Glycemic Control for Critically Ill Patients with Online Identification of Insulin Sensitivity

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Abstract Hyperglycemia is common in critically ill patients and leads to various severe complications and even death. Keeping blood glucose within the range of 80–110 mg/dL (4.4–6.1 mmol/L) has been shown to reduce mortality and morbidity in intensive care units (ICU). Many studies on BG control systems for ICU patients have been reported. However, it is not easy to maintain blood glucose within the desired range because of the time variability of insulin sensitivity in critically ill patients. In this study, to improve the prediction accuracy of blood glucose level in patients, we modified a glycometabolism model developed in our previous study, by identifying parameter values from clinical ICU data. Then, we modified insulin sensitivity online identification algorithm to avoid a sudden change in insulin sensitivity during online identification that updates insulin sensitivity value at intervals of 30 min. Finally, since hypoglycemia prevention as important, we designed a glycemic control system using nonlinear model predictive control based on the modified model and the online identification algorithm of insulin sensitivity. The new glycemic control system achieved 71% of blood glucose measurements within the range of 80–110 mg/dL and 1.5% of measurements below 80 mg/dL, which indicated effectiveness and safety.

Keywords: glycemic control, insulin sensitivity, model predictive control, critically ill patient, intensive care unit.

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1. Introduction

Hyperglycemia is very common in critically ill patients, even in those without diabetes, and may lead to various severe complications such as sepsis, multiple organs failure, and even death [1]. To avoid hyperglycemia, doctors or nurses administer insulin to these patients according to insulin infusion protocols such as protocols for intensive care units (ICU) [2, 3]. Although tight glucose control (TGC) to maintain blood glucose (BG) within the range of 80–110 mg/dL (4.4–6.1 mmol/L) reduces mortality and morbidity in ICU [4], it is difficult to maintain normoglycemia without hypoglycemic events, due to long intervals of BG measurement and time-varying insulin sensitivity in ICU patients. Furthermore, measurement of BG for a period of 15–60 minutes, which is rec-

ommended in protocols for ICU [2, 3], imposes a huge burden on patients and medical staffs.

To solve such problems, glycemic control for ICU patients to normalize BG without causing hypoglycemia has been studied [5–14], and computer-based insulin infusion protocols [5–9] have been shown to provide more effective and safer BG control for ICU patients than paper-based protocols. The Glucosafe system [5] for tight glucose control in critical care is a model-based decision support system that utilizes BG trajectory prediction based on the Glucosafe model [15]. A subsequent study by the same group [6] evaluated modifications of penalty functions in the Glucosafe system. Stochastic model predictive (STOMP) glycemic control system [7] is a model predictive control system based on a glycometabolic model (Intensive Control Insulin-Nutrition-Glucose (ICING) model [16]) that uses stochastic forecasting method to predict the future insulin sensitivity. A glycemic control system using model predictive control was constructed based on the ICU minimal model (ICUMM) [17], in which the patient-specific parameters were re-estimated at one-hour or four-hour intervals [10]. In a subsequent study, a BG control system based on ICUMM utilizing nonlinear model predictive control with moving horizon was developed, and the potential of regulating BG in ICU was demonstrated [11]. Most of these studies [5–7, 10, 11] utilize model-based BG prediction or

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model predictive control, since it is difficult to determine an appropriate insulin infusion amount only from the current BG measurement. However, the risk of hypoglycemia (e.g. BG < 70 mg/dL [18]), or in some systems even severe hypoglycemia (e.g. BG < 40 mg/dL [18]), remains.

In our previous study [12], we developed a BG control system using nonlinear model predictive control based on ICUMM [17] with no time-varying parameters. Although our system achieved 1.4% of BG below 80 mg/dL when applied to virtual patients with time-varying insulin sensitivity, it did not have sufficient performance to maintain BG within the desired range. To improve the performance of the BG control system, subsequent studies modified the glycometabolism model by introducing a time-varying insulin sensitivity parameter and implemented an online identification algorithm of insulin sensitivity [13, 14]. However, BG of ICU patients may not be estimated accurately since the parameters of the modified glycometabolism model were identified from non-ICU patient data [14].

In this paper, in order to further improve our BG control system, we modify the parameters of the glycometabolism model and the online identification algorithm of insulin sensitivity, and redesign the nonlinear model predictive controller. First, we identify the parameters of the glycometabolism model from clinical data of ICU patients, and show BG estimation accuracy by simulation. Second, we add a penalty of insulin sensitivity change to the cost function for online identification of insulin sensitivity to avoid a sudden change of insulin sensitivity. Third, we redesign the nonlinear model predictive controller by adjusting the weighting parameters and horizons considering safety and the influence of insulin sensitivity. Finally, we apply the modified system to virtual patients with time-varying insulin sensitivity constructed in [13, 14] to assess the effectiveness and safety of the system.

The paper is organized as follows. In Section 2, we describe the glycometabolism model of ICU patients, identify the model parameters from clinical data of ICU patients, and compare the accuracy of the modified model with that of our previous model. In Section 3, we explain the algorithm and modification of the online identification of insulin sensitivity, and design strategy of the closed-loop BG control system based on the modified model. Section 4 assesses the effectiveness and safety of the BG control system by simulation of its application to virtual patients.

2. Glycometabolism model

In this section, we explain in detail the glycometabolism model in this paper and identify the model parameters

for ICU patients.

Many glycometabolism models for ICU patients have been developed and utilized to date. In this paper, we utilize the model with an insulin sensitivity parameter proposed previously [14]. The model parameters, however, were determined from data of obese patients with low glucose tolerance. To obtain more appropriate parameter values for ICU patients, we identify them from clinical data of ICU patients.

The model utilized in this study was constructed previously [13, 14]. First, a time-varying parameter of insulin sensitivity, nonlinear functions of insulin dependent and independent glucose uptakes and saturation of interstitial insulin effect were introduced into the ICUMM [17] to cope with the difficulty of online identification of insulin sensitivity due to the lack of its independent parameter in ICUMM [13]. Then, we added a basal insulin term to fix the problem of low plasma insulin concentration, and a compartment of glucose absorption from the small intestine to enable enteral glucose infusion through the intestine [14].

The complete model is shown in **Fig. 1** and given by Eqs. (1)–(6), which consists of five compartments of BG G , interstitial insulin I_i , plasma insulin I_p , pancreas insulin I_s and small intestinal glucose E , with three inputs of parenteral glucose F_G , enteral glucose F_E and intravenous insulin F_I , and insulin effect $i(t)$ with a time-varying insulin sensitivity parameter S_I .

$$\frac{dG(t)}{dt} = -i(t) \frac{k_{a2}G(t)}{k_{b2} + G(t)} - (p_1 i(t)G(t) - H) - \frac{k_{a3}G(t)}{k_{b3} + G(t)} + \frac{F_G + p_6 p_5 E(t)}{V_G}, \quad (1)$$

$$\frac{dI_i(t)}{dt} = p_3 I_p(t) - p_2 I_i(t), \quad (2)$$

$$\frac{dI_p(t)}{dt} = \alpha \{ \max(0, I_s(t)) + I_b \} - p_3 I_p(t) - p_4 I_p(t) + \frac{F_I}{V_I}, \quad (3)$$

$$\frac{dI_s(t)}{dt} = \beta \gamma (G(t) - h) - n I_s(t), \quad (4)$$

$$\frac{dE(t)}{dt} = F_E - p_5 E(t), \quad (5)$$

$$i(t) = S_I \frac{k_{a1} I_i(t)}{k_{b1} + I_i(t)}. \quad (6)$$

Here, k_{a1} is a coefficient to keep the unit correctly. k_{b1} is a parameter of interstitial insulin saturation. k_{a2} and k_{b2} are the coefficients of nonlinear insulin dependent glucose uptakes. k_{a3} and k_{b3} are the coefficients of nonlinear insulin independent glucose utilization. Equation (1) represents that BG is determined by nonlinear insulin-dependent (the first term) and -independent glucose uptake (the third term) [15, 19, 20], hepatic glucose balance (the second term) obtained by simplifying the he-

Fig. 1 The structure of a glycometabolism model.

patic glucose balance model [15], and parenteral glucose input and glucose absorption from the small intestine (the fourth term). Equations (2) and (3) represent interstitial and plasma insulin kinetics, respectively, and the first term in Eq. (3) is insulin secretion from pancreas with basal insulin, the second term is insulin distribution from plasma to interstitium, the third term is insulin excretion and the fourth term is exogenous insulin input. Equation (4) means that endogenous insulin is released proportionally to glucose above a threshold level h , which is taken from previous report [17]. In Eq. (5), the small intestinal glucose increases by enteral glucose delivery and decreases by absorption. Equation (6) represents insulin effect $i(t)$, which is obtained from insulin sensitivity and effect of interstitial insulin saturation as shown in previous studies [16, 20, 21].

With the ethical approval (No. 2018–147) by the Ethics Committee of Kagawa University Hospital, we identify model parameters from the clinical data of BG measurements, parenteral glucose and enteral glucose infusion rates, and insulin infusion rates obtained from 17 ICU patients (M/F 9/8, age 67 ± 13 years, height 161 ± 8 cm, weight 56 ± 10 kg, ICU stay 4 ± 3 days) who stayed in ICU of Kagawa University Hospital after surgeries for pancreas cancer, bile duct cancer, major duodenal papilla cancer and others, and needed BG management from 2016 to 2017. The ICU stay ranged from 1 to 16 days; seven and four patients stayed three and four days, respectively, and no other patients stayed the same days. To obtain typical parameters of ICU patients, we use the data from patients who stayed three or four days, excluding two patients due to the lack of BG measurements. Hence, the model parameters are identified from nine ICU patients whose demographic data are given in

Table 1 Details of the nine ICU patients.

Gender	Stay (days)	Age	Weight (kg)	Height (cm)
Male/ Female	Mean (Std)	Mean (Std)	Mean (Std)	Mean (Std)
5/4	3.4 (0.5)	65.7 (5.4)	57.5 (12.7)	163.1 (7.9)

Table 1.

Since our model can represent the BG change of clinical data considering time variability of insulin sensitivity as shown in our previous study [14], we assume that only insulin sensitivity parameter varies with time. We estimate the parameter values of the model for each patient utilizing Matlab function 'lsqnonlin' from clinical data of BG, glucose and insulin infusion rates from the ICU patients. **Table 2** shows the mean values of the identified parameters, which are used as the parameter values of ICU patient model in this paper.

We simulate BG responses of the models with the identified parameter values and with our previous model parameters from non-ICU (obese and low glucose tolerance) patients [14] to evaluate the accuracy. Insulin sensitivity varies with time and is identified from BG measurements, insulin and glucose infusion rates. **Figure 2** illustrates the usage of BG measurements in identification of insulin sensitivity and the usage of the identified insulin sensitivity in the BG estimation. We identify insulin sensitivity from four successive BG measurements. BG response between the first and third measurements is estimated from the model with the identified insulin sensitivity from the first four successive BG measurements.

Table 2 Parameters of the model.

Patient features	Values	Patient features	Values
S_I	To be identified	V_G (dL)	1.88 BW [19]
BW	Body weight	V_I (mL)	120 BW [17]
Parameters	Values	Parameters	Values
h (mg/dL)	107.4 [17]	β (min)	1 [17]
p_1	0.1503	p_2 (min ⁻¹)	0.1560
p_3 (min ⁻¹)	0.1643	p_4 (min ⁻¹)	0.1212
k_{a1} (min ⁻¹)	1	k_{a2} (mg/dL)	0.3746
k_{a3} (mg/dL/min)	0.3095	k_{b1} (μ U/mL)	171.0552
k_{b2} (mg/dL)	94.4792	k_{b3} (mg/dL)	8.0479
H (mg/dL/min)	0.7686	n (min ⁻¹)	5.9027
α (min ⁻¹)	0.5417	γ ($\frac{\mu\text{U}\cdot\text{dL}}{\text{mL}\cdot\text{mg}\cdot\text{min}^2}$)	0.1457
I_b (μ U/mL)	13.3909	p_5 (min ⁻¹)	0.5719
p_6	0.2872

Fig 2 The durations of insulin sensitivity identifications and insulin sensitivity values during the simulation based on four successive BG measurements.

After the third BG measurement, BG response between k -th and $(k + 1)$ -th measurements is estimated from the model with the insulin sensitivity identified from $(k - 1)$ -th to $(k + 2)$ -th BG measurements.

Simulation results of the models with the parameters identified in this paper and with the parameters in our previous study for No. 4 and No. 7 patients are given in **Fig. 3**. Note that No. 7 is one of the nine ICU patients whose data is used for identification, while No. 4 is not. To compare the accuracy of model parameters identified

in this paper with those of the previous study, the mean percentage errors (MPEs) of BG estimated from the both model parameters are calculated. The MPE of BG is obtained by

$$\text{MPE} = \frac{\sum_i^N \frac{|G_i - G_{p,i}|}{G_i}}{N} \times 100\%, \quad (7)$$

where G_p is the estimated BG, G is the measured BG, and N denotes the number of measured BG. **Table 3** shows the MPEs of BG of the 17 ICU patients, estimated from the models with the identified parameters in this study and with the parameters in our previous study. We also compare the MPEs of BG of the patients whose data are used to identify the parameters in this study as listed in **Table 1** and the patients whose data are not used in identification. The MPE values are analyzed by two-tailed paired t -test. The results show that the model identified from ICU patient data has significantly lower MPE values than that from non-ICU patient data for all the patients, the patients used and the patients not used for identification. Therefore, the model parameters identified in this paper are more accurate than those of previous models.

3. Glycemic control

As shown in **Fig. 3**, insulin sensitivity of ICU patients may largely vary with time during ICU stay. Since the variability of insulin sensitivity has great influence on BG, we must always grasp the insulin sensitivity and estimate BG as accurately as possible to keep BG within the desired range. Thus, we previously performed online identification of insulin sensitivity [13]. In this section,

(A) ICU patient No. 4

(B) ICU patient No. 7

Fig. 3 Comparison of predicted and measurement BG based on insulin sensitivity identified by four successive measurements in an ICU patient. The top panel shows the measurement BG, simulations by the present model (blue line) and the previous model (red line). The bottom panel shows the identified insulin sensitivity by the present model.

Table 3 Comparison of the MPE (%) of predicted BG in 17 ICU patients.

	Present model	Previous model [14]	
All patients	8.17	9.60	$p = 0.00001$
Patients used for identification	7.51	9.15	$p = 0.00003$
Patients not used for identification	8.92	10.10	$p = 0.03$

we explain the modification of the online identification algorithm of insulin sensitivity and design strategy of nonlinear model predictive control of BG. We utilize nonlinear model predictive control because it has the advantage of accurate consideration of the effect of future insulin input on the future BG levels even under constraints of insulin input as well as BG levels.

3.1 Online identification of insulin sensitivity

As mentioned above, it is not easy to normalize BG in ICU patients due to the time variability and unmeasurability of insulin sensitivity. To cope with such problem, we estimate the insulin sensitivity parameter S_I in Eq. (6) at every sampling. We set the sampling period Δt to 30 minutes since a period of 15–60 min of BG measurements for ICU patients is recommended by the insulin infusion protocol [3]. S_I is estimated from the past and current BG measurements and insulin and glucose infusion rates by minimizing a cost function given by

$$\begin{aligned} \min_{S_I} J_s = & \sum_{n=0}^1 (G(k-n) - G_p(k-n))^2 \\ & + W(S_I(k) - S_I(k-1))^2 \end{aligned} \quad \text{subject to } S_I \geq 0. \quad (8)$$

where $G(k)$ and $G_p(k)$ denote measured BG and estimated BG at time $k\Delta t$, respectively, $S_I(k)$ is the value of insulin sensitivity parameter in Eq. (6) at time $k\Delta t$, W is the weighting coefficient fixed to $500 \text{ mg}^2/\text{dL}^2$. The cost function consists of errors between measured BG and estimated BG, and a difference between the present and the previous insulin sensitivity values, which is a new term in this study to avoid a sudden change in estimated insulin sensitivity. Matlab function 'lsqnonlin' is utilized to solve the optimization problem. The estimated value of insulin sensitivity parameter is regarded as that of the patient at present and used for prediction of future BG for the following hours.

The initial value of the insulin sensitivity is set to 0.3 at admission to ICU from the identification result of insulin sensitivity [12] and the results in Section 2, and the other parameters are set to the values listed in **Table 2**.

3.2 Nonlinear model predictive glycemic control

Based on the glycometabolism model (1)–(6), we construct a nonlinear model predictive control system as shown in **Fig. 4**, with online identification of insulin sensitivity. We design the nonlinear model predictive control system to keep BG within the desired range by smaller amount of insulin infusion to avoid hypoglycemia. Considering that ICU patients receive continuous nutrition at a known rate, insulin infusion rate is determined by solving the optimization problem:

Fig. 4 A closed-loop glycemic control system with insulin sensitivity online identification.

$$\begin{aligned} \min_u J_u &= Q_1(G_p(k+P) - G^*)^2 \\ &+ \sum_{i=1}^P Q_2(G_p(k+i) - G^*)^2 \\ &+ \sum_{j=0}^{M-1} \{R_1(u(k+j) - u(k+j-1))^2 + R_2 u(k+j)^2\}, \quad (9) \end{aligned}$$

subject to

$$G_p(k+i) \geq 80 \text{ mg/dL } (i = 1, 2, \dots, P)$$

$$0 \leq u(k+j) \leq u_{\max} \quad (j = 0, 1, \dots, M-1),$$

where P and M are prediction and control horizons, respectively, $G^* = 95 \text{ mg/dL}$ is the target BG level, $u(k)$ denotes the insulin infusion rate at time $k\Delta t$, $u_{\max}$ represents the maximum insulin infusion rate, and Q_1 , Q_2 , R_1 and R_2 are weighting coefficients. The prediction and control horizons are set to $P = 4$ and $M = 1$, respectively, and the weighting coefficients are adjusted considering robustness and time variability of insulin sensitivity as:

$$Q_1 = \begin{cases} 1000, & G(k) \geq 110 \text{ mg/dL} \\ 400, & 95 \leq G(k) < 110 \text{ mg/dL} \\ 10, & 80 \leq G(k) < 95 \text{ mg/dL} \\ 1000, & G(k) < 80 \text{ mg/dL} \end{cases},$$

$$Q_2 = Q_1/4,$$

$$R_1 = \begin{cases} 10^{-7}, & S_1 > 0.3 \\ 10^{-5}, & S_1 \leq 0.3 \end{cases},$$

$$R_2 = \begin{cases} 1.19 \times 10^{-3}/\text{BW}, & S_1 > 0.3 \\ 2.8 \times 10^{-4}/\text{BW}, & S_1 \leq 0.3 \end{cases},$$

where BW is body weight of the patient. Note that Q_1 and Q_2 for BG out of the desired range are set to be a large value to keep BG within the desired range, and R_1 and R_2 are dependent on the insulin sensitivity S_1 to avoid hypoglycemia due to a large insulin infusion rate for a small S_1 . The optimization problem is solved by the Matlab function 'fmincon' based on the sequential quadratic programming method. If insulin infusion rate cannot be obtained under the constraint in Eq. (9), i.e. when the

predicted BG $G_p(k+i)$ is smaller than 80 mg/dL , the insulin infusion rate $u(k)$ is determined to 0.

4. Simulation

In this section, we assess the performance of the nonlinear model predictive BG control system constructed in Section 3. First, we make a brief explanation of virtual patients, which were constructed in [14] for evaluation of the developed BG control system. Then, we make simulations of the developed BG control system and compare the results with the existing control systems.

4.1 Virtual patients

We apply the glycemic control system to 30 virtual patients with time-varying insulin sensitivity developed in our previous study [13, 14] to assess the effectiveness of our system. Glucose and insulin dynamics in virtual patients are simulated by the Glucosafe model [15], which consists of four compartments of plasma insulin, peripheral insulin, blood glucose and carbohydrate content in the gut, and several linear and nonlinear functions, with more than 40 parameters and one time-varying insulin sensitivity parameter.

The 30 virtual patients are constructed as follows. First, we identify the insulin sensitivity parameter value of the Glucosafe model at one-hour intervals using clinical data of BG, nutrition and insulin infusion rates described previously [20], assuming that only the insulin sensitivity varies with time. The identified insulin sensitivity profile is designated profile No. V1. Profiles No. V2–V7 are constructed by adding uniformly distributed random values within the specific range to the profile No. V1. Profiles No. V8–V10 are constructed by increasing the insulin sensitivity to represent the change of insulin sensitivity with patient recovery after surgery. All the profiles are listed in **Table 4**.

We construct 30 patients by combining the ten different insulin sensitivity profiles with patients weighing 50, 60 and 70 kg (female, 48 years of age, 170 cm in height, no history of diabetes) due to less influence of gender, age and height [12].

4.2 Setting

Here, the simulation settings are given. Considering that the patients are admitted to ICU with no BG management, the initial BG level is assumed to be 200 mg/dL (11.1 mmol/L) at admission. To keep BG level within 80 – 110 mg/dL the target BG level is 95 mg/dL . Parenteral glucose for nutrition is infused at a constant rate of 2.86 mg/kg/min , which is known because it is set by doctors or nurses. The maximum insulin infusion rate is 200 mU/min to avoid hyperinsulinemia. To evaluate simulation results, we calculate mean BG levels, mini-

Table 4 Description of the ten insulin sensitivity profiles [13, 14].

Profile	Description
V1	Identified from clinical data from [20] at one-hour intervals
V2, V3	No. V1 profile + random value between -0.05 and 0.05 with uniform distribution
V4, V5	No. V1 profile + random value between 0 and 0.1 with uniform distribution
V6, V7	No. V1 profile + random value between 0.05 and 0.15 with uniform distribution
V8	No. V1 profile + 0.05 increase at 10-hour intervals after 30 h
V9	No. V4 profile + 0.05 increase at 10-hour intervals after 30 h
V10	No. V6 profile + 0.05 increase at 10-hour intervals after 30 h

mal BG levels, percentage durations of BG level within the range of 80–110 mg/dL and below 80 mg/dL after two hours from the start of glycemic control assuming hyperglycemia at the time of admission.

Furthermore, to assess robustness of our system, a simulation of changing the parenteral glucose infusion rate from 2.86 mg/kg/min to 2.38 mg/kg/min at 20 h is performed, assuming that the change of glucose infusion rate is unknown.

4.3 Results

Figure 5 illustrates the simulation result of a virtual patient weighing 60 kg with insulin sensitivity profile No. V8. In the top panel, the dot-dashed line is the target BG level (95 mg/dL), and the dotted lines are the upper and lower bounds of the desired BG range. The second panel shows parenteral and enteral glucose infusion. The third panel shows insulin infusion obtained by the system. The fourth panel shows insulin sensitivity of the patient. The bottom panel shows insulin sensitivity identified by the system.

Figure 5 illustrates the simulation result of a virtual patient weighing 60 kg with insulin sensitivity profile No. V8. In the top panel, the dot-dashed line is the target BG level (95 mg/dL), and the dotted lines are the upper and lower bounds of the desired BG range. The second panel shows parenteral and enteral glucose infusion. The third panel shows insulin infusion obtained by the system. The fourth panel shows insulin sensitivity of the patient. The bottom panel shows insulin sensitivity identified by the system.

Figure 6 shows the simulation result of No. V8 with parenteral glucose infusion rate decreased from 2.86 mg/kg/min to 2.38 mg/kg/min at 20 h. From the figure, the estimated insulin sensitivity is slightly different from that in Figure 5 due to the difference in glucose infusion rate, and the control system is able to maintain BG level against such a disturbance.

Fig. 5 Simulation result of BG control in a virtual patient with insulin sensitivity profile No. V8, 60 kg. The top panel shows the patient's BG, the desired BG range of 80–110 mg/dL (dotted line) and the target BG level of 95 mg/dL (dot-dashed line). The second panel shows parenteral and enteral glucose infusion. The third panel shows insulin infusion obtained by the system. The fourth panel shows insulin sensitivity of the patient. The bottom panel shows insulin sensitivity identified by the system.

Table 5 shows the simulation results of mean BG levels, minimal BG levels, and percentage durations of BG within the range of 80–110 mg/dL and below 80 mg/dL for each insulin sensitivity profile. **Table 6** compares the glycemic control system developed in this study and our previous system with respect to mean BG, minimal BG and percentage durations of BG within the range of 80–110 mg/dL and below 80 mg/dL, tested on 30 virtual patients. The duration with BG level within the desirable BG range improves significantly with the system developed in this study, and the duration of BG level below 80 mg/dL tends to be shorter, while the minimal BG becomes lower.

Fig. 6 Simulation result of BG control in a virtual patient (insulin sensitivity profile No. V8, 60 kg) with parenteral glucose infusion rate decreased from 2.86 mg/kg/min to 2.38 mg/kg/min.

Table 5 Results of glycemic control in 30 virtual patients grouped in 10 insulin sensitivity profiles.

Profile No.	Mean BG (mg/dL)	Min BG (mg/dL)	80–110 mg/dL (%)	< 80 mg/dL (%)
V1	115.1	85	50.1	0.0
V2	115.7	82	49.9	0.0
V3	115.3	89	49.9	0.0
V4	104.5	68	74.2	2.0
V5	106.9	70	64.4	2.3
V6	101.1	60	85.2	2.3
V7	100.6	72	86.5	1.3
V8	105.8	71	82.7	1.5
V9	100.8	68	86.7	1.5
V10	98.6	60	85.2	4.5
Mean	106.4	60	71.5	1.5

5. Discussion

In the present study, we develop a glycometabolism model of critically ill patients considering a time-varying parameter of insulin sensitivity, nonlinear insulin-depen-

Table 6 Comparison of the performance of the glycemic control system proposed in this study and the system in previous study [14] tested on 30 virtual patients.

	Present	Previous [14]	
Mean BG (mg/dL)	106.4	106.8	$p = 0.1271$
Min BG (mg/dL)	60	68	—
80–110 mg/dL (%)	71	69	$p = 0.0028$
< 80 mg/dL (%)	1.5	1.9	$p = 0.0995$

dent and independent glucose uptake, saturation of interstitial insulin effect and input of parenteral and enteral glucose and exogenous insulin. In our previous study [14], we identified the model parameters from the data of obese patients with low glucose tolerance [22], and the model predictive BG control system based on that model showed insufficient performance to avoid hypoglycemia. In this study, the model parameters are identified from clinical data of BG as well as glucose and insulin infusion rates from ICU patients. The simulation results (**Table 3**) demonstrate higher accuracy of the model. However, only postoperative patients are taken into consideration, which is a limitation of the present study.

Our glycometabolism model also contains a compartment of small intestinal glucose absorption, which allows administration of enteral glucose through the intestine. We obtain a low intestinal glucose absorption rate p_6 of 0.2872 in Eq. (1) (see **Table 2**), which demonstrates a reduced small intestinal glucose absorption rate in ICU patients as pointed out in a previous report [23]. However, we believe that the small intestinal glucose absorption rate in critically ill patients may vary, especially upon recovery from illness. Therefore, we still need to improve the small intestinal glucose absorption model in critically ill patients.

To cope with the time variability of insulin sensitivity in critically ill patients as well as to achieve an accurate glycemic control, we perform online identification of the value of insulin sensitivity parameter in Eq. (6) at 30 min intervals utilizing the preceding 30-min data of measured blood glucose levels as well as glucose and insulin infusion rates. As shown in the bottom panel of **Fig. 5**, the identified insulin sensitivity value appears to increase slowly corresponding to the insulin sensitivity profile in patient No. V8, which indicates good performance of online identification of insulin sensitivity. It should be noted that the identified insulin sensitivity may include the influence of the inter- and intra-patient differences of other parameters on BG.

When applying to 30 virtual patients, our glycemic

control system achieves 71% of BG measurements within the range of 80–110 mg/dL and 1.5% of BG measurements under 80 mg/dL. The percentage durations of BG within the ranges of 80–125 mg/dL and 80–144 mg/dL using the system developed in this study vs our previous system are 88% vs 87% and 94% vs 94%, respectively. The minimal BG measurement of our system is 60 mg/dL and no severe hypoglycemic events of BG under 40 mg/dL [18] is observed. Although our system yields similar results for mean BG, percentage durations of BG within the ranges of 80–110 mg/dL, 80–125 mg/dL and 80–144 mg/dL compared to our previous study [14], percentage duration of BG under 80 mg/dL is reduced. In previous studies, percentage duration of BG within 80–125 mg/dL was 76.8% and that within 80–144 mg/dL was 87.7% [7]; and the minimal BG measurements during glycemic control was 59 mg/dL [6] and 26 mg/dL [9]. Severe hypoglycemic events of BG under 40 mg/dL [18] was observed in 0.04% of BG measurements [7, 9]. These results suggest the safety of our system. However, it is difficult to compare our results with other studies [6, 7, 9], because of the differences in BG control conditions and patients.

In this study, we construct our glycemic control system utilizing nonlinear model predictive control because this method provides more accurate prediction of BG than linear model predictive control. In the linear model predictive control system utilizing a linearized model, the controller cannot predict BG with sufficient accuracy (results not shown) and the percentage durations of BG within the ranges of 80–110 mg/dL and 80–125 mg/dL are 20% and 60%, respectively, which demonstrates more precise prediction of BG by the nonlinear glycometabolism model than the linearized one.

In **Fig. 6**, the system reduces insulin infusion rate rapidly to maintain normoglycemia when parenteral glucose infusion rate decreases at 20 h, which shows sufficient ability of BG prediction for the change in glucose infusion rate. Only parenteral glucose infusion is considered in the simulation because there were no results of enteral glucose infusion in our previous study, and because the absorption rate of enteral glucose may be time-varying as mentioned above. For a precise prediction of BG in critically ill patients, improvement on BG prediction method may be needed. Future work also includes BG control in ICU patients under both parenteral and enteral glucose infusions.

6. Conclusion

In this study, we improve the glycometabolism model of ICU patients using clinical data from ICU patients, and construct a BG control system using nonlinear model predictive control method with insulin sensitivity online

identification based on the model. Simulation results demonstrate that our model represents glycometabolism of ICU patients better than our previous model, and that our BG control system based on the new model provides safe BG control for ICU patients. For clinical application, further improvement of performance and model of enteral glucose is necessary.

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