denotes the m input variables and the $n \times 1$ vector e denotes the error. The model coefficients to be estimated are represented by the $m \times 1$ vector β as $\beta = (a_1 \quad a_2 \quad b_1 \quad b_2 \quad b_3 \quad b_4)$ from (1). This set of (initial) model coefficients is estimated for each permutation. In the validation process, this estimated set has two different functions. If the adaptive modeling methodology (2.3.3) is applied, this set will only equal the initial set of coefficients. At each time step, the model coefficients will then be adapted based on the recent data originating from the specific validation patient. If there is no adaptive modeling strategy to be applied, this initial set will be kept constant during the full validation process.

2.3.3. Adaptive model. 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, insulin resistance, etc), the use of the initial model for accurately predicting glycemia may be insufficient. Therefore, we propose the implementation of an adaptive modeling technique. In the presented procedure, the model coefficients belonging to each test patient and each validation patient (both are called the *considered* patient) are re-estimated at each time step t by combining two different datasets. The first dataset is fixed and consists of the data from the estimation set (i.e., the data used for the initial model). The second part denotes the data from the *considered* patient up to time $t-1$ and grows as a function of time, consequently. In the estimation process, we use weighted least squares (WLS) (Maddala 2001). In our implementation, the weighting factor is used to increase the influence of the squared errors of the second dataset such that the model is more influenced by the data of the new patient. This minimization process can be summarized as follows:

$$\min_{\beta,e} \quad e^t \Phi e, \qquad \text{s.t.} \quad Y = X\beta + e, \tag{3}$$

where the diagonal $n \times n$ matrix Φ consists of elements equal to 1 (in the case of errors related to the estimation set of patients) and equal to the hyperparameter ϕ (in the case of errors related to the data from the considered patient).

In order to optimize the hyperparameter ϕ, the latter is varied from 1 to 30. The total MSE is calculated considering all 500 permutations per weighting factor. The applied methodology to optimize ϕ is summarized as follows:

(i) For weighting factor $\phi = 1$ to 30.
  (a) Repeat $k = 1$ to 500.
    (1) Define a set of eight patients (called $S_{\mathrm{E},k}$) for estimating the initial model.
    (2) Define a set of four patients (called $S_{\mathrm{T},k}$) for testing the adaptive model.
    (3) For test patients $p = 1$ to 4
      (A) Estimate a new model M_t at each time step t by using WLS based on the fixed estimation set $S_{\mathrm{E},k}$ (dataset 1) and on the data of the test patient p (who is part of $S_{\mathrm{T},k}$) up to time $t-1$ (dataset 2). The squared errors, that are related to dataset 2, are amplified by ϕ.
      (B) Predict glycemia $\hat{y}_{t+1}$ with the designed model M_t.

(C) Compute the error at $t + 1$ (i.e., the difference between the predicted ($\hat{y}_{t+1}$) and the observed (y_{t+1}) glycemia value at time step $t + 1$).

(4) Store all errors that are generated for $S_{T,k}$.

(b) Compute the total MSE of all stored errors corresponding to the respective ϕ.

(ii) The weighting factor that is used to generate the smallest total MSE is the *optimal* weighting factor, ϕ_{opt}, that will be used in the adaptive model simulations for each validation set $S_{V,k}$ (see section 2.4).

2.4. Validation strategy

After selecting ϕ_{opt}, the initial and the adaptive modeling algorithms are used for every randomly selected validation set (three patients per permutation). The MSE is computed for every permutation. To compare the MSE sets from the initial and the adaptive model, the Wilcoxon signed rank test is used. The overall methodology is explained below:

(i) Repeat $k = 1$ to 500.

(a) Define a set of eight patients (called $S_{E,k}$) for estimating the initial model.

(b) Define a set of four patients (called $S_{T,k}$) for testing the adaptive model in order to optimize ϕ (full procedure described in section 2.3.3).

(c) Define a set of the remaining three patients (called $S_{V,k}$) for validating the initial and the adaptive model.

(d) For validation patients $p = 1$ to 3

(1) Predict glycemia during the considered time horizon (which is 1 h (section 2.4.1) or 4 h (section 2.4.2)) by implementing the initial and the adaptive model (by using ϕ_{opt}) at every time step. The input variables are assumed to be known in the considered time horizon.

(2) Compute the difference between the predicted and the observed glycemia value (i.e., the error).

(e) Compute the MSE belonging to $S_{V,k}$.

(ii) Compare the 500 MSEs from the initial model with those from the adaptive model.

2.4.1. One-hour-ahead predictions. To validate the developed initial and adaptive models, a one-hour-ahead prediction is performed using the data of each validation set. Equation (1) is applied in every time step with the estimated coefficients from (2) and (3). The model performance is measured by computing the MSE given by $\sum \frac{(\hat{y}_{t+1}-y_{t+1})^2}{N}$, where y_t is the actual glycemia value, $\hat{y}_t$ is the predicted glycemia value and N is the number of errors.

2.4.2. Four-hours-ahead simulations. Since a model operating in a real-life ICU should also be able to predict glycemia for a longer time horizon and since the current manual control strategy imposes a glycemia sample period of 4 h (Van den Berghe *et al* 2003), we also validated our developed models with a 4 h time horizon. In the simulation process, the input variables are assumed to be known during this time horizon which is a clinically feasible assumption. The simulation process can be presented as follows:

$$\begin{aligned}
\hat{y}_{t+1} &= \hat{a}_1 y_t + \hat{a}_2 y_{t-1} + \hat{b}_1 u_{1,t} + \hat{b}_2 u_{1,t} D_{F,t} + \hat{b}_3 u_{3,t} + \hat{b}_4 u_{4,t},\\
\hat{y}_{t+2} &= \hat{a}_1 \hat{y}_{t+1} + \hat{a}_2 y_t + \hat{b}_1 u_{1,t+1} + \hat{b}_2 u_{1,t+1} D_{F,t+1} + \hat{b}_3 u_{3,t+1} + \hat{b}_4 u_{4,t+1},\\
\hat{y}_{t+3} &= \hat{a}_1 \hat{y}_{t+2} + \hat{a}_2 \hat{y}_{t+1} + \hat{b}_1 u_{1,t+2} + \hat{b}_2 u_{1,t+2} D_{F,t+2} + \hat{b}_3 u_{3,t+2} + \hat{b}_4 u_{4,t+2},\\
\hat{y}_{t+4} &= \hat{a}_1 \hat{y}_{t+3} + \hat{a}_2 \hat{y}_{t+2} + \hat{b}_1 u_{1,t+3} + \hat{b}_2 u_{1,t+3} D_{F,t+3} + \hat{b}_3 u_{3,t+3} + \hat{b}_4 u_{4,t+3},
\end{aligned} \tag{4}$$

Table 5. Results for the initial model considering all 500 permutations.

Variables	Corresponding model coefficient	Estimation	Standard deviation
Output variables			
Glycemia at t	$\hat{a}_1$	0.9648	0.1043
Glycemia at $t-1$	$\hat{a}_2$	−0.0278	0.1085
Input variables at t			
Insulin	$\hat{b}_1$	−2.1375	0.5517
Insulin × dummy fever	$\hat{b}_2$	0.1472	0.5172
Total carbohydrate calories	$\hat{b}_3$	0.3193	0.1353
Dopamine	$\hat{b}_4$	6.6625	2.9161

where y_t and $\hat{y}_t$ denote the observed and predicted glycemia values, respectively. The model performance (measured by MSE) is now computed as $\sum \frac{(\hat{y}_{t+4}-y_{t+4})^2}{N}$.

3. Evaluation

In this section, the results of the initial model are presented, followed by the consideration of the optimal weighting factor used in the adaptive modeling procedure. Finally, the outcomes after applying the initial and the adaptive modeling strategy in a one-hour-ahead prediction scenario and a four-hours-ahead simulation scenario are also shown.

3.1. Initial model

Since 500 different permutations to randomize the selected estimation, test and validation sets of patients were considered, also 500 initial models were developed. Table 5 shows the mean of the estimated coefficient values and the corresponding standard deviations.

As clinically expected, $\hat{b}_1 < 0$ and $\hat{b}_1 + \hat{b}_2 < 0$. The extra insulin resistance in the case of fever is captured by $\hat{b}_2 > 0$. The latter causes a smaller glycemia reduction when insulin is administered to a patient with fever than without fever. The positive value of $\hat{b}_3$ indicates the glycemia raising effect with the intake of carbohydrate calories. Finally, the positive value of $\hat{b}_4$ was also clinically expected, due to the features of the catecholamine drugs.

3.2. Optimal adaptive model

The process to optimize the weighting factor ϕ is applied on all *test* sets as explained in section 2.3.3. In figure 3, the MSEs as a function of ϕ are shown. The weighting factor that generates the smallest MSE over all permutations, ϕ_{opt}, is 5. Consequently, this value is introduced in the adaptive modeling process used for the *validation* sets (see section 2.4).

3.3. Validation simulations

The validation of the developed model is performed with the data of the *validation* set during every permutation. Both one-hour-ahead prediction scenario and four-hours-ahead simulation scenario are considered.

3.3.1. One-hour-ahead predictions. In the first phase, the models are validated by using a time horizon of 1 h: the patient's glycemic value at time step t is predicted by means of the last two glycemia values (at $t-1$ and $t-2$) and the considered input variables at $t-1$. The MSE of every validation set is computed as a function of the model type (initial or adaptive)

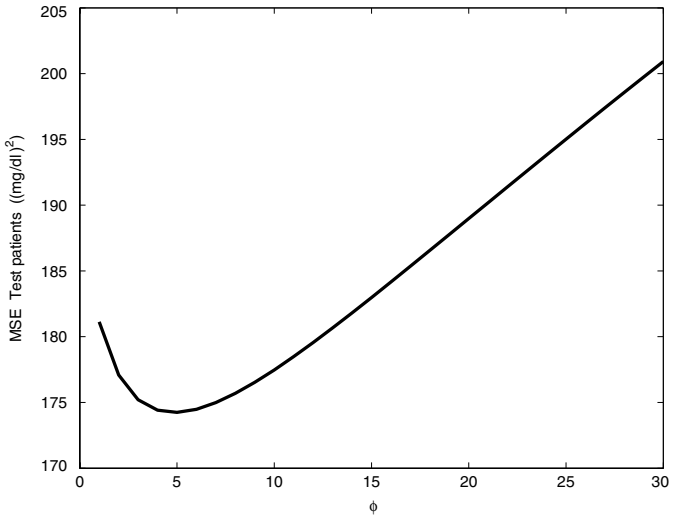

Figure 3. The MSE from the errors obtained for all permutations and for all test patients is computed as a function of the weighting factor ϕ. The optimal weighting factor (ϕ_{opt}) is found to be 5.

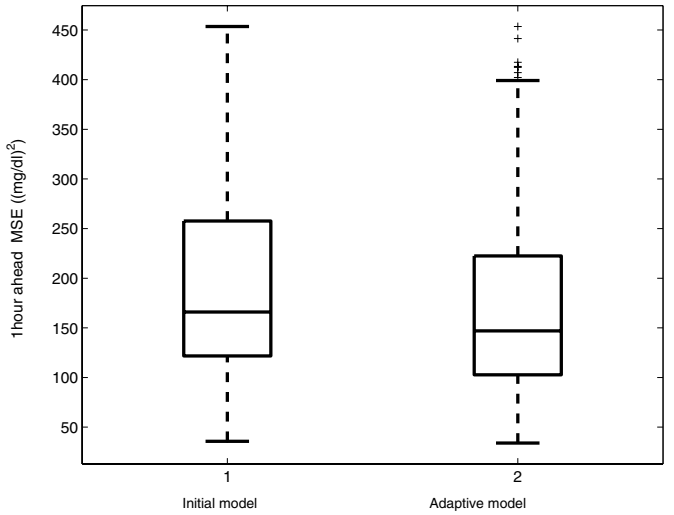

Figure 4. Boxplot of the MSEs obtained for all validation sets in a one-hour-ahead prediction scenario and after 500 permutations.

and the permutation. The spread of the MSEs is visualized by means of a box and whisker plot in figure 4. There is a significant difference ($p < 0.001$) between the MSEs belonging to the initial model and those belonging to the adaptive model. The mean MSE and its standard deviation after using the initial model are 188 (mg dl^{-1})^2 and 84 (mg dl^{-1})^2, respectively. The use of the proposed adaptive modeling technique (with ϕ_{opt}) results in 171 (mg dl^{-1})^2 as mean MSE and 90 (mg dl^{-1})^2 as standard deviation.

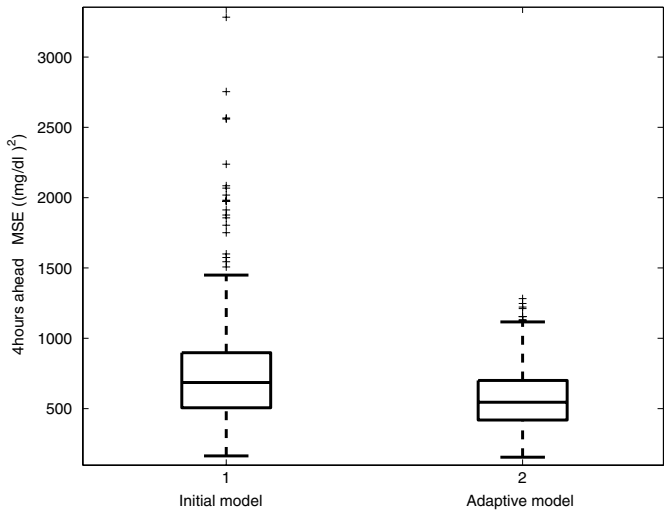

Figure 5. Boxplot of the MSEs obtained for all validation sets in a four-hours-ahead simulation scenario and after 500 permutations.

3.3.2. Four-hours-ahead simulations. The use of a 4 h time horizon results in a larger difference in performance between the initial and the adaptive modeling strategy. The use of the former results in 761 (mg dl^{-1})^2 as mean MSE and 400 (mg dl^{-1})^2 as standard deviation in comparison with 582 (mg dl^{-1})^2 (mean MSE) and 224 (mg dl^{-1})^2 (standard deviation) for the adaptive model. Again, a significant difference ($p < 0.001$) exists between those two groups. The spread of the MSEs is visualized by means of a box and whisker plot in figure 5.

4. Discussion

The signs of the estimated model coefficients (table 5) correspond to their clinical expectations. Although this is no strict validation, this result is important since this initial coefficient set may serve as *initial guess* in the adaptive modeling procedure applied to new ICU patients. In the case of a 1 h time horizon, root-mean-squared errors of 13.7 mg dl^{-1} and 13.1 mg dl^{-1} for the initial and the adaptive modeling strategy, respectively, are obtained. The difference between the initial and adaptive modeling methodology becomes more clear by considering the 4 h time horizon: 27.6 mg dl^{-1} as root-mean-squared error for the initial model and 24.1 mg dl^{-1} for the adaptive model.

As is shown in figures 4 and 5, the proposed adaptive modeling strategy results in significantly smaller MSEs than the initial model methodology for 500 particular definitions of the validation data. This is an important result since it proves the interest to consider individual patient features in the modeling process. The initial model is too 'general' to cover the glucose–insulin dynamics of each patient admitted to the ICU. In the adaptive modeling procedure presented in this paper, we estimated a new model at each time step t based on both the fixed estimation data and the data from the specific validation patient up to time $t - 1$, giving more importance to the latter. We only considered the first 2 days after admission to the ICU. However, it should be noted that for a given (validation) patient, the performance difference between the initial and the adaptive modeling approach may increase over time, due to the evolving dynamics of the patient. Therefore, we most likely underestimate the

advantage of the adaptive modeling strategy, since only a time span of 48 h per patient is considered in this study, due to the manual nature of the data collection.

The initial model described above is based on the input–output data of patients admitted to the *surgical* ICU. Further research is required to check the feasibility of the designed model in a longer time framework and in the *medical* ICU. Also, the use of this model and its adaptive modeling characteristics in a predictive control system will be verified.

5. Conclusion

In this paper, we present an initial input–output model to predict glycemia of critically ill patients. Different dynamical input variables and a combined approach to the insulin resistance (by considering the body temperature) are implemented, in order to give the model a clinical interpretation. Second, we also present an adaptive modeling strategy that is based on giving more importance to the individual patient data by applying WLS. By using a methodology based on random partitions of the data between estimation, test and validation sets, the independence on the selected data is enforced.

The estimated coefficients of the initial model show clinical relevance with respect to the behavior of glycemia in relation to insulin, insulin resistance, intake of carbohydrate calories, etc. The application of an adaptive modeling strategy on the data of the validation sets of patients results in a significantly better performance (measured by computing the MSE) than that of the initial model. Both one-hour-ahead prediction scenario and four-hours-ahead simulation scenario are considered. The performance difference between the initial and the adaptive model is larger when a 4 h time horizon is introduced. In future research, we will consider the designed models in a time period longer than 2 days and in a larger patient dataset. Also, the feasibility to introduce the initial and the adaptive model in a predictive control system will be assessed.

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