Glycemia Prediction in Critically Ill Patients Using an Adaptive Modeling Approach

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Abstract

Background:

Strict blood glucose control by applying nurse-driven protocols is common nowadays in intensive care units (ICUs). Implementation of a predictive control system can potentially reduce the workload for medical staff but requires a model for accurately predicting the glycemia signal within a certain time horizon.

Methods:

GlucoDay (A. Menarini Diagnostics, Italy) data coming from 19 critically ill patients (from a surgical ICU) are used to estimate the *initial* ICU "minimal" model (based on data of the first 24 hours) and to *reestimate* the model as new measurements are obtained. The reestimation is performed every hour or every 4 hours. For both approaches the optimal size of the data set for each reestimation is determined.

Results:

The prediction error that is obtained when applying the 1-hour reestimation strategy is significantly smaller than when the model is reestimated only every 4 hours ($p < 0.001$). The optimal size of the data set to be considered in each reestimation process of the ICU minimal model is found to be 4 hours. The obtained average "mean percentage error" is 7.6% (SD 3.1%) and 14.6% (SD 7.0%) when the model is reestimated every hour and 4 hours, respectively.

Conclusions:

Implementation of the ICU minimal model in the appropriate reestimation process results in clinically acceptable prediction errors. Therefore, the model is able to predict glycemia trends of patients admitted to the surgical ICU and can potentially be used in a predictive control system.

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Abbreviations: (BIT) back-in-time, (ICU) intensive care unit, (ICU-MM) intensive care unit–minimal model, (IVGTT) intravenous glucose tolerance test, (MPE) mean percentage error, (MSE) mean squared error, (N-LSQ) nonlinear least squares

Keywords: glycemia prediction, intensive care unit, minimal model, parameter estimation, physical models

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Introduction

Hyperglycemia and insulin resistance are common in critically ill patients (even those without diabetes mellitus) and are associated with adverse outcomes. Tight glycemia control (with 80–110 mg/dl as target range) by applying intensive insulin therapy in patients admitted to the medical and the surgical intensive care unit (ICU) results in a spectacular reduction in mortality and morbidity.[1,2] Currently, ICU patients are treated through a manual and rigorous administration of insulin.[3] In the available literature several physical models that describe the glucose dynamics and the insulin kinetics of healthy and diabetic subjects are used for glycemia control simulations in "mathematical" diabetic (type I) patients.[4,5] A (semi-)automated predictive control system can be developed for glycemia control in the ICU.[6] This system has the potential to further reduce mortality and morbidity in the ICU and to restrict the workload for medical staff. Because patients who are admitted to the ICU show a significantly different clinical behavior than patients with diabetes,[6] a model specifically developed for describing the glucose and the insulin dynamics of ICU patients is required. In this study an existing ICU model structure is estimated based on a real-life ICU data set and a reestimation strategy to improve the performance of predicting glycemia in the ICU is proposed.

Subjects and Methods

Subjects

The GlucoDay system (A. Menarini Diagnostics, Italy), which is a portable instrument provided with a micropump and a biosensor coupled to a microdialysis system, was used to measure the glucose concentration that was (manually) controlled by nurses using a standard protocol.[3] After informed consent from the next of kin, a microfiber was implanted in 19 ventilated adult patients admitted to the surgical ICU of the University Hospital K.U. Leuven (Belgium) for a variety of reasons (see **Table 1**). After implantation of the fiber in the periumbilical subcutaneous tissue, near-continuous subcutaneous glucose levels were recorded for 48 hours. Every 3 minutes the mean value of the last 3 minutes was exported.

The use of near-continuous glucose measurement devices has the potential to improve glycemia control in patients with diabetes. The introduction of these sensors in a (future) predictive control system for normalizing glycemia of critically ill patients also reveals interesting opportunities. Unfortunately, *accurately* measuring near-

Table 1.
Patient Population (Coming from a Surgical Intensive Care Unit)

Variable	Value
Male sex—no (%)	13 (68.4)
Age (years) (SD)	61.7 (13.8)
Body mass index (kg/m^2) (SD)	26.9 (4.7)
Reason for intensive care—no (%)	
Cardiac surgery	8 (42.1)
Noncardiac indication	11 (57.9)
Neurologic disease, cerebral trauma, or brain surgery	3 (15.8)
Thoracic surgery, respiratory insufficiency, or both	2 (10.5)
Abdominal surgery or peritonitis	3 (15.8)
Vascular surgery	2 (10.5)
Other	1 (5.3)
APACHE II score (first 24 hours) (SD)	17.5 (5.6)
Mean glycemia (mg/dl) (SD)	111 (26)
Minimal glycemia (mg/dl)	50
Maximal glycemia (mg/dl)	223

continuous sensor devices are not yet available.[7,8] Therefore, it was required to retrospectively calibrate this near-continuous GlucoDay signal with arterial blood glucose values measured concomitantly every hour using the ABL machine (Radiometer, Copenhagen, Denmark) during the first 24 hours. During the next 24 hours, arterial blood glucose was measured every 4 hours. The administered flows of carbohydrate calories and insulin were also stored. The study protocol was approved by the Institutional Ethical Review Board (ML2637).

The ICU "Minimal" Model

The presented model structure originates from the known "minimal" model developed by Bergman and colleagues.[9] This model consists of a single glucose compartment. Plasma insulin is assumed to act through a so-called remote compartment to influence net glucose uptake.[10] The model reliably describes plasma glucose disappearance[11] and insulin kinetics[12] during an intravenous glucose tolerance test (IVGTT) in a healthy person. In this test, 300 mg glucose/kg body weight is administered intravenously to a person after which the plasma glucose and insulin concentration are measured with a high sampling frequency.

In Van Herpe *et al.*[13] the original minimal model was extended to the ICU "minimal" model (ICU-MM) by taking into consideration some features typical of ICU patients. First of all, the ICU-MM contains an endogenous and an exogenous insulin section, whereas the exogenous part is not included in the original Bergman model. Because the majority of critically ill patients are nondiabetic, the endogenous insulin section is still active. Due to the increased insulin resistance and the insufficient activity of the pancreas, some exogenously administered insulin flow is required for most of the patients. Second, the endogenous insulin section in the original Bergman model is transformed mathematically into a set of two equations with the goal of the model to not be an explicit function of time. Indeed, the original minimal model is considered to describe the glucose and insulin dynamics only during a single IVGTT (taken into account the time related to the start of the glucose shot). The ICU-MM is developed for use in a predictive control system with a continuous flow (i.e., a series of single shots) of delivered carbohydrates (and other input variables[6]). Consequently, resetting time to 0 at each administered glucose shot is not feasible, explaining the need for the mathematical manipulation. The ICU-MM is presented as

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

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

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

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

where G and I_1 are the glucose and the insulin concentrations in the blood plasma. The variable X describes the effect of insulin on net glucose disappearance and is proportional to insulin in the remote compartment. The variable I_2, which is introduced for mathematical reasons, does not have a strictly defined clinical interpretation but can be approached by the fraction of insulin concentration derived from the endogenous insulin secretion. The parameters G_b and I_b denote the basal value of plasma glucose and plasma insulin, respectively. The model consists of two input variables: the exogenous insulin flow (F_I) and the carbohydrate (glucose) calories flow (F_G), both administered intravenously. The glucose distribution space and the insulin distribution volume are denoted as V_G and V_I, respectively. The coefficient P_1 represents the glucose effectiveness (i.e., the fractional clearance of glucose) when insulin remains at the basal level; P_2 and P_3 are the fractional rates of net remote insulin disappearance and insulin-dependent increase, respectively. Endogenous

insulin is represented as the insulin flow that is released in proportion (by γ) to the degree by which glycemia exceeds a glucose threshold level h. The time constant for insulin disappearance is denoted as n. In case glycemia does not surpass the glucose threshold level h, the first part of the I_1 equation (that represents the endogenous insulin production) equals 0. In order to keep the correct units, an additional model coefficient, $\beta = 1$ min, is added. Finally, the coefficient α is a scaling factor for the second insulin variable I_2. **Table 2** gives an overview of the variables, patient features, and coefficients used in the ICU-MM. **Figure 1** illustrates the ICU-MM structure.

Table 2.
Variables, Patient Features, and Coefficient Values Applicable in the ICU-MM

Variable	Unit	Variable	Unit
G	mg/dl	I_2	µU/ml
X	1/min	F_I	µU/min
I_1	µU/ml	F_G	mg/min
Patient feature	**Unit**	**Value**	
BM	kg	Body mass	
V_G	dl	1.6 BM [5]	
V_I	ml	120 BM [5]	
G_b	mg/dl	Basal glycemia	
I_b	µU/ml	Basal insulin	
Coefficient	**Unit**	**Value**	
P_1	1/min	-1.31×10^{-2a}	
P_2	1/min	-1.35×10^{-2a}	
P_3	ml/(min² µU)	2.90×10^{-6a}	
h	mg/dl	136[a]	
n	1/min	0.13[a]	
α	1/min	3.11	
β	min	1	
γ	$\dfrac{\mu U \ dl}{ml \ mg \ min^2}$	5.36×10^{-3a}	

[a]As initial value for the model estimation process, mean model coefficient values for the obese–low glucose tolerance patient group, described in Bergman *et al.*,[9] are used.

Adaptive Modeling Approach: Study Design

In this study the model structure described earlier (ICU-MM) is estimated on a real-life ICU data set. Because of the large inter- and intrapatient variability that exists in the ICU (e.g., patient-specific initial and dynamical known input variables, reaction on medical treatment, time-varying
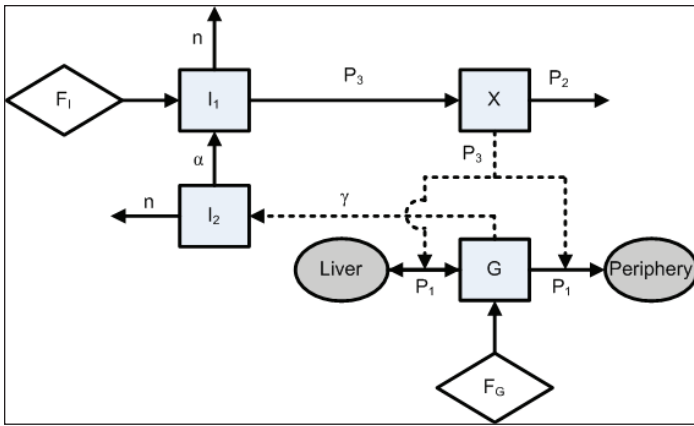
Figure 1. Representation of the ICU-MM. The state variables of the model (G, X, I_1, and I_2) and the body segments (liver and periphery) are denoted as squares and ellipses, respectively. The exogenous input variables (F_I and F_G, administered intravenously to the patient) are illustrated as rhombi. The model parameters (P_1, P_2, P_3, n, α, and γ) are related to the respective variables. A direct physical relation is represented by a solid arrow, whereas a rather mathematical relationship is denoted as a dashed arrow.

insulin resistance), it is required to reestimate the ICU-MM at frequent time intervals to capture dynamic features as much as possible.[6] The main contribution of this study is the performance improvement of this reestimation process. In general, the adaptive modeling approach can be described as follows.

First of all, the ICU-MM is used as a general template, which is estimated for each individual patient (based on data belonging to the first 24 hours of each patient's data set and leading to the "initial" model for that patient) such that the model parameters P_1, P_2, P_3, n, α, and γ are patient specific. The parameter estimation is solved as a nonlinear least-squares (N-LSQ) program in Matlab®. The least-squares objective function arrives from penalizing deviations between simulated and observed glycemia trajectories using the nonlinear ICU-MM. For the reason of online use in a control scheme the N-LSQ program is solved by means of local optimization. In particular, Nelder-Mead's method is used. Consequently, the optimal model parameters are found to be those that give the best possible representation for true patient behavior during the first 24 hours (i.e., 1440 minutes) given glycemia measurements, input observations, and ICU-MM.[13] To solve this problem, the starting parameters are taken from the obese–low glucose tolerance patient group coming from Bergman and co-workers[9] (see **Table 2**) whose patient characteristics are comparable to ICU patients.

Second, the model is reestimated at certain time periods P for the rest of each patient's data set. Two different settings are proposed: reestimations every hour and every 4 hours.

The number of recent data considered in each reestimation process is called the back-in-time (BIT) number and may influence the performance of the model. Therefore, BIT is varied in each setting. In the reestimation procedure the same nonlinear estimation technique as described earlier is applied. The starting parameters in each optimization process are the end values of the previous period P. The model performance for each patient p is measured by computing the mean squared error,

$$\text{MSE}_p = \frac{\sum_{t=1441}^{N} (G_{t,p} - \hat{G}_{t,p})^2}{N}$$

and the mean percentage error,

$$\text{MPE}_p = \frac{\sum_{t=1441}^{N} \frac{\left| G_{t,p} - \hat{G}_{t,p} \right|}{G_{t,p}}}{N} 100\%,$$

where $G_{t,p}$ and $\hat{G}_{t,p}$ are the actual and predicted glycemia values for patient p. The size of each data set is denoted as N. The overall methodology for optimizing the reestimation process is explained next.

1. Estimate the initial model (ICU-MM) based on the first data set (first 24 hours, see earlier discussion).

2. For a reestimation period $P = 1$ hour and $P = 4$ hours.

   a. For $BIT = 20$-18-16-14-12-10-8-6-5-4-3-2-1-0.5 hours,

      i. Reestimate the ICU-MM based on every last section (i.e., BIT) of the (moving) data set with the starting set of coefficients the values corresponding to the last period P (or the set of coefficients from the initial model for the first reestimation).

      ii. Predict the glycemic course for the next period P (which is the validation set of the reestimated model in this case).

      iii. Compute the MSE and MPE for all validation sets per patient.

   b. Compare the MSEs and/or MPEs that are generated for the different BITs. The BIT that belongs to the smallest (average) MSE and/or MPE is called "optimal" and is ideally used in the reestimation process,

3. Compare the optimal BIT and the computed MSEs and MPEs for the $P = 1$-hour and $P = 4$-hour settings.

The Wilcoxon signed rank test is used to test significant differences (significance level 5%).

Results

Figures 2 and **3** give an overview of the computed MSEs and MPEs as a function of *BIT* and *P*. The prediction performance of the model is higher (i.e., smaller MSEs and MPEs) when the model is reestimated every hour ($P = 1$ hour) in comparison with model reestimations every 4 hours ($p < 0.001$). The optimal *BIT*, with respect to the smallest prediction errors, is found to be 4 hours. Significant differences ($p < 0.05$) with regard to other selected *BIT*s are marked with asterisks in **Figures 2** and **3**. The average MSE (SD) and average MPE (SD) obtained when applying this optimal reestimation strategy ($P = 1$ hour, $BIT = 4$ hours) to present data are 131.9 mg²/dl² (99.9 mg²/dl²) and 7.6% (3.1%), respectively. When model reestimations every 4 hours are preferred ($P = 4$ hours, $BIT = 4$ hours), the average MSE (SD) and average MPE (SD) are equal to 578.0 mg²/dl² (1010.3 mg²/dl²) and 14.6% (7.0%), respectively.

Figures 4 and **5** illustrate the performance of the ICU-MM for predicting glycemia of two patients. Glycemic evolution is shown in the top panels. The solid line represents glycemia measured by the GlucoDay system. Data of the first 24 hours are used to estimate the initial model. The *simulation* of this initial model on the first part of the data set (i.e, in-sample data) is indicated by the dotted line. The reestimation strategy is started after the first 24 hours. Vertical lines in **Figures 4** and **5** indicate the instants when the model is reestimated by considering data of the previous 4 hours ($BIT = 4$ hours). This reestimation process takes place every 4 hours (top panel) or every hour (second panel). The *predicted* glycemia signal is illustrated by the dashed line. Finally, the input variables included in the ICU-MM are shown in the third (administered insulin) and the last (administered carbohydrate calories) panels in **Figures 4** and **5**.

Discussion

This article presented an optimized adaptive "minimal" modeling approach for predicting glycemia of critically ill patients. Simulations are performed with respect to a real-life surgical ICU data set in which glycemia was near-continuously monitored. This high sampling frequency is assumed to be standard practice in the future.[7] For this reason, a *test* near-continuous sensor device (whose signal was retrospectively calibrated with a *reference* sensor) was used for this study in order to propose an "optimal" model reestimation technique that may be applied in a future glycemia predictive control system in the ICU.[6] In that particular setting, data of the first 24 hours after admission to the ICU will be used to estimate the initial ICU-MM. During this first period, glycemia will be
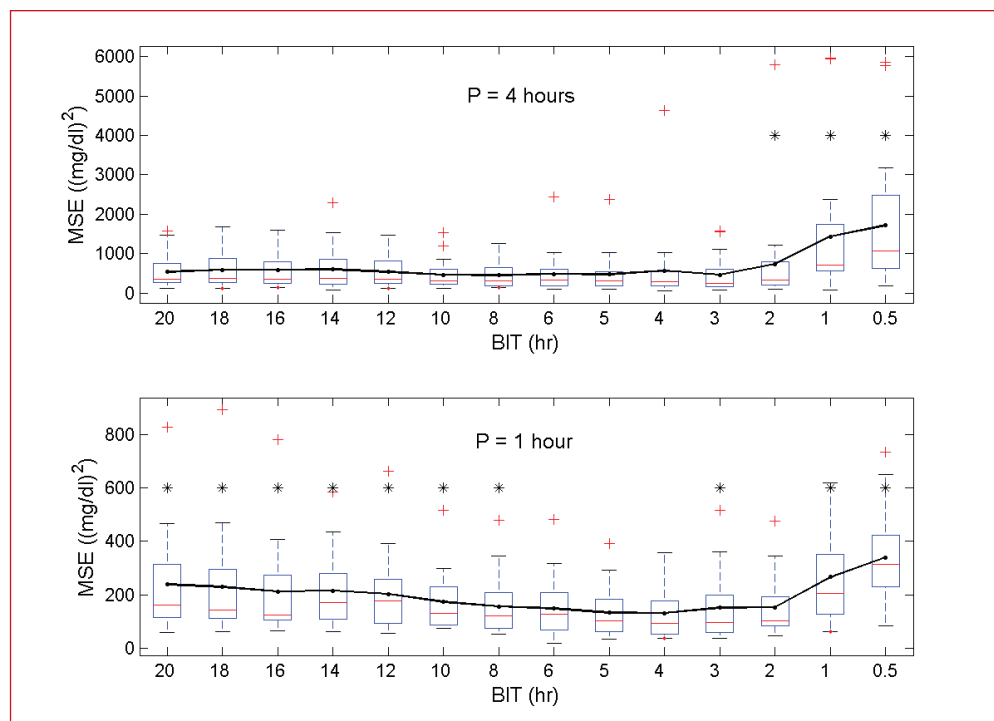

Figure 2. Distribution of the MSEs (generated for each patient) as a function of *BIT* with reestimations every 4 hours (**top**) or every hour (**bottom**). The line connects the averages of the MSEs. In general, reestimations based on the last 4-hour data set ($BIT = 4$) result in the smallest prediction errors. Significant differences with respect to the $BIT = 4$ setting are visualized with an asterisk.
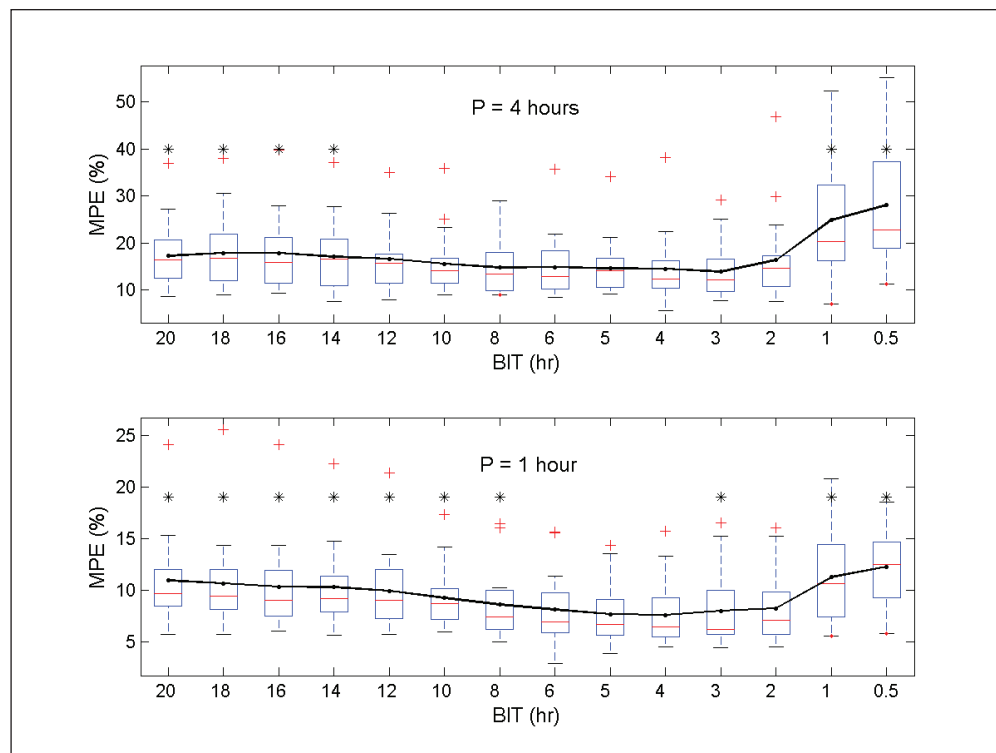
Figure 3. Distribution of the MPEs (generated for each patient) as a function of *BIT* with reestimations every 4 hours (**top**) or every hour (**bottom**). The line connects the averages of the MPEs. Reestimations based on the last 4-hour data set (*BIT* = 4) give the smallest prediction errors. Significant differences with respect to the *BIT* = 4 setting are visualized with an asterisk.
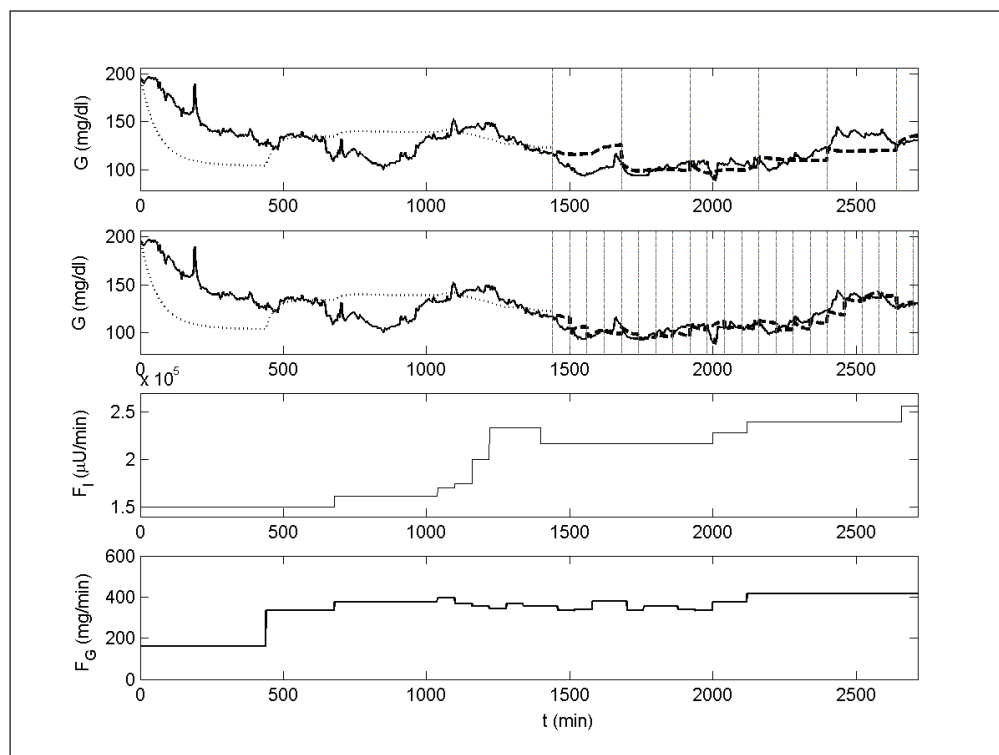
Figure 4. Example of the reestimation strategy applied to the ICU-MM. The evolution of glycemia of patient No. 3, measured with the GlucoDay system, is presented in the first and second panels (solid line). Data of the first 24 hours are used to estimate the initial ICU-MM. The in-sample *simulation* is represented by the dotted line. Glycemia *predictions* present in the other part of the data are illustrated with the dashed line for both the 4-hour (**top panel**) and the 1-hour (**second panel**) reestimation process. Reestimation time instants are illustrated by vertical lines. The flows of insulin and carbohydrate calories are shown in the third and fourth panels, respectively.
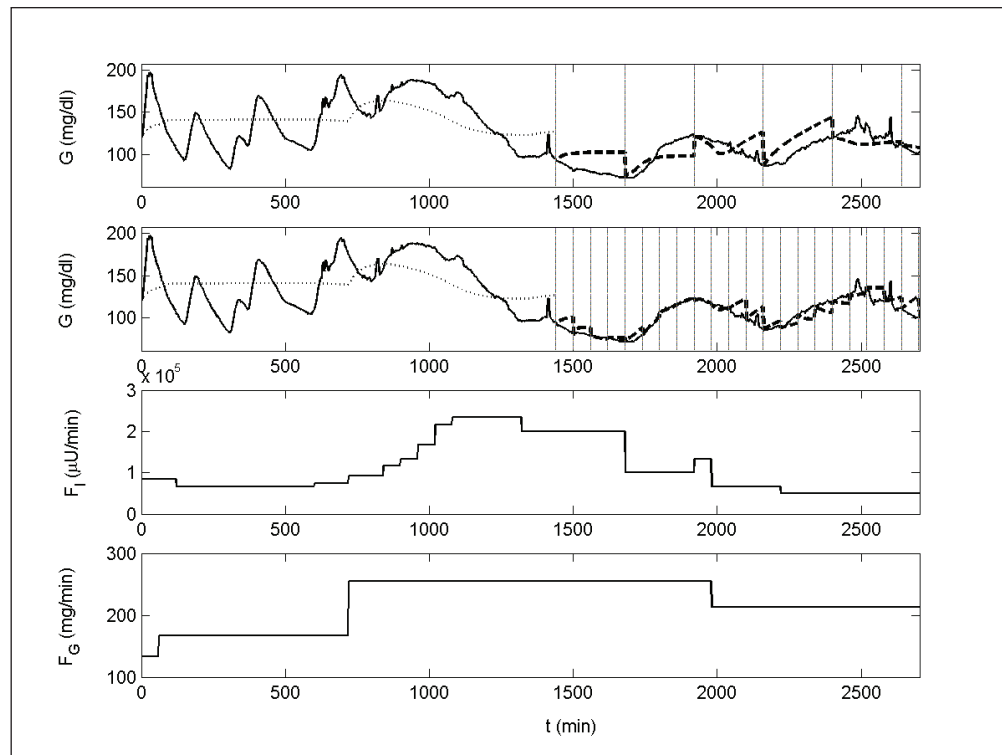
Figure 5. Another example of the reestimation strategy applied to the ICU-MM on patient No. 10. Similar codes as used in Figure 4 are used.

controlled by medical staff using a (manual) nurse-driven protocol[3] that is applied as a standard nowadays. From the second day onward, the predictive control system will (semi-)automatically regulate glycemia. A first model-based predictive controller that incorporates the ICU-MM and a (nonoptimal) reestimation strategy has been described.[14] In the available literature the use of other glycemia controller strategies (both model and nonmodel based) has already been reported.[7,8,15–17] The frequent reestimation of the ICU-MM will incorporate dynamical changes within the critically ill patient (e.g., varying insulin resistance). The feasibility of the reestimation modeling approach is shown in this study.

Reestimating the model every hour results in smaller prediction errors than reestimations that take place every 4 hours. This result is expected, as frequent updates of the model lead to smaller time horizons, meaning smaller simulation periods and, as a usual result, smaller (absolute and relative) prediction errors. As described previously, an appropriate model-based predictive controller is currently under study with the goal of (semi-)automatic glycemia normalization. In a first phase this system will only act as an *advisory* system ("semi"-automatic). This means that confirmation (by a nurse) of the insulin rate adaptations will be mandatory before administering the insulin flow (that is proposed by the controller) to the patient. Consequently, the workload for the medical

staff is expected to increase significantly. For this reason the insulin adaptation frequency will be limited to once per hour.[14] This immediately explains why updating the model more frequently than once per hour is futile. Hence, P was only set to 1 and 4 hour(s) in this study. Of course, after a thorough clinical validation of this semi-automatic system, the insulin adaptation frequency may be increased further (e.g., $P = 15$ min) for use in a fully automatic control system (i.e., confirmation by a nurse is not required any more), which may lead to even smaller prediction errors than obtained when $P = 1$ hour.

The optimal size of the data set to be considered in each reestimation process of the ICU-MM is found to be 4 hours (although no statistically significant difference exists between the $BIT = 4$-hour data set size and the $BIT = 5$- or 6-hour data set size when $P = 1$ hour). This means that only relatively recent data (set to the previous 4 hours due to the smallest average MSE and average MPE obtained when $P = 1$ hour) need to be taken into account in each reestimation process for predicting glycemia trends accurately. **Figures 2** and **3** clearly illustrate the trade-off between overfitting (small BIT) and the restricted modeling capacity of fast-changing dynamics (large BIT). Indeed, reestimations based on large amounts of previous data (e.g., $BIT = 18$ hours) do not efficiently capture the varying patient dynamics typical of critically ill patients. However, only considering the most recent data of the specific patient

(e.g., $BIT = 1$ hour) leads to model overfitting and explains the poor prediction performance in that case.

When the ICU-MM is reestimated every hour and every 4 hours (based on the previous 4 hours of data, $BIT = 4$ hours), the average MPE is equal to 7.6 and 14.6%, respectively. These relative prediction errors are clinically acceptable after comparing *model prediction* behavior with *sensor measurement* behavior. Indeed, the accuracy requirements of a *test* sensor device, which is assessed by considering its signal toward the concomitantly measured *reference* (or "gold" standard) values, are comparable to the prediction performance requirements of a model. 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. The International Organization for Standardization criterion, which is a standard criterion for the binary assessment of the accuracy of glucose sensors, is typically used in the evaluation of test sensor devices.[18] In this criterion the target variability of the test sensor device (with respect to the reference sensor) is defined as ±20% for reference values >75 mg/dl. For reference values ≤75 mg/dl, the test sensor measurements are required to fall within ±15 mg/dl limits. The relative prediction errors obtained when reestimating the ICU-MM every hour and every 4 hours are smaller than the aforementioned 20% target variability, indicating clinical acceptance for both approaches (assuming the availability of an accurate near-continuous glucose sensor device).

Figures 4 and **5** show the predicted glycemia signal of patients 3 and 10. The individual MPEs for these "average" patients are equal to 5.0 and 6.4%, respectively, when $P = 1$ hour and 8.5 and 14.9%, respectively, when $P = 4$ hours. The ICU-MM *approaches* the real glucose dynamics of critically ill patients. Although only two input variables (i.e., the flow of carbohydrate calories and insulin) are effectively taken into consideration, the ICU-MM generally succeeds in predicting glycemia *trends* for both $P = 1$ hour and $P = 4$ hours. The rather *flat* glycemia dynamics that appear in some segments in **Figures 4** and **5** are caused directly by the corresponding *flat* input behavior (e.g., **Figure 4** top panel; starting at $t = 2120$ min the fluctuating glycemia signal is not predicted accurately by the ICU-MM, as its input variables, which play a significant role in predicting the glycemia behavior, have a constant flow). Updating the model frequently (every hour) is advised to compensate for these unavoidable missing glycemia dynamics.

A final feature of the proposed model reestimation strategy is the limited computation time. The current study is (off-line) implemented in Matlab® on Microsoft Windows XP (Intel Pentium, 1400-MHz processor). The N-LSQ program requires only approximately 1 minute to be solved. Accordingly, the online application of this technique is no issue in terms of computation time.

In conclusion, implementation of the ICU-MM that is reestimated every 4 hours or (preferably) every hour gives promising results in terms of prediction performance and indicates its potential use in a predictive control system for critically ill patients admitted to the surgical ICU.

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