DEVELOPMENT OF A CRITICALLY ILL PATIENT INPUT-OUTPUT MODEL

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Abstract: In this paper we apply system identification in order to build a model suitable for prediction of the glycemia levels of critically ill patients in the Intensive Care Unit. These patients typically show increased glycemia levels, and it has been shown that glycemia control by means of insulin therapy reduces morbidity and mortality. Based on a real-life dataset from 41 critically ill patients, an ARX model is estimated which captures the insulin effect on glycemia under different settings. The results are satisfactory both in terms of forecasting ability and in the clinical interpretation of the estimated coefficients.

Keywords: Medical Systems, Insulin Sensitivity, Medical Applications, System Identification, Autoregressive Models, Parameter Identification.

1. INTRODUCTION

In this paper we develop a model for predicting the glycemia levels of critically ill patients admitted to the Intensive Care Unit (ICU) based on clinical observations. A predictive system for glycemia levels can later be used in the development of a semi-automated control system for such purpose, as it has been shown that normalization of glycemia (between 80 and 110 mg/dl = normoglycemia) through a rigorous administration of insulin results in an important reduction in mortality and morbidity. As an example, the number of deaths in patients who required intensive care for more than five days was reduced from 20,2% to 10,6% by normalizing glycemia in a clinical study of 1548 patients (Van den Berghe *et al.*, 2001).

Currently, the administration of insulin in intensive care patients is controlled by medical staff in a very time demanding empirical protocol (Van den Berghe *et al.*, 2003), which requires important expertise from nurses and doctors. The protocol requires blood glucose levels to be measured every four hours (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) [1] , medical history) can influence the reaction to insulin administration.

The glycemia normalization problem can also be encountered in diabetic patients. In literature some physical compartmental models (Bailey and Haddad, 2005) that predict glycemia of type 1 diabetic patients have already been described (Lehmann and Deutsch, 1996; Parker *et al.*, 1999; Parker *et al.*, 2000; Hovorka *et al.*, 2004). In clinical practice, however, those different physical compartmental models are not used due to possibly unacceptable model uncertainty rates (Lehmann and Deutsch, 1998; Parker *et al.*, 2001). Moreover, an ICU population cannot be compared to a diabetic type 1 population. The existence of critical illness causes some important metabolic changes (e.g., increased insulin resistance) that can significantly influence glycemia.

In order to develop a control system that helps to normalize glycemia by automatically infusing insulin (taking into account future disturbances as much as possible) a predictive model needs to be generated. The aim of this paper is to design a first model for this purpose. As far as we know we are the first research group that makes use of real clinical ICU input-output data for the development of a black-box ICU patient model (Van Herpe *et al.*, 2005). The paper is structured as follows: the data are described in Section 2 followed by the modeling methodology in Section 3 and, finally, the modeling results and the clinical interpretation are presented in Section 4.

2. DATA DESCRIPTION

In this section the data that are used in the modeling process are presented. The specific patient features are emphasized and the variables that can influence glycemia (and the different sample frequencies) are described.

2.1 Patient Data

The dataset origins from 41 patients who were admitted to the ICU-division of the University Hospital K.U. Leuven (Belgium) in 2000. All of them had a specific clinical history and particular evolution during his/her stay at ICU. Due to the different nature of the patients, the length of stay at ICU varied. Consequently, the dataset consists of time series of different lengths. Table 1 gives an overview of the study population with some important clinical characteristics.

Table 1. Patient population.

Variable	Value
Male sex - *no* (%)	27.0 (65.8)
Age - yr $(std-dev)$	59.8 (17.6)
Body-mass index - kg/m^2 $(std-dev)$	27.0 (5.2)
Reason for intensive care - *no* (%)	
Cardiac surgery	11 (26.8)
Noncardiac indication	30 (73.2)
Neurologic disease, cerebral trauma, or brain surgery	4 (9.8)
Thoracic surgery, respiratory insufficiency, or both	7 (17.1)
Abdominal surgery or peritonitis	5 (12.2)
Vascular surgery	2 (4.9)
Multiple surgery or severe burns	7 (17.1)
Transplantation	3 (7.3)
Other	2 (4.9)
APACHE II score (first 24 hr) $(std-dev)$	11 (6)
History of diabetes - *no* (%)	7 (17.1)
Type I - diabetes	2 (4.9)
Type II - diabetes	5 (12.2)
Length of stay at ICU - hr $(std-dev)$	174 (154)
Min. length of stay at ICU - hr	36
Max. length of stay at ICU - hr	686
Mean glycemia - mg/dl $(std-dev)$	106 (30)
Minimal glycemia - mg/dl	37
Maximal glycemia - mg/dl	379

2.2 Important Variables

The arterial glucose concentration (i.e., glycemia) is the output variable of the system under study. It was measured at one to four-hour intervals depending on the physical condition of the patient (e.g., in the initial phase a patient is typically unstable, which requires more frequent glycemia measurements). Due to those different time intervals, glycemia values are linearly interpolated to one-hour glycemia data.

Insulin is a protein that decreases glycemia. Because of the critical illness of patients who are admitted to ICU, the insulin resistance increases, which results in the need for exogenous insulin that is administered by an insulin pump. In the dataset at hand this insulin flow was adapted by medical staff with a maximum frequency of once each hour.

There are many other (known, unknown, or immeasurable) input variables that 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

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

variables. The latter's flow was adapted with a maximum frequency of once each hour.

Table 2. Overview of the variables that can influence glycemia.

Initial input variables	Dynamical input variables
BMI	Total carbohydrate calories
APACHE II score	Total fat calories
History of diabetes	Body temperature
Pathology	Administered drugs (e.g., glucocorticoids, noradrenalin, dobutamin, beta-blockers, etc.)

The glucose utilizing tissues can offer resistance to insulin resulting in a glycemia increase (Wolfe *et al.*, 1979; Wolfe *et al.*, 1987; Shangraw *et al.*, 1989). Some methods to estimate this insulin resistance have already been described, e.g., (Bergman *et al.*, 1985; Bergman *et al.*, 1981). However, the use of these methods (e.g., the oral glucose tolerance test) is hardly feasible with ICU patients due to their critical illness (additional physical load should be avoided). The insulin resistance can also fluctuate as a function of time. As described in (Van den Berghe *et al.*, 2001) the insulin resistance with ICU patients is inter and intra patient specific. Initial parameters such as the BMI, the APACHE II-score [2] (whose calculation is based on parameters such as the body temperature, the mean blood pressure, the breathing frequency, etc.), the reason for admission, and the history of diabetes on the one hand or dynamical parameters (e.g., the administration of certain drugs such as glucocorticoids) on the other hand can both influence the insulin resistance and glycemia, consequently. However, the size and the accuracy of the dataset at hand is insufficient to take all those parameters into account individually. Consequently, the insulin resistance is approached by taking only the body temperature into consideration. A body temperature surpassing 37.5°C (e.g., caused by an additional inflammation) may indicate critical illness, which may result in a higher insulin resistance.

3. MODELING METHODOLOGY

The overall modeling methodology that is used is presented in this section. Firstly, a specific model structure is selected after which a method - that is independent on the particular set of patients used for estimating or testing - is described.

3.1 Model Structure

An ARX model structure (Ljung, 1999; Sjöberg *et al.*, 1995) is used in the modeling process to predict glycemia from a set of clinical inputs,

$$\begin{aligned} y_{t+1} = &\sum_{i=1}^{n_a} a_i y_{t-i+1} + b_1 u_{1,t} + b_2 u_{1,t} D_{F,t} \\ &+ b_3 u_{3,t} + b_4 u_{4,t} + b_5 u_{5,t} + b_6 u_{6,t} \\ &+ b_7 u_{7,t} + b_8 u_{8,t} + b_9 u_{9,t} + b_{10} u_{10,t} \\ &+ b_{11} u_{11,t} + b_{12} + e_t, \quad (1) \end{aligned}$$

where $a_i \in \mathbb{R}, b_j \in \mathbb{R}$, $i = 1, \ldots, n_a$, $j = 1, \ldots, 12$ are the model coefficients to be estimated, y_t is the glycemia level at time t, $u_{1,t}$ is the insulin flow at t, $D_{F,t}$ is a dummy variable that takes 1 if the body temperature is above 37.5°C and zero otherwise, $u_{3,t}$ the total of carbohydrate calories, $u_{4,t}$ the total of fat calories, $u_{5,t}$ the body temperature, $u_{6,t}$ the glucocorticoids level, $u_{7,t}$ the adrenalin level, $u_{8,t}$ the noradrenalin level, $u_{9,t}$ the dobutamin level, $u_{10,t}$ the dopamin level, and $u_{11,t}$ the level of the beta-blockers. Table 3 gives an overview of those used input variables and their units. The residuals e_t are assumed to have zero mean and constant (and finite) standard deviation.

Table 3. Overview of the input variables that were used in the modeling process.

Variables	Symbol	Units
Insulin	$u_{1,t}$	U/hr
Insulin*Dummy fever	$u_{1,t}D_{F,t}$	U/hr
Total carbohydrate calories	$u_{3,t}$	kcal/hr
Total fat calories	$u_{4,t}$	kcal/hr
Body temperature	$u_{5,t}$	°C
Glucocorticoids	$u_{6,t}$	mg/hr
Adrenalin	$u_{7,t}$	γ (1)
Noradrenalin	$u_{8,t}$	γ (1)
Dobutamin	$u_{9,t}$	γ (1)
Dopamin	$u_{10,t}$	γ (1)
Beta-blockers	$u_{11,t}$	mg/hr

(1) The unit γ is used in a medical environment to symbolize the amount of the considered catecholamine drug (μgr) per kg body weight and per minute.

It is important to emphasize that the insulin variable is considered both as an independent and as a body temperature dependent input. The latter is the case when fever is present in order to capture the effect of a higher insulin resistance (and thus, a lower insulin effect on glycemia). When the body temperature of the patient is below or equal to 37.5°C (no fever, $D_{F,t} = 0$) the effect of insulin is captured by b_1. In case of fever ($D_{F,t} = 1$) the insulin activity is captured by the total contribution of $(b_1 + b_2)$. This is illustrated in Table 4.

Due to the glycemia lowering effect of insulin, we expect to find $b_1 < 0$. Fever can be associated with a higher insulin resistance; therefore we expect $b_2 > 0$, and $(b_1 + b_2) < 0$. Analogously, the model coefficient values for administered calories are expected to be positive. Although the glycemia reactions of drugs are patient specific, a positive value for catecholamines, beta-blockers, and glucocorticoids can be expected, too.

[2] The APACHE II score (Acute Physiology and Chronic Health Evaluation) is calculated each day and determines the severity of illness.

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

	Effect of insulin	Clinical expectation
No fever	b_1	$b_1 < 0$
$u_{5,t} \leq 37.5$°C		
$D_{F,t} = 0$		
Fever	$b_1 + b_2$	$b_2 > 0$
$u_{5,t} > 37.5$°C		$(b_1 + b_2) < 0$
$D_{F,t} = 1$		

3.2 Order Selection

In order to select the order n_a in equation (1) we use different estimation and test sets defined by random permutations. In this way, and for a given order n_a, we define a set of 30 patients for model estimation and a remaining set of 11 patients for testing. The performance (mean squared error, MSE) is measured on the test set for a particular data partition. Each time, the estimation/test partitions are randomized 500 times. Finally, we select the order $n_a \in [1, 10]$ which gives the lowest MSE averaged over the 500 random partitions.

3.3 Model Estimation and Input Selection

Each model is estimated in the following way. Given the order n_a and the estimation data, a first model $M_{\text{all}}(n_a)$ of the form (1) is estimated by applying Ordinary Least Squares (OLS) using *all* regressors. Based on the $t-$statistics (Rice, 1995) of the estimated coefficients from $M_{\text{all}}(n_a)$, we *select* only those inputs which are statistically different from zero. This is an iterative process, one variable is removed at a time, and the model is re-estimated until all variables are found to be statistically significant (at a 95% level). Call this final model $M_{\text{sel}}(n_a)$. The model $M_{\text{sel}}(n_a)$ is the one used for evaluation with the test set when selecting the order n_a. Once the optimal order n_a^* is selected, a new model $M_{\text{all}}(n_a^*)$ with optimal order n_a^* is estimated using all data from all patients, and its reduced model $M_{\text{sel}}(n_a^*)$ is the final model to be considered. The overall methodology is summarized as follows:

(1) For order $n_a = 1$ to 10,
  (a) Repeat k = 1 to 500,
    (i) Define a set of 30 patients for estimating (X^k) and 11 for testing (T^k) on each repetition k,
    (ii) Estimate model $M_{\text{all}}(n_a)$ with X^k,
    (iii) Based on iterative $t-$tests of significance at 95% level, find model $M_{\text{sel}}(n_a)$ in which all variables are significant,
    (iv) Evaluate $M_{\text{sel}}(n_a)$ on the test data T^k to predict glycemia $\hat{y}_{T^k}$,
    (v) Compute the mean squared error $\text{MSE}_k(n_a)$ between $\hat{y}_{T^k}$ and y_{T^k},
  (b) Compute the average mean squared error $\text{MSE}(n_a) = \frac{1}{500}\sum_{k=1}^{500} \text{MSE}_k(n_a)$,
(2) Find optimal n_a^* that minimizes the average mean squared error $\text{MSE}(n_a)$,
(3) Estimate a model $M_{\text{all}}(n_a^*)$ with optimal order n_a^* using all data from all patients,
(4) Use the iterative $t-$tests until the final model $M_{\text{sel}}(n_a^*)$ is obtained.

4. MODELING RESULTS AND CLINICAL ASSESSMENT

After applying the modeling strategy described above the results are shown in this part. Furthermore the final model is clinically assessed.

4.1 Modeling Results

Figure 1 presents the average normalized mean squared error (NMSE) as a function of the model order. The optimal model order is $n_a^* = 2$. The average NMSE (over 500 randomizations) is 0.0557. Having selected $n_a^* = 2$, now we estimate a unique model $M_{\text{all}}(n_a^*)$ using all data from all patients, the results of which are shown on Table 5. The corresponding final model $M_{\text{sel}}(n_a^*)$, for which all variables are statistically significant, is reported on Table 6.

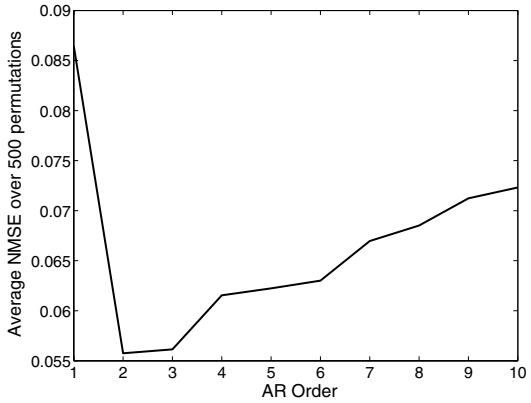

Fig. 1. The average NMSE as a function of the model order. The use of model order 2 resulted in the smallest average NMSE (0.0557).

The predictor of the glycemia value $\hat{y}_{t+1}$ can now be written as

$$\hat{y}_{t+1} = \hat{a}_1 y_t + \hat{a}_2 y_{t-1} + \hat{b}_1 u_{1,t} + \hat{b}_2 u_{1,t} D_{F,t} + \hat{b}_3 u_{3,t} + \hat{b}_{10} u_{10,t}, \quad (2)$$

which results in a NMSE of 0.0514 computed in-sample for the model $M_{\text{sel}}(n_a^*)$. This is not very different from the average NMSE (0.0557) that was obtained for the same order using 500 random test partitions, which indicates that the methodology based on input selection using t-tests is able to produce a model which does not overfit the in-sample data.

Table 5. Results for Model $M_{\text{all}}(n_a^*)$ with $n_a^* = 2$.

Variables	Estimation	Std-Dev	t-stat
Output variables			
Glycemia at t	1.4959	0.0094	159.2171
Glycemia at *t-1*	-0.5692	0.0094	-60.7940
Input variables at t			
Insulin	-0.2145	0.0276	-7.7782
Insulin*Dummy fever	0.0783	0.0347	2.2541
Total carbohydrate calories	0.0257	0.0072	3.5634
Total fat calories	-0.0070	0.0057	-1.2248 *
Body temperature	0.1971	0.0881	2.2365 *
Glucocorticoids	-0.0019	0.0037	-0.5043 *
Adrenalin	-1.3072	1.3534	-0.9659 *
Noradrenalin	0.8073	0.9440	0.8551 *
Dobutamin	0.0153	0.0421	0.3627 *
Dopamin	0.1754	0.0745	2.3545
Beta-blockers	-0.0051	0.0149	-0.3418 *
Constant	-6.8497	3.2746	-2.0917 *

* This variable was not statistically significant (at a 95% level) after applying the full iterative process.

Table 6. Final Model $M_{\text{sel}}(n_a^*)$ containing only statistically significant variables.

Variables	Estimation	Std-Dev	t-stat
Glycemia at t	1.4960	0.0094	159.5903
Glycemia at *t-1*	-0.5690	0.0093	-60.9982
Insulin	-0.2131	0.0267	-7.9857
Insulin*Dummy fever	0.1044	0.0308	3.3859
Total carbohydrate calories	0.0336	0.0030	11.1282
Dopamin	0.2362	0.0697	3.3907

$R^2 = 0.9486$, dw = 1.9775, NMSE = 0.0514

4.2 Clinical Assessment

In this part the model coefficients are clinically interpreted and the clinical features are considered with respect to the generated model errors.

4.2.1. Model coefficients. As clinically expected, $\hat{b}_1 < 0$ and $(\hat{b}_1 + \hat{b}_2) < 0$. The increasing insulin resistance in case of fever is captured by $\hat{b}_2 > 0$. The latter causes a smaller glycemia decrease 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 $\hat{b}_{10}$ was also clinically expected, due to the features of the catecholamine drugs.

4.2.2. Clinical features. As noted above the in-sample NMSE for the model $M_{\text{sel}}(n_a^*)$ was 0.0514. In order to relate the model errors with the clinical features of each patient individually, the normalized average mean squared error (NAMSE_p) is calculated per patient p as follows:

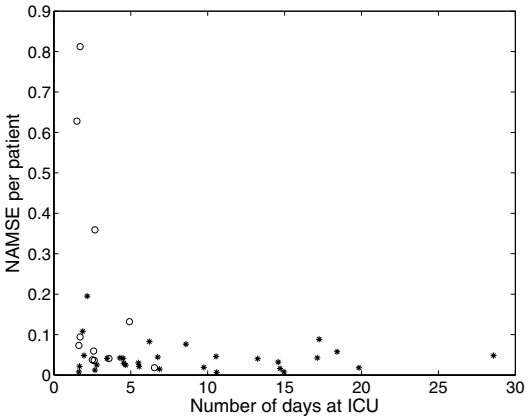

Fig. 2. The NAMSE_p as a function of the individual length of stay at ICU. Cardiac patients (indicated with o) typically stay for a shorter time period at ICU than the other patients (*) and cause larger NAMSE_ps than the other patient groups.

$$\text{NAMSE}_p = \frac{\sum_{t=3}^{N_{t,p}} (y_{t,p}^n - \hat{y}_{t,p}^n)^2}{(N_{t,p} - 2)} , \qquad (3)$$

where $N_{t,p}$ equals the number of data points per patient, and $y_{t,p}^n$ and $\hat{y}_{t,p}^n$ are the normalized actual and predicted glycemia, respectively. The NAMSE_p-values versus the length of stay are plotted for all patients in Figure 2. The different nature of patients influences the length of the stay at ICU.

It is easily seen that the model performs better for patients whose length of stay is more than five days. There are six patients whose NAMSE_p is above 0.1. Four of those patients belong to the cardiac surgery group. The latter patient group is typically characterized with shorter time periods at ICU than patient groups with other pathologies. Future research is needed for differentiating the model with respect to the reason for admission to ICU (or other clinical features).

CONCLUSION

In this paper we present an input-output model to predict glycemia of critically ill patients. Different dynamical input variables and an approach to the insulin resistance (by considering the body temperature) are implemented, in order to give the model a clinical interpretation. By using a methodology based on random partitions of the data between estimation and test sets, the optimal model order is found to be 2. The estimated coefficients show clinical relevance with respect to the behavior of glycemia in relation to insulin, insulin resistance, intake of carbohydrate calories, etc. The model results in a better performance for patients who stayed for more than five days at ICU (i.e., typically noncardiac patients). Further

research is required to relate the model performance to other patient features. A model that is more patient specific (taking into account those features) could also be an interesting potential to further increase the predictive model performance.

ACKNOWLEDGEMENTS

Tom Van Herpe, Marcelo Espinoza, Bert Pluymers (IWT) are research assistants, Frank De Smet is a post-doctoral research assistant, and Bart De Moor is a full professor with Katholieke Universiteit Leuven, Belgium. Greet Van den Berghe holds an unrestrictive Katholieke Universiteit Leuven Novo Nordisk Chair of Research. KUL research is supported by Research Council KUL: OT 03/56, GOA AMBioRICS, several PhD/postdoc & fellow grants; Flemish Government:FWO: projects, G.0278.03, G.0407.02, G.0197.02, G.0141.03, G.0491.03, G.0120.03, G.0413.03, G.0388.03, G.0229.03, G.0452.04, G.0499.04, G.0499.04, IWT: PhD Grants, GBOU-McKnow, GBOU-SQUAD, GBOU-ANA; Belgian Federal Science Policy Office: IUAP P5/22; EU-RTD: FP5-CAGE; ERNSI; FP6-NoE Biopattern; FP6-IP e-Tumours.

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