Prediction Performance Comparison between three Intensive Care Unit Glucose Models

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Abstract: In this paper the prediction performance of two models that were particularly developed for predicting the blood glucose signal in critically ill patients, and a third (rather 'naive') model were compared. The imposed real-life conditions were challenging as the prediction processes started at time step 1 (comparable to the admission of a patient at the intensive care unit) and the prediction horizon was set at 4 hours (although accurate prediction of the blood glucose signal in the initial phase after admission is difficult due to lack of patient-specific data). The results of one of the models was satisfactory in terms of forecasting ability and showed its potential to be validated for use in a predictive control system in real-life.

Keywords: *Intensive Care Unit, Glucose, Insulin, Model, Prediction.*

1. INTRODUCTION

Critically ill patients, typically admitted to the intensive care unit (ICU), show hyperglycaemia and insulin resistance associated with adverse outcomes. It has been demonstrated that strict blood glucose control results in an important reduction in mortality and morbidity with adult and paediatric intensive care unit patients (Van den Berghe et al. [2001], Van den Berghe et al. [2006], Vlasselaers et al. [2009]). Current therapy requires a manual and rigorous administration of insulin ('intensive insulin therapy') by following a set of guidelines aiming at blood glucose levels between 80 and 110 mg/dl for adults, between 50 and 80 mg/dl for infants and between 70 and 100 mg/dl for children.

Although the clinical advantages of intensive insulin therapy are abundantly present, its implementation in intensive care units world-wide is not straightforward (NICE-SUGAR Study Investigators [2009], Brunkhorst et al. [2008], Devos et al. [2007]). Moreover, the workload for the medical personnel increases compared to conventional insulin therapies. Therefore, we want to design a semi-automated predictive control system for normalizing the blood glucose in the critically ill. Such a control system can potentially reduce the workload and lead to the implementation of tight glycemic control (and the related reduction of mortality and morbidity) world-wide. The control system that we are developing comprises a patient model and a predictive controller. The used patient model ('model 1', or more specifically the Intensive Care Unit - Minimal Model, Van Herpe et al. [2007]) is typically used for predicting the blood glucose signal in the critically ill whereas the controller (more specifically a Model based Predictive Controller) optimizes the insulin flow that is administered to the patient (Haverbeke et al. [2008]). The potential of a similar predictive control strategy (but with a different model: 'model 2') has recently been shown in clinical practice (Cordingley et al. [2009], Hovorka et al. [2007]).

The prediction performances of the above mentioned two models and a hypothetical 'naive' model ('model 3') are compared in this paper using a real-life clinical ICU data set where the blood glucose was hourly measured. The ICU data set, the structure of the different models, and the design of the study are described in Section 2. Finally, the results are discussed in Section 3.

2. MATERIALS AND METHODS

In this section the clinical ICU data set is described and the model structures under study are briefly introduced. Next, the used blood glucose prediction procedure is explained in detail.

2.1 ICU Data set

The data consist of 15 adult patients who were treated with the intensive insulin therapy (80-110 mg/dl as target blood glucose range). During the first two days of their stay in the ICU, whole-blood glucose in undiluted arterial blood was measured every hour using the ABL700 Radiometer Medical (Denmark) glucose analyser. After these two intensive sampling days, blood glucose was monitored with a lower sampling frequency (following the general guidelines from the Leuven tight glycemic control protocol). These additional data, however, were not considered in this data set, for the purpose of this study. Therefore, the length of the data set of each patient was limited to the first 50 hours. Table 1 gives an overview of the study population with some important clinical characteristics.

Table 1. Patient population.

Variable	Value
Number of patients - no	15
Male sex - no (%)	9 (65.0)
Age - yr (std-dev)	70.0 (12.6)
BMI [(1)] - kg/m^2 (std-dev)	25.6 (5.8)
Reason for intensive care - no (%)	
Cardiac surgery	10 (66.7)
Complicated abdominal surgery or peritonitis	5 (33.3)
APACHE II score [(2)] (first 24 hr) (std-dev)	18 (4)
Mean blood glucose - mg/dl (std-dev)	101 (23)
Minimal blood glucose - mg/dl	37
Maximal blood glucose - mg/dl	214
Mean duration of stay in ICU - hr (std-dev)	47 (4)
Minimal duration of stay in ICU - hr	36
Maximal duration of stay in ICU - hr	50

[(1)] The body mass index (BMI) is the weight in kilograms divided by the square of the height in meters.
[(2)] The APACHE II score (Acute Physiology and Chronic Health Evaluation) 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.

2.2 Intensive Care Unit - Minimal Model (ICU-MM): 'Model 1'

The first model structure originates from the known *minimal* model developed by Bergman and colleagues (Bergman et al. [1981]). In Van Herpe et al. [2007], the original minimal model was extended to the ICU-MM aiming to predict the blood glucose in critically ill patients. The ICU-MM was already validated on a real-life clinical ICU data set in which the subcutaneous glucose concentrations were near-continuously (i.e., every three minutes) measured. Such monitoring devices, however, are not yet prepared to measure glycemia sufficiently accurate and reliable in this type of patients. Therefore, the presented model structure and the proposed estimation technique are validated here on a new (more realistic) real-life clinical ICU data set in which glycemia was hourly measured (see above). A successful validation of the patient model on this data set is the last step before the full control system (i.e., patient model and predictive controller) can be tested under real-life circumstances (hourly blood glucose measurements).

The structure of the ICU-MM (with 4 state variables) is presented as follows:

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

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

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

$$\frac{dI_2(t)}{dt} = \beta \ \gamma \ (G(t) - h) - nI_2(t), \tag{1d}$$

where G and I_1 denote the glucose and the insulin concentration in the blood plasma. The second insulin variable, I_2, approaches the fraction of insulin concentration derived from the endogenous insulin secretion. The variable X describes the effect of insulin on net glucose disappearance and is proportional to insulin in the so-called "remote" compartment. The symbols G_b and I_b represent the basal value of plasma glucose and plasma insulin, respectively. The model consists of two input variables: the intravenously administered (exogenous) insulin flow (F_I) and the parenteral carbohydrate calories flow (F_G). The glucose distribution space and the insulin distribution volume are denoted as V_G and V_I, respectively.

The ICU-MM comprises seven coefficients that are (re-) estimated at each time instant: P_1 (glucose effectiveness when insulin remains at the basal level), P_2 (fractional rate of net remote insulin disappearance), P_3 (fractional rate of insulin dependent increase), h (glucose threshold level), n (time constant for insulin disappearance), α (scaling factor for the second insulin variable), and finally γ (degree by which glycemia exceeds the glucose threshold level). In order to keep the correct units, an additional model coefficient, $\beta = 1$ min, was added.

The set of coefficients characteristic of the obese and low glucose tolerance patient group that is described in (Bergman et al. [1981]) is used for the initial estimation process. This patient group is mostly comparable to ICU patients with regards to insulin resistance. The units of all used variables and parameters and their initial coefficient values are represented in Table 2.

2.3 ICU Simulation model: 'Model 2'

Recently a different model of glucoregulation for the critically ill, particularly aimed for simulation purposes, was presented (Hovorka et al. [2008]). This model structure includes five submodels: a submodel of endogenous insulin secretion, a submodel of insulin kinetics, a submodel of enteral glucose absorption, a submodel of insulin action and a submodel of glucose kinetics. Since the size of the model is much larger and its complexity level much higher (19 model parameters to be estimated) than the previously described ICU-MM, and since space in the paper is limited, we prefer to refer to the original article in which the model is explained in detail. Important to note is that the model contains 9 state variables: the blood glucose (G), the plasma insulin concentration (I), the absorption of enteral glucose (A_1 and A_2), three actions of insulin on glucose kinetics (x_1, x_2, and x_3), and finally the glucose kinetics themselves (Q_1 and Q_2).

Table 2. Variables, patient features, and coefficient values applicable in the ICU-MM.

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 (body weight)	
V_G	dl	BM*1.6 (Hovorka et al. [2004])	
V_I	ml	BM*120 (Hovorka et al. [2004])	
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.

Similar to the ICU-MM, only the administered insulin flow and the carbohydrate content of parenteral and enteral nutrition are input variables of the model.

2.4 Hypothetical 'naive' model: 'Model 3'

The 'naive' prediction model keeps the blood glucose constant for the specified prediction period (i.e., 4 hours for this work). This prediction method can be considered as a worst-case prediction scenario that should be outperformed by the models 1 and 2 that are especially designed for glycemia prediction in the critically ill.

2.5 Study design

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 the nursing staff is a prerequisite. This set of guidelines requires blood glucose levels to be measured every four hours or even hourly in the initial phase or after complications. In this study the prediction horizon was set at 4 hours as the predictive control system should be able to give an appropriate insulin flow advice to the nurse for this period. However, we acknowledge that in real-life the blood glucose is measured more frequently during the first hours of a stay in the ICU (due to the instability of the patients). Still, we opted to challenge all three models under 'difficult' conditions. Accordingly, model predictions were also started at time step 1. In other words, glucose predictions in the first prediction period were only based on initially assigned model coefficients (originated from the available literature). Next, the models were (re-)estimated using the past patient-specific data for the coming prediction horizons.

Estimations and re-estimations of model 1 and 2 were done by minimizing the squared *normalized* errors between the simulated and observed glycemia trajectories (by using non-linear least squares, Matlab®-function 'fminsearch'). The errors were normalized to make the severity of error independent of the actual blood glucose value. The used normalization function was based on the International Organisation for Standardization - criterion (ISO [2003]) which is a standard criterion used for assessing glucose sensors. This criterion can be summarized as follows:

- for reference sensor values $\leq$75 mg/dl the value resulting from the test sensor is required to fall within $\pm$15 mg/dl limits,
- for reference sensor values >75 mg/dl the target variability is defined as $\pm$20%.

Next, the used normalization function is formulated as follows:

$$u_{t,p} = f(G_{t,p} - \hat{G}_{t,p}) = \frac{1}{15}[G_{t,p} - \hat{G}_{t,p}] \quad \text{if } G_{t,p} \leq 75\text{mg/dl}, \tag{2a}$$

$$u_{t,p} = f(G_{t,p} - \hat{G}_{t,p}) = 5[\frac{G_{t,p} - \hat{G}_{t,p}}{G_{t,p}}] \quad \text{if } G_{t,p} > 75\text{mg/dl}, \tag{2b}$$

where $G_{t,p}$ is the actual and $\hat{G}_{t,p}$ the predicted glycemia value of patient p at time t. The *normalized* glycemia error is called $u_{t,p}$. An error violating the ISO-criterion translates to an absolute normalized error ≥ 1 (Van Herpe et al. [2008]). Further, the mean squared normalized error is denoted as:

$$\text{MSnE}_p = \sum^{N} \frac{(u_{t,p})^2}{N}, \tag{3}$$

where N represents the number of evaluation points (i.e., the size of each patient-specific data set).

Models 1 and 2 were re-estimated every 4 hours ($P = 4$ hours). The number of recent data that were considered in each re-estimation process is called the Back-In-Time (BIT) number and may influence the performance of the model. The starting parameters in each optimization process were the coefficient values described in the available literature (for model 1: Bergman et al. [1981]; for model 2: Hovorka et al. [2008]). The initial state variables for model 1 were defined as: $\hat{G}(0) = G(0)$, $\hat{X}(0) = 0$, $\hat{I}_1(0) = I_b$, and $\hat{I}_2(0) = 0$. Next, the initial state variables for model 2 were set as follows: $\hat{G}(0) = G(0)$ and $\hat{A}_1(0) = \hat{A}_2(0) = 0$. For the remaining state variables steady-state conditions were assumed: $\frac{\mathrm{d}I(0)}{\mathrm{d}t} = \frac{\mathrm{d}x_1(0)}{\mathrm{d}t} = \frac{\mathrm{d}x_2(0)}{\mathrm{d}t} = \frac{\mathrm{d}x_3(0)}{\mathrm{d}t} = \frac{\mathrm{d}Q_1(0)}{\mathrm{d}t} = \frac{\mathrm{d}Q_2(0)}{\mathrm{d}t} = 0$ (Hovorka et al. [2008]).

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

(1) For both model structure 1 and model structure 2:
  (a) For BIT $= 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 20,$ and 25 hours:
    (i) Re-estimate the model based on every last section (i.e., BIT) of the (moving) data set with starting set of coefficients the values obtained from the available literature. Consider the full past data when the passed data

set size (in the initial phase) is smaller than BIT.

(ii) Predict the glycemic course for the next period P (which is the validation set of the re-estimated model in this case). Recall that the only measured state variable is the blood glucose (G), meaning that the glucose signal *in the first prediction horizon* is mainly predicted with the literature coefficient values as no estimation data are available then.

(iii) Compute the root mean squared normalized error (RMSnE_p) for all validation sets per patient p by computing the square root of MSnE_p.

(b) Compare the RMSnEs generated for the different BITs. The BIT that belongs to the smallest RMSnEs (and preferably with a small distribution of RMSnEs) is called 'optimal' and is ideally used in the re-estimation process.

(2) Compare the distributions of smallest RMSnEs for model structure 1 and 2, and additionally for the 'naive' model structure 3.

We want to stress that no model estimations were performed for model 3 as the glycemia predictions were based on keeping the previous blood glucose constant for the next prediction horizon (4 hours). Finally, the Wilcoxon signed rank test was used to test significant differences (significance level 5%).

3. RESULTS AND DISCUSSION

In this section the prediction performance of the three models under study are compared and discussed.

3.1 Results

Figures 1 and 2 give an overview of the computed RMSnEs as a function of BIT for model 1 and model 2, respectively. The optimal BIT was found to be 7 hours for model 1 as the set of RMSnEs was the smallest in that case. The average RMSnE (std-dev) that was obtained when applying this 'optimal' re-estimation strategy was 0.78 (0.26). In case of model 2, the optimal BIT was found to be 10 hours (small RMSnE values, smallest distribution of RMSnEs) resulting in an average RMSnE (std-dev) equal to 1.1 (0.27). Finally, the average RMSnE (std-dev) for model 3 was 0.92 (0.34).

Figure 3 presents the best prediction performance results of model 1 (BIT = 7 hours) and model 2 (BIT = 10 hours) versus the 'naive' model 3. A statistical difference was found between the sets of RMSnEs corresponding to model 1 and model 2 ($p < 0.05$) and between the sets of RMSnEs corresponding to model 1 and model 3 ($p < 0.05$). No statistical difference was found between the sets of RMSnEs corresponding to model 2 and model 3 ($p \geq 0.05$).

Figure 4 represents the real-life glucose evolution (solid line) of patient no. 11, hourly measured with the ABL700 Radiometer Medical glucose analyser and linearly interpolated. The glucose prediction behaviour of model 1 is represented by the dashed line whereas the predicted glucose signal of model 2 is denoted by the dashed-dotted line.

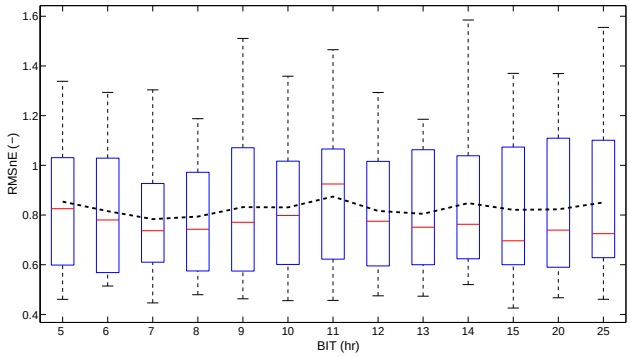

Fig. 1. Set of distributions of the RMSnEs (generated for each patient) as a function of BIT with re-estimations every four hours (P = 4 hours) for model 1. The dashed line connects the averages of the RMSnEs. Re-estimations based on the last 7 hours data set (BIT = 7) result in the smallest prediction errors.

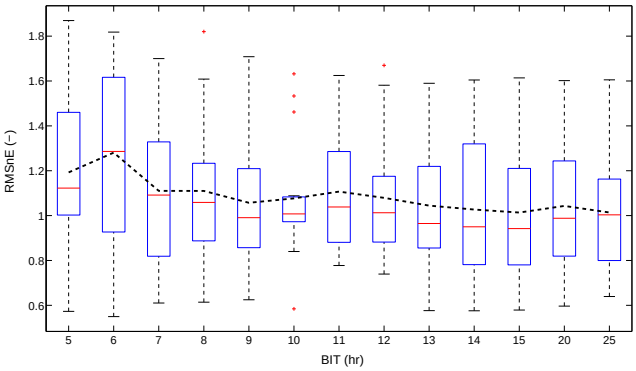

Fig. 2. Set of distributions of the RMSnEs (generated for each patient) as a function of BIT with re-estimations every four hours (P = 4 hours) for model 2. The dashed line connects the averages of the RMSnEs. Re-estimations based on the last 10 hours data set (BIT = 10) result in the smallest prediction errors.

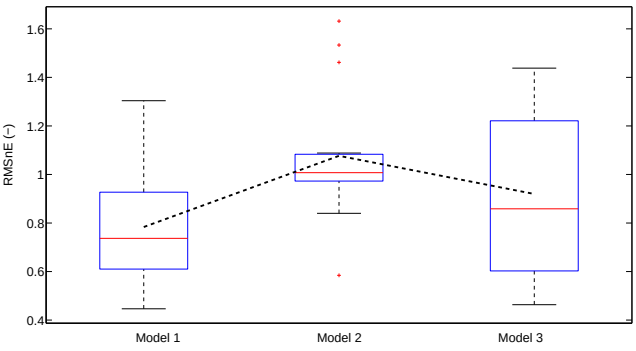

Fig. 3. Comparison between the distributions corresponding to the best prediction performances of model 1 (left) and model 2 (middle) versus the 'naive' model 3 (right). The dashed line connects the averages of the RMSnEs.

Further, the glucose signal that was kept constant during each prediction period (model 3) is illustrated with the dotted line. Finally, it is easily observed that models 1 and 2 were (re-)estimated every 4 hours ($P = 4$ hours) and, at those time-instants, that the predicted glucose signal was reset towards the measured (known) blood glucose value.

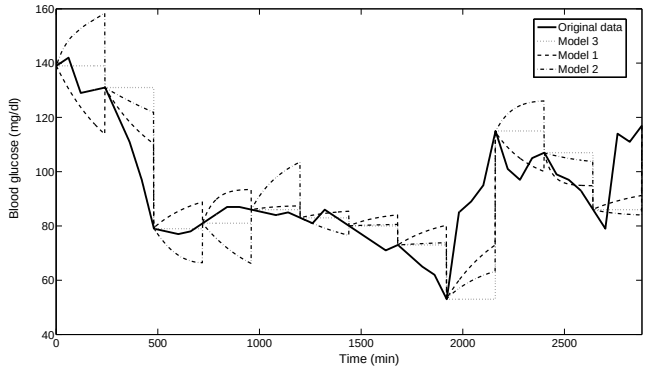

Fig. 4. The blood glucose signal of patient no. 11, measured with the ABL700 Radiometer Medical glucose analyser, is presented by the solid line. Glucose predictions are illustrated with a dashed line for model 1, a dashed-dotted line for model 2, and a dotted line for model 3. It is important to note that glucose predictions *in the first prediction horizon* (till time $t = 240$ min) were only based on model coefficient values from the available literature (no estimation data available in the beginning). The RMSnE for this patient equals 0.63 for model 1 (BIT = 7 hours).

3.2 Discussion

First of all, it is important to note that a normalization function (based on the ISO-criterion) was used in the cost function (minimization of MSnE) and in the evaluation process (computation of RMSnE). This clinically defined ISO-criterion is a standard norm for the binary assessment of the accuracy of glucose sensors. However, the accuracy requirements of a test *sensor* device, which is assessed by considering its signal toward the concomitantly measured reference (or gold standard) sensor values, are in fact comparable to the prediction performance requirements of a *model*. Indeed, both sensor and model are crucial elements in (future) predictive control systems in terms of determining the optimal insulin flow to be administered to the patient. Therefore, we recommend to use this normalization function in a cost function (for estimating glucose models) or as assessment procedure (for evaluating glucose models) rather than traditional methods. These traditional methods (e.g., mean squared error, mean percentage error) typically lack clinical interpretation and/or underestimate hypoglycemic errors (Van Herpe et al. [2008]).

Secondly, it can be observed that the set of RMSnEs of model 1 was significantly smaller than the set of RMSnEs corresponding to model 2 and 3. Therefore, it can be concluded that model structure 1 outperformed models 2 and 3 for this ICU data set (15 patients). Statistically no difference was found between model 2 and the 'naive' model 3. This indicates that the glucose prediction performance using the 'naive' model 3 is similar to the prediction performance obtained with model 2 (which was particularly designed for simulating virtual ICU patients). This unexpected result may be caused by the limited size of the data set but possibly also by the high complexity level of the model that may have led to overfitting.

Thirdly, the majority (80%) of the RMSnEs of model 1 were smaller than 1 indicating that this model suited the predefined ISO accuracy requirements (see above). It is important to stress that the model predictions started already at time step 1 (i.e., comparable to a real-life situation where the blood glucose of a new patient entering the ICU should be controlled from the beginning). This also means that no data were available to train the model for the first prediction horizon. Moreover, compared to a similar study concerning the model prediction performance of model 1 (Van Herpe et al. [2007]), no semi-continuous glucose sensor was available here (only time-discrete measurements were used as no reliable semi-continuous sensor could be validated for use in the ICU so far). In spite of these challenging (but realistic) conditions, model 1 was able to predict the blood glucose signal sufficiently accurate for the majority of the patients.

Finally, in most ICUs nowadays, the nurses measure the blood glucose more frequently (e.g., every hour) in the initial phase of the patient's stay at the ICU since the glucoregulatory system of most patients behaves unstable then. Therefore, it is probably utopian to expect that a semi-automated blood glucose control system (that gives advice to the nurse concerning the insulin dose) would require glycemia values measured only every 4 hours in this initial phase. Indeed, as present practice already allows, glycemia will be hourly or two-hourly measured in this phase. Moreover, it would also be utopian to expect that model predictions in this early phase (with only few patient-specific estimation data) are always accurate. Accordingly, the model prediction performance of models 1 and 2 would have significantly increased if the prediction processes would have started *after* this initial phase. Let us give an example. Under the assumption that the first 10 hours of data would not have been taken into account in the evaluation process, the average RMSnE (std-dev) for model 1 (BIT = 7) and 2 (BIT = 10) would have been reduced to 0.66 (0.28) and 0.95 (0.25), respectively. This confirms the previous reasoning that the model predictions are more accurate when more estimation data (to train the model) are available.

4. CONCLUSIONS AND FUTURE WORKS

In this paper we compared the model prediction performance of three model structures. The first two models were particularly aimed for describing the glucoregulatory system of critically ill patients whereas the third model was a rather 'naive' model. The prediction horizon was set at 4 hours and the model prediction processes started at the beginning of each patient's data set. The first model significantly outperformed the other two model structures and returned RMSnEs that were smaller than 1 for the

majority of the patients (with an optimal BIT equal to 7 hours). In spite of the imposed challenging conditions the prediction results showed the potential of using model structure 1 in a semi-automated blood glucose control system. Future work is conducted to the clinical validation of the full control system, i.e., the patient model 1 and the predictive controller (that has already been presented in Haverbeke et al. [2008]), in a group of critically ill patients under real-life circumstances (hourly blood glucose measurements).

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