CHALLENGES IN DATA-BASED PATIENT MODELING FOR GLYCEMIA CONTROL IN ICU-PATIENTS

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ABSTRACT
In this paper, we investigated the possibility of designing a system to control glycemia, i.e. the blood glucose concentration, in patients admitted in an Intensive Care Unit. The system consists of a patient model and a controller. This paper describes the first results of data-based patient modeling. System theoretically, the identification problem was considered to be open-loop. Two input-output models were discussed: an AutoRegressive with eXogeneous inputs (ARX) and a Prediction-Error-Model (PEM). Glycemia simulations applied to a training set resulted in an acceptable performance. ARX-models outperformed PEM-models. However, the use of these models on a validation set was clinically not yet feasible due to large glycemia errors. Future research is needed to develop a more accurate patient model.

KEY WORDS
Patient modeling, Intensive Care Unit, glycemia, ARX, PEM.

1. Introduction

This paper considers a control system for the blood glucose concentration (i.e. glycemia) of patients who are admitted in an Intensive Care Unit (ICU). Recently a manuscript was published in The New England Journal of Medicine [1] in which the authors report the effects of *intensive* insulin therapy in critically ill patients requiring intensive care (including mechanical ventilation) mostly after major surgery. It is known that insulin resistance and associated hyperglycemia are common in such patients (even if they have not had diabetes before). In the past, this was ignored because it was believed that hyperglycemia was a beneficial reaction to stress. In that *conventional* insulin therapy, insulin was only infused if glycemia exceeded 215 mg per deciliter, after which maintenance of glycemia between 180 and 200 mg per deciliter was persued.

In the clinical study mentioned above (with more than 1500 patients), it is shown that normalization of glycemia (between 80 and 110 mg/dl = normoglycemia) results in a spectacular reduction in mortality and morbidity through a rigorous administration of insulin. 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%.

In Figure 1 the manual control of a patient's glycemia is shown. In this example glycemia was measured every 3 minutes as described later in this paper. For the moment, the administration of insulin in intensive care patients is controlled by a **labor intensive** (considerable workload for the nurses) and **empirical** protocol (in which a certain degree of freedom, depending on the human experience, is still present).

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 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 the 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 (e.g. 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, medical history) can influence the reaction to insulin administration.

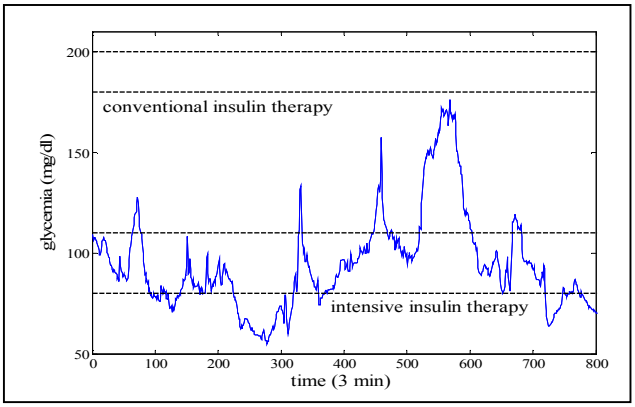

Figure 1. Example of glycemia data of a patient (who received intensive insulin therapy) as a function of time. Glycemia is measured every 3 minutes. This sampling frequency is not yet common.

In this paper we considered the first results of the development of a control system that adapts the flow of the insulin infusion using the measurements of the blood glucose levels. This system could (continuously or discontinuously) advise the medical team (physicians or nurses) about the desired insulin administration rate or can, after further validation, apply a more automatic control.

2. General solution strategy

Figure 2 gives a global overview of the system. Three main parts can be recognized:

1. **Sensor:** Arterial glycemia is measured every 4 hours. However, this paper uses subcutaneous glycemia data measured every 3 minutes. The sensor used is one of A.Menarini Diagnostics and is being validated by K.U. Leuven. In case of frequent retrospective calibrations with arterial glycemias, these subcutaneous measurements may be used for this study.

2. **Control system:** The control system consists of 2 subparts. The first one is the ***patient model***. This model represents a "mathematical" patient. It allows to predict glycemia of a specific patient, taking into account complicating factors such as the ones described above. The patient model consists of a number of model parameters that are very *patient specific*. The model structure and its parameters are determined by using input-output data that had been gathered before. The second subpart is the ***controller*** itself. It determines the rate of insulin a certain patient needs, taking into account the disturbance factors described above.

3. **Actuator:** The actuator is the insulin pump that will administer the insulin to the patient. In a first phase this will be done semi-automatically, i.e. after *confirmation* of the advised insulin flow. In a second phase this process can be performed automatically.

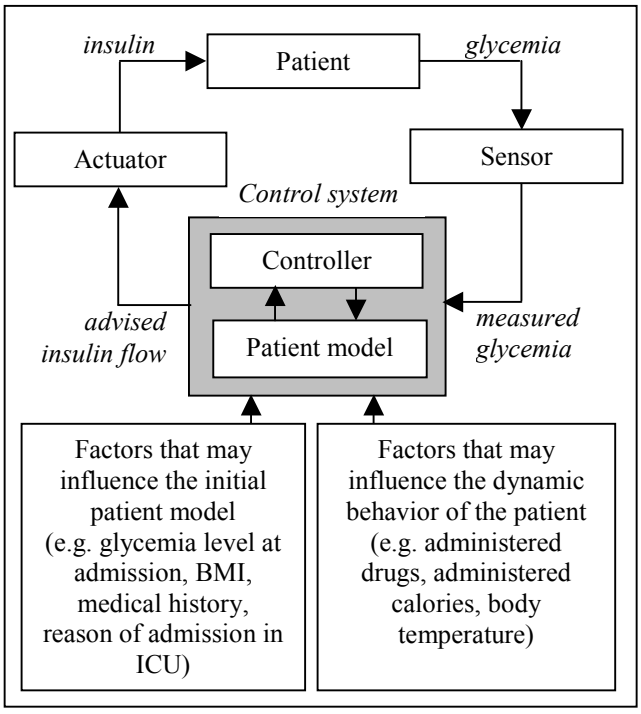

Figure 2. Global overview of the system.

This paper describes the first research results towards an accurate patient model. Some research has already been done in the field of glycemia control for (type I –) diabetics. The glycemia control aim within this latter patient group is comparable with that of ICU-patients, although there are some important differences. Most research activities in diabetic control are based on physical compartmental models [2,3,4,5]. However, these models are hardly clinically feasible due to high uncertainty rates [6]. This problem could be overcome by using data-based modeling. However, as is indicated in this paper, black-box modeling should further be improved.

3. Data description

The development of the ICU – patient model is based on input-output-data of a randomized group of 14 patients. During the first 40 hours of their stay in ICU the subcutaneous glycemia (output) is measured every 3 minutes. Besides these semi-continuous measurements arterial glycemia is measured every hour during the first day and every 4 hours during the second day in order to calibrate the subcutaneous measurements retrospectively.

In a first research phase, 10 different input variables that may influence glycemia, are taken into account [7]. The first and probably most important input is the insulin flow. This is the single input that can be regulated by the control system. The other inputs are known, but cannot be used to *control* glycemia. Nurses and doctors determine their rates or they are autonomous.

The second main input is the group of the administered calories. It consists of 4 subinputs: the number of carbohydrate calories and the number of fat calories that are administered intravenously (parenteral infusion, PI), and the number of carbohydrate calories and the number of fat calories that are delivered by enteral infusion (EI).

Administered drugs form the third main input. Again, there are 4 subinputs: the group of corticoids, noradrenalin, dobutamin and beta-blockers. Finally, body temperature is taken into account, as well, because of its relation with illness and, consequently, possibly with increased glycemia.

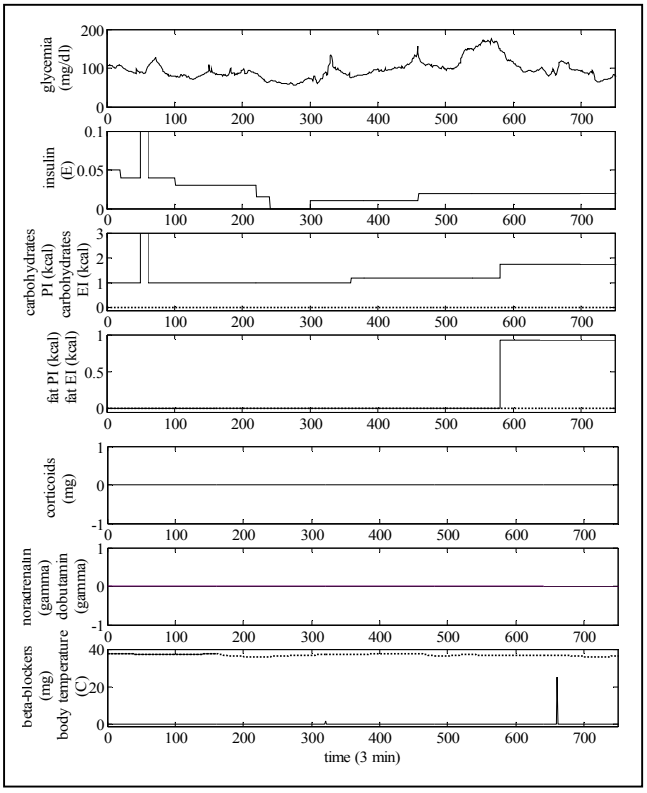

Figure 3. Data of one patient. The upper part represents glycemia (output). The 6 plots below are the 10 input variables that may influence glycemia.

In Figure 3 an example of all the input variables is shown for one patient. Clearly, glycemia fluctuates much more than the input variables do. The entropy of the output is much higher than the entropy of the inputs. This can probably be attributed to unknown or unmeasurable input variables that significantly influence glycemia.

4. Patient model

The main part of the control system is the patient model. An accurate patient model is necessary for a well performing control system. Ideally, a general patient model that is accurate for all ICU-patients or for a subgroup of this population should be developed. In a first research phase we attempted to construct a patient model based on the clinically available data.

The entire system was approximated to be *open-loop*. However, in fact the system is *closed-loop* due to the influence of previous glycemia levels on future settings for the insulin flow, determined by nurses and doctors. In the near future, closed-loop modeling will be considered. Possibly, this will result in a more accurate patient model than the one that is constructed by applying the open-loop approximation [8].

The sampling frequency of the output (20 times per hour) is much higher than that of the different input variables (at most once per hour). Different open-loop model identification approaches have been investigated, although in this paper we emphasize only two of them: autoregressive models with exogeneous inputs (ARX) and Prediction-Error-Models (PEM).

4.1 ARX

The input-output correlation can be described by means of a linear difference equation:

$$y_{k+1} = a_1 y_k + a_2 y_{k-1} + \ldots + a_n y_{k-n+1} + b_1 u_k + b_2 u_{k-1} + \ldots$$
$$\ldots + b_m u_{k-m+1} + \sum_{j=1}^{Z}\left[c_1^j v_k^j + c_2^j v_{k-1}^j + \ldots + c_m^j v_{k-m+1}^j\right] + e_{k+1} \quad (1),$$

where:

- y_k = glycemia (output) at time k,
- u_k = insulin rate between k and k+1,
- v_k^j = value of known factor j that may influence the dynamic behavior of the patient at time k (e.g. administered glucocorticoids at time k, administered number of calories at time k),
- a_i, b_i, c_i^j = model parameters,
- Z = number of factors that are considered in the model,
- e_{k+1} = error, i.e. the difference between predicted glycemia at k+1 and real glycemia at k+1.

Figure 4 and 5 show the results of a simulation applying an ARX-model on the same patient. Figure 4 considers glycemia simulations on the full dataset of the patient. The ARX-model parameters were first determined by using the same dataset. Consequently, the *training set* and the *validation set* are both the same. In the same figure,

glycemia simulations based on *general* ARX-model parameters are shown as well. These general parameters were calculated based on the data of 14 different patients, including the patient whose data are shown. Both glycemia simulations (individual and general ARX-model) have a comparable performance.

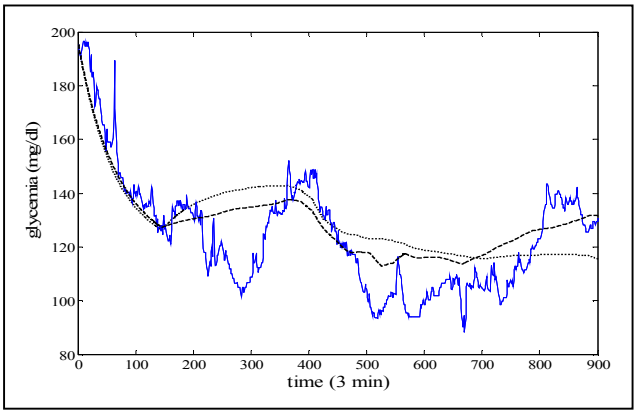

Figure 4. Simulation of glycemia applying ARX on the full dataset of a specific patient. The solid line represents real glycemia, the dashed line represents simulated glycemia based on an individual ARX-model (3th order) and the dotted line represents a simulation based on a general ARX-model (3th order) (constructed with a dataset of 14 patients).

In Figure 5, glycemia simulations for the same patient as in Figure 4 are shown. In this case, however, the data of this patient were divided into two parts. The first two-thirds of the dataset, i.e. the *training set*, were used to determine the model parameters. The last third is called the *validation set* and was used to 'validate' the model parameters derived from the training set. In Figure 5, only the validation set is visualized.

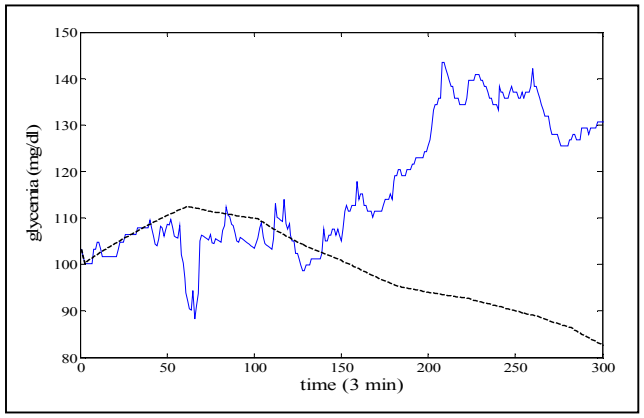

Figure 5. Simulation of glycemia using ARX on a validation set (last third of data) of the same patient as in Figure 4. The solid line represents real glycemia and the dashed line represents simulated glycemia based on the individual ARX-model that was constructed by using the first two-thirds of data of this patient (3th order).

These validation results (Figure 5), however, indicate the use of simple ARX-models alone is not feasible in clinical practice. This was proven by applying a modified *Bland-Altman-analysis*.

The Bland-Altman-analysis is a statistical method for assessing the agreement between two clinical values [9]. The difference between real and simulated glycemia (i.e. glycemia error) and the mean of those two values (both at each time step) are plotted. In this analysis, the measurements themselves (i.e. real and simulated glycemia) are not required to follow a normal distribution; however the differences are. Since the distribution of these differences turned out to be not 'normal', we applied a *modified* Bland-Altman-analysis (Figure 6). Hence, the 10 (P10) and 90 (P90) percentiles of glycemia errors were determined instead of the standard deviation of glycemia errors.

In Figure 6 the P10 and P90-limits (prediction bounds) are also shown. The value of P10 and P90 indicate the *clinical relevance*. P10 and P90, respectively –5,5 and 47,0 mg/dl, were calculated based on the validation data of the patient who was considered in Figure 5. The mean of glycemia errors for these data is 16,8 mg/dl. Especially the high P90-value is not acceptable to use this ARX-model in clinical practice.

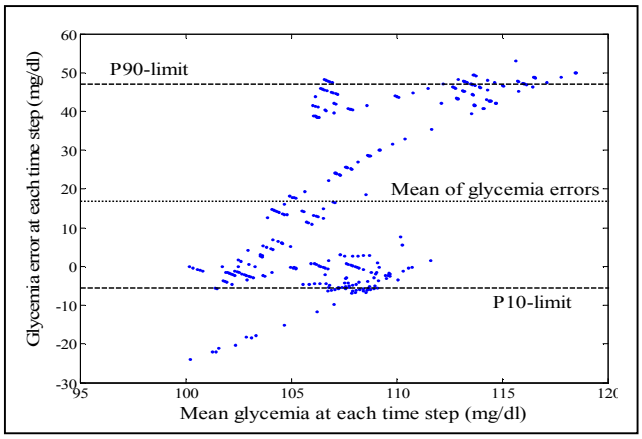

Figure 6. A modified Bland-Altman-analysis that considers the clinical relevance of the validation results shown in Figure 5. The P90-value of glycemia errors (47,0 mg/dl) indicates the developed ARX-model is not feasible in clinical practice.

The reason for the validation failure is that ARX models do not take into account any noise influences. Consider a certain amount of output noise w_k that is added to a system without inputs. In this case, the resulting AR-model (i.e. without exogeneous inputs) is then given by:

$$y_{k+1} + w_{k+1} = \sum_{i=1}^{n} a_i (y_{k-i+1} + w_{k-i+1}) + e_{k+1}$$

$$y_{k+1} = \sum_{i=1}^{n} a_i (y_{k-i+1}) + \sum_{i=1}^{n} a_i (w_{k-i+1}) + e_{k+1} - w_{k+1} \qquad (2).$$

The underlined part of Equation (2) is the noise term that is not being modeled using AR. Model classes such as AR and ARX, are restrictive. A certain bias does exist. A general model, like a PEM-model, could give better results [10].

4.2 PEM

A PEM-model is the sum of a deterministic subsystem and a stochastic subsystem. It allows to model the noise term which could probably result in a model with higher performance. The general model structure is given by:

$$A(q).y_k = \frac{B(q)}{F(q)}.u_k + \frac{C(q)}{D(q)}.e_k \qquad (3),$$

where: $A(q) = 1 + a_1.q^{-1} + ... + a_{n_a}.q^{-n_a}$,

$B(q) = b_1 + ... + b_{n_b}.q^{-n_b+1}$,

$C(q) = c_1 + ... + c_{n_c}.q^{-n_c+1}$,

$D(q) = d_1 + ... + d_{n_d}.q^{-n_d+1}$,

$F(q) = f_1 + ... + f_{n_f}.q^{-n_f+1}$.

However, applying this model does not guarantee better results, as is shown in Figure 7 in which glycemia of the patient of the former example is simulated.

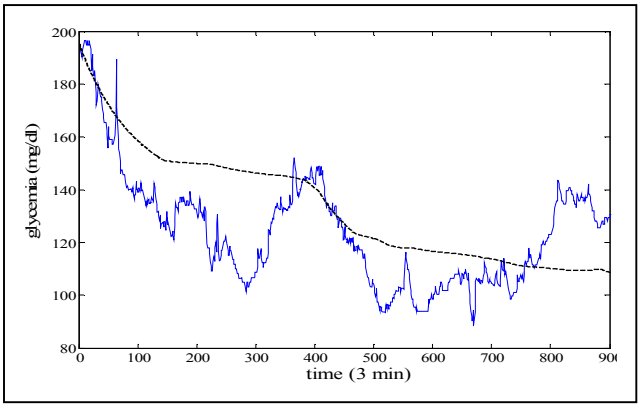

Figure 7. Simulation of glycemia applying PEM on the full dataset of a specific patient. The solid line represents real glycemia; the dashed line simulated glycemia based on an individual PEM –model (3th order).

4.3 Model comparison

Calculating the prediction error (PE) is a technique to validate different simulations. The use of the PE results in a comparison between different models. The PE can be calculated as follows:

$$PE = \sum \left[\frac{(y_{prediction} - y_{real})^2}{y_{real}^2} \right] \qquad (3).$$

In Table 1 the PEs are shown for each patient. The mean PEs for ARX and PEM-simulations are 12,8 and 25,8 respectively; the standard deviations 5,1 and 24,9. To compare the two sets of PEs, we applied the Wilcoxon signed rank test which resulted in a p-value of 1,22e-4. This value indicates that ARX-models result in a better performance than PEM. In case two outliers (patient 7 and 10) are removed from the dataset, the resulting p-value remains small (4,88e-4).

As described above, PEM-models are more complex than ARX-models. Since the number of parameters increases with the complexity degree of the model and the dataset is not enlarged, the *variance* on the model parameters increases as well. This could be the reason why the performance of PEM is worse despite the more complete model structure.

Theoretically, the use of *non-linear* models could result in a more accurate glycemia simulation. However, the compexity degree of such models is even higher and the results will be even worse than with PEM-models. In the near future more data will be available and the use of these more complex models will be feasible.

Table 1. Prediction Errors of each patient applying ARX and PEM simulation on the full dataset.

Patient	*ARX (3th order) (%)*	*PEM (3th order) (%)*
1	14.5	17.3
2	14.3	14.7
3	10.0	15.2
4	11.6	16.2
5	10.1	15.7
6	7.9	12.4
7	9.6	91.0
8	13.1	15.9
9	10.1	14.2
10	15.1	74.7
11	27.6	32.9
12	10.5	11.8
13	16.9	18.9
14	8.0	10.7

5. Conclusion

This paper discussed the results of two input-output models (ARX and PEM) used to model a patient in ICU. Both models showed fairly good results in case the simulation was executed on the *training* set of each patient seperately. As proven by calculating the prediction error, ARX-models outperformed PEM-models. The latter

ones typically need more patient data to develop an accurate model.

Simulations performed on a *validation* set, however, showed that ARX-models were not yet ready to be used in clinical practice. A possible reason for this failure could be the open-loop identification of what is essentially a closed-loop system. Future adaptations will take the control behavior of the nurse into account. When more patient data will be available, non-linear models will be developed as well.

6. Acknowledgements

Tom Van Herpe is a research assistant at Katholieke Universiteit Leuven, Belgium. Ivan Goethals is a research assistant with the F.W.O. at the Katholieke Universiteit Leuven, Belgium. Bert Pluymers is a research assistant with the I.W.T. Flanders at the Katholieke Universiteit Leuven, Belgium. Frank De Smet is a post-doctoral research assistant at the Katholieke Universiteit Leuven, Belgium. Greet Van den Berghe holds an unrestrictive Katholieke Universiteit Leuven Novo Nordisk Chair of Research. Bart De Moor is a full professor with Katholieke Universiteit Leuven, Belgium.

KUL research is supported by Research Council KUL: OT 03/56, GOA-Mefisto 666, GOA AMBioRICS, several PhD/postdoc & fellow grants; Flemish Government:FWO: PhD/postdoc grants, projects, G.0278.03, G.0240.99, G.0115.01, 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, research communities (ICCoS, ANMMM, MLDM); AWI: Bil. Int. Collaboration Hungary/ Poland; IWT: PhD Grants, STWW-Genprom, GBOU-McKnow, GBOU-SQUAD, GBOU-ANA; Belgian Federal Science Policy Office: IUAP P5/22; PODO-II; EU-RTD: FP5-CAGE; ERNSI; FP6-NoE Biopattern; FP6-IP e-Tumours, FP5-Quprodis; Eureka 2063-IMPACT; Eureka 2419-FliTE; Contract Research/agreements: ISMC/IPCOS, Data4s, TML, Elia, LMS, Mastercard.

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