Mathematical Model of Glucose-Insulin Metabolism and Model Predictive Glycemic Control for Critically Ill Patients Considering Time Variability of Insulin Sensitivity

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Doctoral Dissertation

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Abstract

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Hyperglycemia is very common in critically ill patients or patients after surgery even if those have no history of diabetes, and is associated with bad outcomes such as sepsis, multiple organ failure, and even death. These patients are usually admitted into intensive care units (ICUs). Since the landmark study of tight glucose control (TGC) maintaining blood glucose (BG) levels within the range of 80–110 mg/dL has shown the benefit in the reduction of not only mortality and morbidity but also medical cost, TGC has been widely studied and glycemic control systems that can provide personalized infusion advice have been developed. Among them the glycemic control systems using model predictive control (MPC) method deal with inter- and intra-individual differences by setting the model parameters according to the patient and have shown effectiveness and safety. Nevertheless, some hypoglycemic episodes (BG $<$ 80 mg/dL) with several severe hypoglycemic events (BG $<$ 40 mg/dL) still remained. The purpose of the thesis is to develop a closed-loop glycemic control system for critically ill patients that can provide safer and more effective BG control.

Firstly, we develop a closed-loop glycemic control system using nonlinear MPC method based on an existing glycometabolism model with no time-varying parameter, which is regarded as an early stage of the development of our BG control system for critically ill patients. We also create a set of virtual patients from clinical data given in literature with typical variations of insulin sensitivity to assess the performance of the system. Simulation results of the BG control system show that the percentage of duration time

within the desired range for patients with unknown insulin sensitivity is smaller than that for patients with known insulin sensitivity, which suggests that it is important to grasp insulin sensitivity for the glycemic control for critically ill patients.

Secondly, to easily deal with time variability of insulin sensitivity and to predict BG in critically ill patients as precisely as possible we modify the glycometabolism model by introducing a parameter corresponding to insulin sensitivity, nonlinear effects of glucose utilization, a saturation of insulin effect, and a route of enteral glucose infusion. The parameter values of the modified model are identified from clinical data of patients collected in the ICU of Kagawa University Hospital with the approval of the Ethics Committee of Kagawa University Hospital.

Then, we construct an online identification algorithm of insulin sensitivity to easily cope with inter- and intra-individual differences of insulin sensitivity in critically ill patients. With the online identification of insulin sensitivity, a new glycemic control system using nonlinear MPC based on the modified model is developed. We apply the glycemic control system to the aforementioned virtual patients and a new set of virtual patients created from the clinical data of the patients in the ICU of Kagawa University Hospital to assess the performance of the new system. Simulation results show an improvement in glycemic control. However, the ability to prevent hypoglycemia is insufficient and needs to be improved.

Lastly, regarding hypoglycemia prevention as important, we further improve the glycemic control system using zone MPC, which is suitable for maintaining BG within a range. Simulation results of the system using zone MPC show an improvement on the percentage of duration time of BG below 80 mg/dL and comparable performance of glycemic control maintaining BG within the desired range of 80–110 mg/dL to the system using nonlinear MPC, which demonstrates successfulness of preventing hypoglycemia by using zone MPC.

The present study shows effectiveness and safety of the developed glycemic control system utilizing zone model predictive control with online identification of insulin sensitivity for critically ill patients *in silico*.

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Contents

Chapter 1

Introduction

1.1 Background

Stress-induced hyperglycemia is a transient elevation of the blood glucose (BG) due to the stress of illness or injury. It is very common in critically ill patients or patients after surgery even if those have no history of diabetes. These patients are often called "ICU patients" because they are usually admitted into intensive care units (ICUs). In a retrospective cohort study with patients admitted to 173 medical, cardiac, surgical and mixed ICUs, there are only approximate 30% of patients who have mean BG levels within the range of 70–110 mg/dL (3.9–6.1 mmol/L), approximate 70% of patients suffering from hyperglycemia with mean BG levels above 110 mg/dL, furthermore approximate 10% of patients suffering from BG exceeded 200 mg/dL (11.1 mmol/L) [1]. The abnormally elevated BG level in these patients is caused by a disorder of hormones by severe injury or infection [2], such as diminished secretion of insulin, a hormone decreasing BG, and increased counter-regulatory hormones. Thus, changes in glucose metabolism of the whole body together with excessive nutrition delivery result in stress-induced hyperglycemia.

Hyperglycemia in ICU patients is associated with high mortality and morbidity such as multiple organ failure and sepsis [1,3]. According to [1], the mortality is 7.3% when mean BG is kept within the range of 70–110 mg/dL (3.9–6.1 mmol/L), 10.2% within the range of 111–145 mg/dL (6.2–8.0 mmol/L), 14.8% within the range of 146–199 mg/dL (8.1–11.0 mmol/L), 17.3% within the range of 200–300 mg/dL (11.1–16.7 mmol/L), and increases to 21.9% when mean BG exceeds 300 mg/dL. It has also been indicated that the mortality increase by hyperglycemia is independent of types of ICUs, levels of severity of illness, and history of diabetes. Similarly, according to [3], hospital mortality increases from 9.6% for patients with mean BG between 80 and 99 mg/dL (4.4–5.5 mmol/L) during ICU stay to

12.5% for patients with mean BG between the range of 100–119 mg/dL (5.6–6.6 mmol/L) and rises to 42.5% for patients with mean BG over 300 mg/dL. In this way, mortality caused by hyperglycemia is a big problem in ICU patients. Therefore, hyperglycemia in ICU patients is treated by administering exogenous insulin, whose amount or rate is adjusted by medical staff based on their experience or insulin infusion protocols.

There have been many studies on blood glucose management for critically ill patients [3–23]. The landmark study on BG management for ICU patients by Van den Berghe *et al.* [4] in 2001 demonstrated that in-hospital mortality in a surgical ICU was reduced by 34% when maintaining BG of critically ill patients within the range of 80–110 mg/dL (4.4–6.1 mmol/L) by intensive insulin therapy (IIT) using continuous intravenous insulin (7.2% in-hospital mortality), compared with treatment by the conventional therapy (10.9% in-hospital mortality) maintaining BG within the range of 180–200 mg/dL (10.0–11.1 mmol/L). The treatment of maintaining BG within the range of 80–110 mg/dL by IIT is called tight glucose control (TGC). TGC also contributes to morbidity reduction in multiple-organ failure, bloodstream infections, red-cell transfusions, acute renal failure requiring dialysis or hemofiltration, and reduction of the period of mechanical ventilation and duration of ICU stay [4]. Krinsley [3] also showed decrease in hospital mortality, length of ICU stay and morbidity in medical-surgical ICU patients when treating them with intensive glycemic management protocol (target BG level: < 140 mg/dL (7.8 mmol/L)) compared with before the use of the protocol. As demonstrated in [24], there is a strong relationship between survival in critically ill patients without diabetes and more than 80% of duration time rate in BG range of 70–140 mg/dL (3.9–7.8 mmol/L).

In addition, the utilization of TGC shows benefit in substantial cost savings in ICU [25, 26]. In a 14-bed mixed medical-surgical adult ICU, cost-saving was USD 1,580 per patient because of decreases in all major categories of resource utilization such as imaging, pharmacy, laboratory, insulin, and supplies [25]. In a randomized study of 1,548 mechanically ventilated patients receiving IIT or conventional therapy in a surgical ICU [26], the total hospitalization cost was EUR 7,931 and EUR 10,569 per patient in IIT group and conventional group, respectively, with cost savings of EUR 2,638 per patient.

However, the subsequent study by Van den Berghe *et al.* [5] in medical ICU patients and other studies [6–10] did not show any benefit on mortality from TGC due to increase of hypoglycemia caused by IIT. Because of the risk of hypoglycemia, the American Association of Clinical Endocrinologists and American Diabetes Association consensus statement [11] recommends a relaxation of target BG range to 140–180 mg/dL (7.8–10.0 mmol/L) for ICU patients. However, BG control with a high target BG range may not give intrinsic merit on mortality and morbidity.

Since the landmark study by Van den Berghe *et al* [4] in 2001, TGC has been widely discussed in the world, which propels improvement (and standardization) of insulin infusion protocols in ICU and development of computer-based glycemic control systems to provide effective glycemic management without causing the patients hypoglycemia.

Paper-based insulin infusion protocols [3, 6, 12] give simple algorithms written in tables and provide information on when BG levels should be measured and how many units of insulin should be infused. Computer-based glycemic control systems are based on paper-based insulin infusion protocols or using proportional-derivative (PD) control, proportional-integral-derivative (PID) control, or model predictive control (MPC) methods. The use of computer-based systems enables a more complex insulin infusion algorithm and reduces human errors. PD or PID glycemic control systems, such as Glucommander [13] and GRIP [14], determine the insulin infusion rate from the difference between BG measurement and desired BG level, and can give personalized insulin advice on insulin infusion considering the intra-individual difference in ICU patients. The disadvantage of the PD or PID control system is the lack of consideration of the glucose-insulin dynamics of the patients. On the other hand, MPC systems predict the future BG levels in an ICU patient from the current BG measurement, glucose and insulin infusion rates using a mathematical model with patient-specific parameter(s) of glucose-insulin dynamics of the patients, and determine the optimal insulin infusion rate or both insulin and glucose infusion rates. MPC systems can deal with inter- and intra-individual differences among ICU patients considering patient-specific parameters. Due to these benefit, glycemic control systems for TGC of critically ill patients using MPC method have been developed, such as:

- LOGIC-Insulin algorithm [15,16] (target BG range: 80–110 mg/dL (4.4–6.1 mmol/L)),
- Stochastic targeted glycemic control system [17, 18] (target BG range: 80–145 mg/dL (4.4–8.0 mmol/L)),
- Stochastic model predictive glycemic control system [19] (target BG range: 80–145 mg/dL (4.4–8.0 mmol/L)),
- Enhanced model predictive control system [20,21] (target BG range: 80–110 mg/dL (4.4–6.1 mmol/L)),
- Glucosafe system [22,23] (target BG range: 80–110 mg/dL (4.4–6.1 mmol/L)).

Although all of them have demonstrated effectiveness through virtual or clinical trials, hypoglycemic events of approximate 1–3% BG measurements [15–20] and even severe

hypoglycemia (BG $<$ 40 mg/dL (2.2 mmol/L) [11]), which is dangerous for the patients, still occurred.

1.2 Objective

As mentioned above, a glycemic control system for critically ill patients with sufficient safety and control performance has not been developed yet. In this thesis, aiming to realize a safe and efficient glycemic control for critically ill patients, we study glucose-insulin dynamics in critically ill patients and their inter- and intra-individual differences, and closed-loop BG control systems for TGC of critically ill patients. To put it concretely, we improve the ICU minimal model given by Van Herpe *et al.* [27], one of the representative model of glucose-insulin dynamics in critically ill patients, to easily deal with inter- and intra-individual differences in insulin sensitivity and to precisely represent insulin effect on BG. Then, we develop an online identification algorithm of the insulin sensitivity to cope with inter- and intra-individual differences and design several glycemic control systems for critically ill patients utilizing nonlinear MPC and zone MPC strategies to maintain BG levels within the desired range and to prevent hypoglycemic events. In addition, to assess the performance of closed-loop glycemic control systems for critically ill patients, we create virtual patients with time-varying insulin sensitivity that changes as that of critically ill patients in ICU.

1.3 Structure

In Chapter 2, we give a brief introduction of glucose-insulin metabolism in the body and stress-induced hyperglycemia in critically ill patients. Then, the landmark study of tight glucose control and the subsequent studies, and several paper-based insulin infusion protocols and computer-based ones using PD, PID control and MPC methods are introduced. In the last part of this chapter, we introduce the existing model predictive glycemic control systems and give descriptions of mathematic models of glucose-insulin dynamics of critically ill patients that the systems are based on.

In Chapter 3, we construct a closed-loop glycemic control system using nonlinear model predictive control method based on the ICU minimal model [27], which is regarded as an early stage of the development of glycemic control system in this thesis. We treat patient-specific parameters as constants during glycemic control. The purpose of the early-stage system is to assess the performance of the nonlinear MPC controller with a fixed model when the averaged insulin sensitivity of the patient is known and to confirm

the importance of grasping insulin sensitivity. In addition, we create virtual patients with time-varying insulin sensitivity from clinical data of BG measurements, glucose, and insulin infusion rates given in a literature [42], which are used to assess the performance of glycemic control systems developed in Chapter 3 and the following chapters.

Considering that the insulin sensitivity may be the key of glycemic control from the simulation results in Chapter 3, we modify the glycometabolism model in Chapter 4 by introducing a parameter of insulin sensitivity to easily deal with inter- and intra-individual differences, nonlinear effects of insulin-dependent and insulin-independent glucose utilization, a saturation of interstitial insulin effect and a compartment for enteral nutrition to precisely represent glucose-insulin metabolism in critically ill patients. We identify the parameter values of the modified model from clinical data of ICU patients collected in the ICU of Kagawa University Hospital with the approval (No. 2018-147) of the Ethics Committee of Kagawa University Hospital. Then, we confirm that the developed model can represent clinical BG responses of critically ill patients only by changing the insulin sensitivity parameter. We also analyze the time variability of insulin sensitivity in ICU patients.

In Chapter 5, we develop an online identification algorithm of insulin sensitivity to cope with inter- and intra-individual differences of BG response to insulin. Then, a new glycemic control system with the developed online identification algorithm of insulin sensitivity using nonlinear model predictive control based on the new model is constructed. We also generate a new set of virtual patients from the ICU clinical data collected in the ICU of Kagawa University Hospital to more appropriately evaluate the practical performance of the glycemic control system. We apply the developed control system to the virtual patients created in Chapter 3 and the virtual patients created in this chapter to assess the effectiveness and safety of the developed system and compare the performance of the developed system with those in Chapter 3 and other existing systems.

In Chapter 6, to improve the ability to prevent hypoglycemia we construct a glycemic control system using zone model predictive control because it is a control method that keeps the controlled variable within a target range, which may be suitable for maintaining BG within a range. Then, we apply the developed glycemic control system to the virtual patients created in Chapter 3 and in Chapter 5 to assess the effectiveness and safety of the control system and compare the performance of the developed systems in Chapter 5 and Chapter 6.

In the last chapter, we summarize the thesis and give future works.

Chapter 2

Stress-Induced Hyperglycemia and Previous Studies on Glycemic Control of Critically Ill Patients

We aim to develop a safe and effective glycemic control system for critically ill patients so that it is necessary to know glucose-insulin dynamics in the patients. In this chapter, first, we give a brief introduction on glucose-insulin action, *i.e.* glucose utilization and insulin-mediated glucose translocation into cells, and mechanism of hyperglycemia in critically ill patients. Then, we review tight glucose control in ICUs, one of the treatments of hyperglycemia in critically ill patients, including several previous studies of paper-based and computer-based insulin infusion protocols. Furthermore, we focus on model-based insulin infusion protocols, one type of computer-based protocols, due to the merit of considering inter- and intra-individual differences in ICU patients and introduce the mathematic models used in the protocols.

2.1 Glucose-Insulin Metabolism

Glucose is the main energy for the brain and cells in the whole body and low glucose concentration in the blood causes loss of consciousness and even death. Blood glucose is regulated tightly within a normal range by glucose removal from the blood in a high glucose concentration and glucose release into the blood in a low glucose concentration. Insulin is an important hormone related to glucose regulation, which is secreted from the pancreas β-cells. There are two ways of glucose removal from the blood; one is stimulated by insulin (insulin-dependent glucose removal), and the other is not (insulin-independent

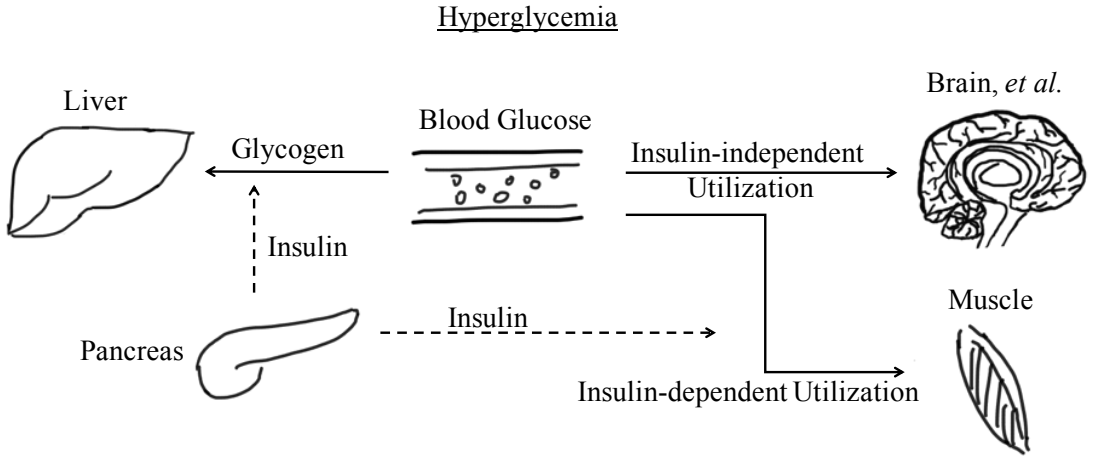


Figure 2.1: In hyperglycemia, blood glucose is removed by insulin-dependent utilization promoted by the insulin secretion from the pancreas and storage as glycogen in the liver.

glucose removal).

In a normal BG level, 80% of whole-body glucose is utilized by insulin-independent glucose uptake, mainly by the central nervous system, the rest of 20% is taken by skeletal muscle, half of which is insulin-independent and the other half is insulin-dependent [2]. The elevated glucose level in the blood (*i.e.* hyperglycemic state), *e.g.* after taking a meal, stimulates the secretion of insulin from the β-cells that promotes glucose storage into muscle and adipocytes to maintain BG within the normal range [28] (see Figure 2.1). The liver removes 30%–40% of ingested glucose and stores it as glycogen, which depends on the activity of enzymes such as glucokinase, intermediates such as glucose-6-phosphate, and glucose concentration in the portal vein [2]. Insulin decreases blood glucose level by promoting glucose uptakes and glycogen synthesis and suppressing gluconeogenesis, glucose generation from certain non-carbohydrate carbon substrates such as proteins and lipids.

In contrast, in the hypoglycemic state, the pancreas α-cells secrete glucagon that promotes the breakdown of glycogen into glucose, which is also called glycogenolysis or endogenous glucose production (EGP), to elevate blood glucose level and inhibits the secretion of insulin as shown in Figure 2.2. The glycogenolysis provides approximately 50% of overall hepatic glucose output during overnight fasting [2]. In this way, the liver also plays an important role in BG regulation.

Glucose transporters, membrane proteins that transport glucose across the cell membrane, play an important role in glucose utilization. There are five glucose transporters

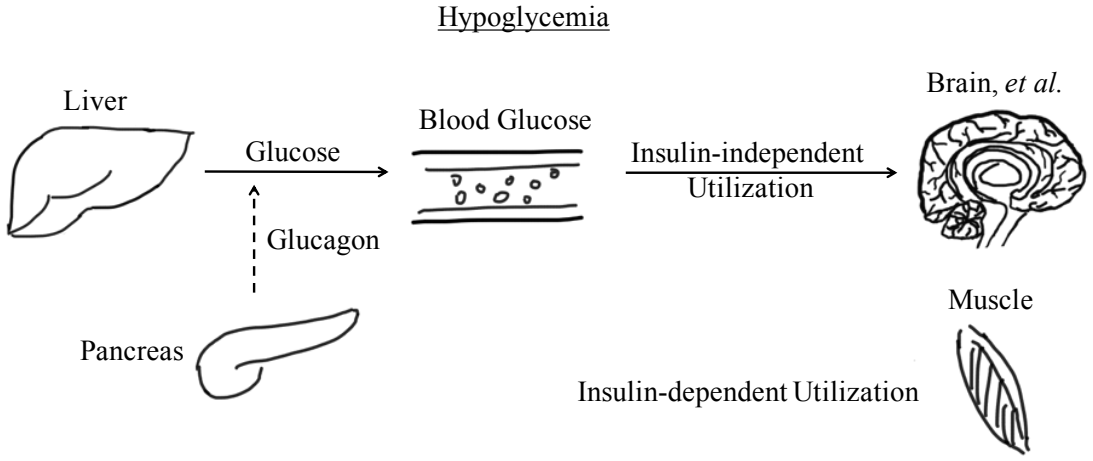


Figure 2.2: In hypoglycemia, blood glucose is elevated by the breakdown of glycogen into glucose, which is stimulated by the secretion of glucagon from the pancreas.

(*i.e.* GLUT-1, 2, 3, 4 and 5) relating to glucose uptake into cells:

- GLUT-1: High-affinity glucose transporter. Widely appearing in the whole body, high concentration in the brain, erythrocytes, and endothelial cells;
- GLUT-2: Low-affinity glucose transporter. Appearing in the kidney, small intestinal epithelium, liver, pancreatic beta cells;
- GLUT-3: High-affinity glucose transporter. Appearing mainly in neurons;
- GLUT-4: High-affinity insulin-dependent glucose transporter. Appearing in skeletal muscle, cardiac muscle, adipose cells;
- GLUT-5: Fructose transporter. Very low-affinity for glucose.

Among them, GLUT-1, GLUT-2, and GLUT-4 are especially important for glucose uptake [28]. GLUT-1 is responsible for basal glucose uptake even under the hypoglycemic condition. GLUT-2 is involved in uptake and release of glucose by the liver and ensures the permeability of glucose to the liver. GLUT-4 relates to insulin-stimulated glucose uptake in muscle and adipose tissue [29]. Note that only GLUT-4 is activated by insulin. Usually, GLUT-4 exists in the intracellular compartment not in the plasma membrane in the absence of insulin. Binding of insulin to the insulin receptor in the plasma membrane involves translocation of GLUT-4 from the intracellular compartment to the plasma membrane, which results in glucose transport into the cell [28, 29].

2.2 Stress-Induced Hyperglycemia in Critically Ill Patients

Severe injury or infection involves a disorder of hormones that results in the whole body changes in glucose uptakes [2]. Insulin resistance is common in critically ill patients, which appears as a decreased effect of insulin on glucose uptake. However, the mechanism of insulin resistance in these patients is complex. It is suggested that illness causes defective translocation of GLUT-4 and diminishes glucose uptake in skeletal muscle and fat tissue [29, 30]. In addition, a high level of tumor necrosis factor-α (TNF-α), one of the cytokines, may play an important role in reducing insulin sensitivity. It has been demonstrated that TNF-α directly interferes insulin signaling through its receptor, blocks insulin action, and reduces insulin-stimulated glucose uptake [31].

Furthermore, during a critical illness such as trauma and sepsis, blood glucose level rises by glucagon, catecholamines, cortisol, and growth hormone (stimulating glycogenolysis and gluconeogenesis), which results in excessive hepatic glucose production [2]. It is suggested that low to the normal insulin level during critical illness together with insulin resistance and increased secretion of counter-regulatory hormones result in stress-induced hyperglycemia [29]. Other factors that promote hyperglycemia are exogenous dextrose delivery or pre-existing diabetes [2].

2.3 Tight Glucose Control

Although glucose is the main energy for the whole body, excessive glucose in the blood in critically ill patients is associated with bad outcomes such as sepsis, multiple organ failure, and an increase of mortality. There is a J-shaped relationship between blood glucose level and mortality in ICU (Figure 2.3), especially BG over 145 mg/dL raises the mortality risk [32].

Since the landmark study of the Leuven intensive insulin therapy trial by Van den Berghe *et al.* [4] in 2001 demonstrated that in-hospital mortality in a surgical ICU was reduced by 34% when maintaining BG of critically ill patients within the range of 80–110 mg/dL (4.4–6.1 mmol/L) by TGC (7.2% in-hospital mortality), compared with the treatment of conventional therapy (10.9% in-hospital mortality) of maintaining BG within the range of 180–200 mg/dL (10.0–11.1 mmol/L), TGC of maintaining BG within the range of 80–110 mg/dL has been widely discussed in the world. However, in their subsequent study [5] in 2006, in which they applied the same BG therapy to patients in medical ICU, there was no significant improvement of in-hospital mortality by the intensive treatment

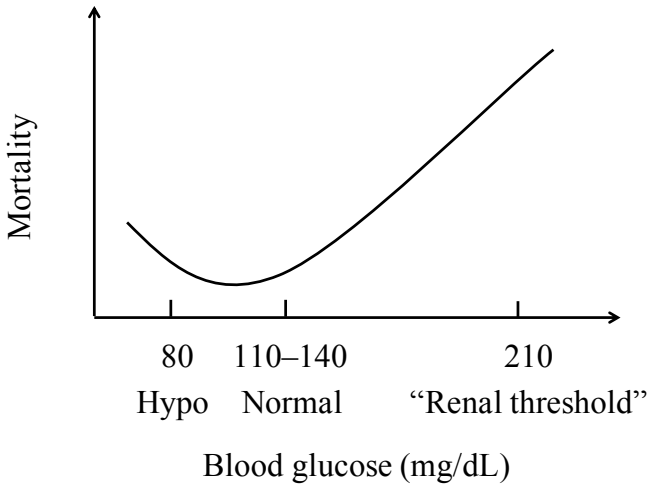


Figure 2.3: J-shaped mortality relationship for glycemia for patients in ICU [32]

(37.3% in the intensive treatment vs 40.0% in the conventional treatment, $p = 0.33$), despite reductions of morbidity of acquired kidney injury, earlier weaning from mechanical ventilation and earlier discharge from medical ICU.

The benefit of TGC in mortality has not found in other studies [6–10]. There was no significant difference of mortality between the intensive treatment with target BG at 80–110 mg/dL (4.4–6.1 mmol/L) and the conventional treatment with BG target at 180–200 mg/dL (10.0–11.1 mmol/L) in [7]. Although ICU mortality in the intensive group was reduced [6] from 17.1% in the conventional group to 13.5% ($p = 0.30$) and 28-days mortality in the intensive group was decreased from 26.0% in the conventional group to 24.7% ($p = 0.74$) in [8], the p values did not show significant benefit of the intensive insulin therapy. In the Glucontrol study [9], mortality in ICU was 17.2% in intensive group with BG target at 80–110 mg/dL (4.4–6.1 mmol/L) compared to 15.3% in conventional group with BG target at 125–180 mg/dL (7.8–10.0 mmol/L). In the NICE-SUGAR study [10], mortality within 90 days was 27.5% in the intensive group with target BG of 81–110 mg/dL (4.5–6.0 mmol/L) versus 24.9% in the conventional group with target BG of 144–180 mg/dL (8.0–10 mmol/L), and the mortality was not reduced by the intensive treatment.

The different outcomes between the Leuven studies [4, 5] and others [6–10] may be explained by differences in glucose delivery methods between the studies; only the Leuven studies utilize a high rate of parenteral nutrition [33]. Excessive parenteral glucose leads to hyperglycemia and affects the gut, immune system, liver, endocrine, and metabolic condition that is associated with organ failure and death [33, 34]. It is suggested that intensive insulin therapy improves the outcome of patients who mainly receive parenteral

nutrition, in contrast, the increased mortality in the other studies with enteral feeding may be associated with hypoglycemia by receiving intensive insulin [33].

The American Association of Clinical Endocrinologists and American Diabetes Association (AACE/ADA) consensus statement [11] gives relaxation of BG target range of 140–180 mg/dL (7.8–10.0 mmol/L) for the majority of critically ill patients with insulin therapy due to the risk of hypoglycemia. However, as shown in Figure 2.3, hyperglycemia increases mortality especially when BG exceeds 145 mg/dL in critically ill patients, and hypoglycemia causes patients' death without a doubt. AACE/ADA also suggests that improved and standardized insulin infusion protocols, careful implementation, and frequent glucose monitoring can minimize the risk of hypoglycemia [11].

There is no clear cutoff value of BG for hyperglycemia. Before 2001 hyperglycemia was defined as BG level above 180–200 mg/dL (10.0–11.1 mmol/L). The Leuven study in 2001 has defined hyperglycemia as the BG level above 110 mg/dL (6.1 mmol/L) [4]. According to AACE/ADA [11], hyperglycemia is defined as BG level above 140 mg/dL (7.8 mmol/L), hypoglycemia as BG level below 70 mg/dL (3.9 mmol/L) and severe hypoglycemia as BG level below 40 mg/dL (2.2 mmol/L). In this way, the definition of hypo- and hyperglycemia is not identical by insulin infusion protocols.

2.4 Insulin Infusion Protocols

An insulin infusion protocol is a guideline for managing BG in patients that guides doctors or nurses on how to determine insulin infusion rates and frequency of BG measurements. Insulin infusion protocols can be written in paper, recently computer-based protocols have been developed.

2.4.1 Paper-Based Insulin Infusion Protocols

Paper-based insulin infusion protocols have simple algorithms and always contain tables of correspondence between BG levels and insulin infusion rates. According to [3,6,12], the insulin infusion rate is adjusted only based on BG levels, which may be easy for doctors or nurses to use. However, a lack of considering inter-individual differences between patients may be the main limitation in such standardized protocols. Here, we give two examples of paper-based insulin infusion protocols, one is simple, and the other is slightly complex.

The Stamford Hospital ICU Protocol

The Stamford Hospital ICU Protocol for glycemic management [3] was written by a multidisciplinary group of physicians and nurses at Stamford Hospital, Connecticut,

USA in 2003. The goal of the protocol is regulating BG in patients below 140 mg/dL (7.8 mmol/L). The continuous insulin infusion starts when BG exceeds 200 mg/dL (11.1 mmol/L) on two successive measurements and then hourly BG measurement is taken. The protocol is a simple static sliding scale that adjusts insulin infusion rate only based on BG level as shown in Figure 2.4, the area inside the yellow dashed line which shows the continuous insulin infusion part.

According to [3], the use of the protocol improves BG management without a significant increase in hypoglycemic episodes and decreased 29.3% hospital mortality. The benefit of the protocol may also be contributed by a high nurse-patient ratio of 2:1 and full-time respiratory therapists, however, there is no significant change in staffing requirements in the ICU.

Yale Insulin Infusion Protocol

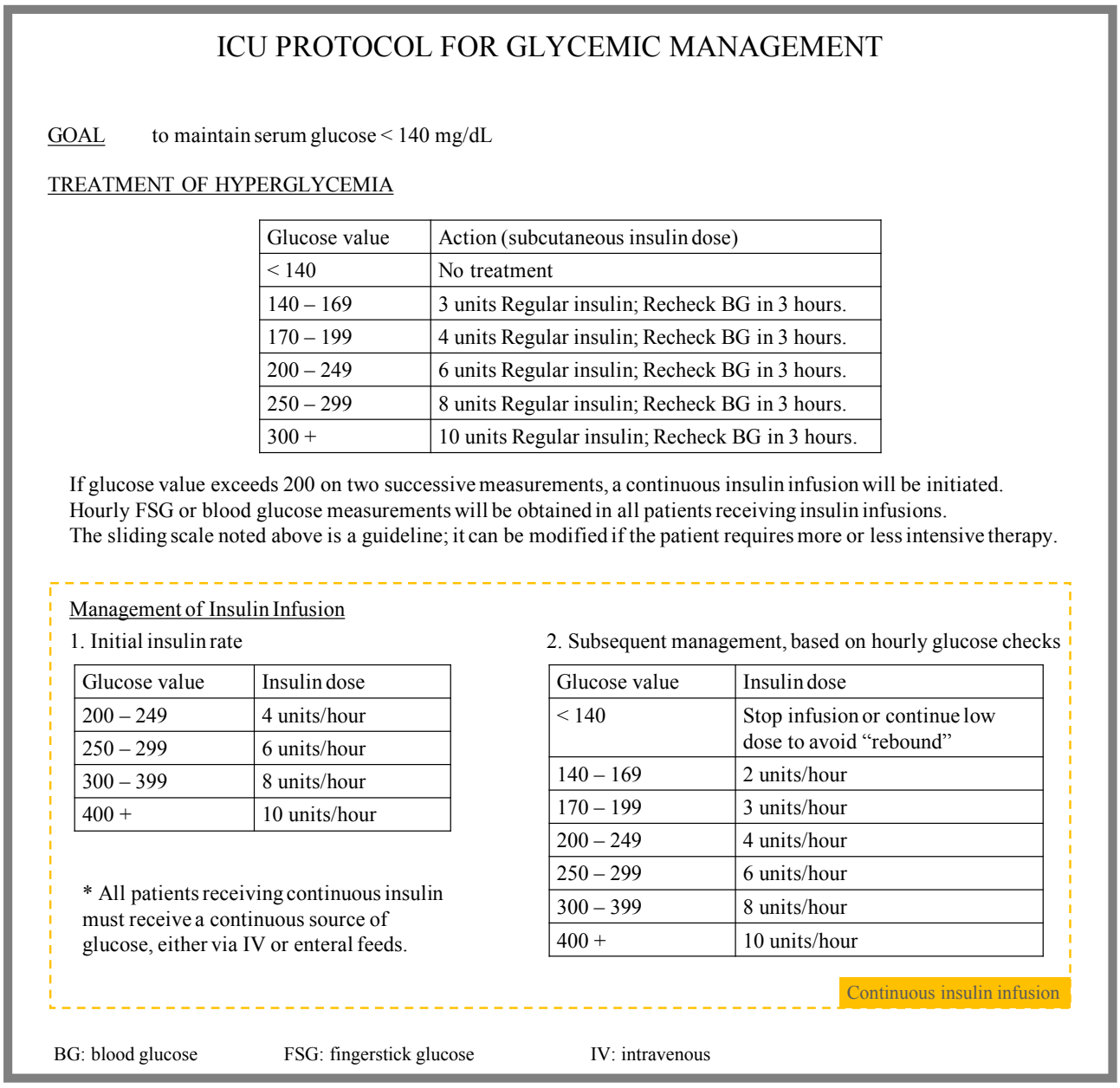
Yale insulin infusion protocol [12] was written by medical ICU directors and endocrine section clinical directors at Yale New Haven Hospital, Connecticut, USA where patient to nurse ratio is either 1:1 or 2:1. The goal of the protocol is to maintain BG levels within the range of 100–139 mg/dL (5.6–7.7 mmol/L). Unlike the Stamford Hospital ICU protocol, Yale insulin infusion protocol is a dynamic scale that adjusts insulin infusion rate based on glycemic change rate (the current and the prior BG levels in a patient) and current insulin infusion rate. First, a staff measures the current BG level in a patient. Then, the hourly rate of BG change is calculated based on the current and prior BG levels. Finally, based on the current insulin infusion rate the staff finds insulin infusion rate change from the table on the protocol shown in Figure 2.5. The protocol starts when BG level in a MICU patient exceeds 200 mg/dL (11.1 mmol/L), and requires hourly BG check in general and recommends every 15–30 minutes measurement when BG below 75 mg/dL (4.2 mmol/L) and every 4 hours measurement when BG is stable.

The protocol shows safety with only 0.3% of BG values under 60 mg/dL (3.3 mmol/L) and better glycemic control than the historical treatments [12].

The Yale protocol that adjusts insulin infusion rate based on the BG change rate and current insulin infusion rate may solve the intra-individual differences more appropriately than the other one. However, it is difficult for paper-based insulin infusion protocols to give personalized advice.

2.4.2 Computer-Based Insulin Infusion Protocols

There are several kinds of computer-based insulin infusion protocols; protocols based on paper protocols, utilizing proportional-derivative (PD) or proportional-integral-derivative



ICU PROTOCOL FOR GLYCEMIC MANAGEMENT

GOAL to maintain serum glucose < 140 mg/dL

TREATMENT OF HYPERGLYCEMIA

Glucose value	Action (subcutaneous insulin dose)
< 140	No treatment
140 – 169	3 units Regular insulin; Recheck BG in 3 hours.
170 – 199	4 units Regular insulin; Recheck BG in 3 hours.
200 – 249	6 units Regular insulin; Recheck BG in 3 hours.
250 – 299	8 units Regular insulin; Recheck BG in 3 hours.
300 +	10 units Regular insulin; Recheck BG in 3 hours.

If glucose value exceeds 200 on two successive measurements, a continuous insulin infusion will be initiated.
Hourly FSG or blood glucose measurements will be obtained in all patients receiving insulin infusions.
The sliding scale noted above is a guideline; it can be modified if the patient requires more or less intensive therapy.

Management of Insulin Infusion

1. Initial insulin rate

Glucose value	Insulin dose
200 – 249	4 units/hour
250 – 299	6 units/hour
300 – 399	8 units/hour
400 +	10 units/hour

* All patients receiving continuous insulin must receive a continuous source of glucose, either via IV or enteral feeds.

2. Subsequent management, based on hourly glucose checks

Glucose value	Insulin dose
< 140	Stop infusion or continue low dose to avoid "rebound"
140 – 169	2 units/hour
170 – 199	3 units/hour
200 – 249	4 units/hour
250 – 299	6 units/hour
300 – 399	8 units/hour
400 +	10 units/hour

Continuous insulin infusion

BG: blood glucose FSG: fingerstick glucose IV: intravenous

Figure 2.4: ICU protocol for glycemic management described in [3], yellow area shows the continuous insulin infusion part. The unit of glucose in this table is mg/dL.

YALE INSULIN INFUSION PROTOCOL

TARGET BLOOD GLUCOSE (BG) LEVELS 100 – 139 mg/dL

CHANGING THE INSULIN INFUSION RATE

If BG < 50 mg/dL
Recheck BG in 15 minutes
When BG ≥ 100 mg/dL, wait 1 hour, then restart insulin infusion at 50% of original rate.

If BG 50 – 74 mg/dL
If symptomatic, recheck BG in 15 minutes.
If asymptomatic, recheck BG in 15 – 30 minutes.
When BG ≥ 100 mg/dL, wait 1 hour, then restart infusion at 75% of original rate.

If BG ≥ 75 mg/dL

1. Determine the **current BG level** – identifies a column in the table:

BG 75 – 99 mg/dL	BG 100 – 139 mg/dL	BG 140 – 199 mg/dL	BG ≥ 200 mg/dL

2. Determine the **rate of change** from the prior BG level – identifies a cell in the table – Then move right for INSTRUCTIONS:

BG 75 – 99 mg/dL	BG 100 – 139 mg/dL	BG 140 – 199 mg/dL	BG ≥ 200 mg/dL	INSTRUCTIONS*
		BG ⬆ by > 50 mg/dL/h	BG ⬆	⬆ infusion by "2Δ"
	BG ⬆ by > 25 mg/dL/h	BG ⬆ by 1–50 mg/dL/h or BG UNCHANGED	BG UNCHANGED or BG ⬇ by 1–25 mg/dL/h	⬆ infusion by "Δ"
BG ⬆	BG ⬆ 1–25 mg/dL/h, BG UNCHANGED or BG ⬇ 1–25 mg/dL/h	BG ⬇ by 1–50 mg/dL/h	BG⬇ by 26–75 mg/dL/h	No infusion change
BG UNCHANGED or BG ⬇ by 1–25 mg/dL/h	BG ⬇ by 26–50 mg/dL/h	BG ⬇ by 51–75 mg/dL/h	BG ⬇ by 76–100 mg/dL/h	⬇ infusion by "Δ"
BG ⬇ by > 25 mg/dL/h	BG ⬇ by > 50 mg/dL/h	BG ⬇ by > 75 mg/dL/h	BG ⬇ by > 100 mg/dL/h	Hold × 30 min, then ⬇ infusion by "2Δ"

*Changes in infusion rate ("Δ") are determined by the current rate:

Current Rate (U/h)	Δ = Rate Change (U/h)	2Δ = 2 × Rate Change (U/h)
< 3.0	0.5	1
3.0 – 6.0	1	2
6.5 – 9.5	1.5	3
10 – 14.5	2	4
15 – 19.5	3	6
20 – 24.5	4	8
≥ 25	≥ 5	10

Figure 2.5: Yale insulin infusion protocol [12]. Only the compartment of CHANGING THE INSULIN INFUSION RATE is shown here.

(PID) control method, and model-based control method. Comparing to paper-based protocols, computer-based protocols enable more complex algorithms and reduce human errors. Some studies have demonstrated improvement in glycemic control when using a computer-based protocol [13–23, 35, 36].

We divide computer-based protocols into two types:

- based on paper protocols and PD or PID control method,
- based on model-based control method.

The former always gives insulin infusion rates from BG levels or BG changes, and the latter provides insulin infusion rate or both insulin and glucose infusion rates from predicted BG using glycometabolism models that can simulate glucose-insulin dynamics in patients.

Based on paper protocols or PID control method

Most of the computer-based protocols based on paper protocols or using PD or PID control method [13, 14, 35, 36] calculate insulin infusion rate from the recent BG measurement(s) and determine the time of the next BG measurement. For example, the GlucoCare IGC System [35] is an insulin-dosing calculator based on the Yale insulin infusion protocol [12].

PID control determines the manipulated input (*i.e.* insulin delivery rate) as a sum of the terms proportional to the error of the controlled output (*i.e.* BG measurement) from the desired setpoint (P), integral of the error (I) and derivative of the error (D) [37]. GRIP [14], Glucommander [13] (proportional-only) and GlucoStabilizer [36] are such type of computer-based protocols.

For example, the Glucommander system calculates the insulin infusion rate in a simple formula:

$$\text{insulin dose/h} = (\text{blood glucose} - 60\ \text{mg/dL}) \times \text{multiplier},$$

where the multiplier starts at 0.02 and shifts depending on the change of BG levels [13]. Different from the Glucommander system, the GRIP system calculates insulin infusion rate based on the previous insulin infusion rates, error of current BG from the target level and BG level changes as the following equation,

$$\Delta I = (1 + 0.25\overline{I_{-4\text{h}}})(0.2(G_0 - G_{\text{target}}) + 0.3\Delta_{-4\text{h}}G),$$

where ΔI is the proposed change of insulin infusion, $\overline{I_{-4\text{h}}}$ is the mean value of insulin infusion rate over the preceding 4 hours, G_0 is the current BG measurement, G_{target} is

the target BG level and $\Delta_{-4\mathrm{h}}G$ denotes the difference between the current BG level and 4 hours earlier BG level [14]. Although the GRIP algorithm is more complex than the Glucommander system, both systems have simple algorithms compared with model-based control systems that we will review below.

The use of such protocols have been demonstrated improvement in glycemic control, for example in [35] severe hypoglycemia readings of 0% and patients of 0% were achieved by the implementation of the GlucoCare while 0.05% and 5.8% in the use of the paper protocol, respectively; in [36], 51.5% of BG measurements were below 110 mg/dL with only 0.4% of hypoglycemia (BG $<$ 50 mg/dL) when using the Clarian GlucoStabilizer program while 31.5% of BG measurements before introduction of the program with 0.5% of hypoglycemia, however, lack of consideration of patient-specific responses and/or inputs of nutrition and prior insulin infusions may be disadvantages of such protocols, which model-based predictive control can deal with.

Based on model-based control method

Model-based control requires a mathematical model that represents the dynamics of blood glucose and insulin concentration in ICU patients and that includes patient-specific parameters (*e.g.* insulin sensitivity) and inputs of nutrition and insulin. Hence, it is not difficult to predict the future change of BG in patients from nutrition and insulin infusion rates and to avoid the risk of hypoglycemia using a model that can represent glucose-insulin dynamics precisely in an ICU patient. Comparing to PID control method, model-based control method can deal with inter- and intra-individual differences in ICU patients by setting model parameter(s) (*e.g.* insulin sensitivity) based on clinical data (*e.g.* BG measurements), and can adjust both glucose and insulin inputs to control BG level.

Several model-based predictive control systems have been developed for ICU patients and demonstrated safety and effectiveness. The representative systems are:

- LOGIC-Insulin algorithm [15, 16],
- Stochastic TARgeted (STAR) glycemic control system [17, 18],
- Stochastic model predictive (STOMP) glycemic control system [19],
- Enhanced model predictive control (eMPC) system [20, 21].
- The Glucosafe system [22, 23].

Before clinical trials with the LOGIC-Insulin algorithm, two virtual trials were made by the same group [39, 45]. In [39] a glycemic control system using model predictive control (MPC) method was constructed, in which the ICU Minimal Model [27, 38] was used to predict BG levels in ICU patients. The patient-specific parameters were re-estimated at one-hour or four-hour intervals after the identification of the initial model for each patient during the first 24 hours. Approximate 60% of BG measurements were kept within the range of 80–110 mg/dL in both simulations. However, more than 10% of BG measurements below 80 mg/dL were observed. In their subsequent study [45], they applied nonlinear MPC with moving horizon method and demonstrated its potential to control BG in ICU patients.

LOGIC-Insulin algorithm [15, 16] is a tight glucose control system for ICU patients that regulates BG levels within the range of 80–110 mg/dL. The control algorithm can be switched to MPC method or PID control method and adapts model parameters automatically using the incoming measurements so that it can deal with inter- and intra-individual differences between the patients. In a single-center trial (LOGIC-1 trial) [15], the LOGIC system reduced hypoglycemia with 2.3% of BG samples under 70 mg/dL (3.9 mmol/L) with no severe hypoglycemic (BG $<$ 40 mg/dL (2.2 mmol/L)) sample compared to 3.8% of BG samples under 70 mg/dL with 0.1% of severe hypoglycemic samples in a paper protocol group. It also achieved 68.6% of BG measurements within the target range compared to 60.1% in the paper protocol group. In their subsequent trial (LOGIC-2 trial) [16] for medical and surgical ICU patients of three hospitals, the percentage of duration time within the target range of the LOGIC system was improved to 67% from 47.1% in paper protocol group, and the LOGIC system gave comparable results in hypoglycemia compared with the paper protocol (1.5% vs 1.8% of BG samples below 70 mg/dL and 0.04% vs 0.05% of BG samples under 40 mg/dL). It indicated the improvement of TGC and the reduction of hypoglycemia by using the LOGIC system.

Stochastic TARgeted (STAR) glycemic control system [17, 18] uses Intensive Care Insulin-Nutrition-Glucose (ICING) model [41] (see the next section) and set the target BG range to 80–145 mg/dL (4.4–8 mmol/L). The system uses stochastic forecasting method that identifies the current insulin sensitivity based on the ICING model from the present BG measurement and predicts insulin sensitivity values over the next 1–3 hours based on a stochastic model, and can adjust both insulin and glucose infusion rates. In an *in silico* trial [17], the two-hourly version of STAR reduced 79% of patients from suffering severe hypoglycemia compared with the paper-based SPRINT protocol (3 vs 14 patients), and kept 82.5% of BG measurements within the range of 80–125 mg/dL (4.4–7 mmol/L) compared to 78.5% in SPRINT, which demonstrated safety and effectiveness of STAR.

In a trial comparing STAR and SPRINT protocols [18] in Christchurch Hospital ICU, Christchurch, New Zealand, although 43.9% of the time in the range of 72–110 mg/dL (4–6.1 mmol/L) was achieved by STAR compared with 71.4% by SPRINT and 82.6% in the range of 80–144 mg/dL (4.4–8.0 mmol/L) was obtained by STAR compared to 87.2% by SPRINT, STAR decreased hypoglycemia (BG $<$ 80 mg/dL) successfully (1.4% vs 7.4%).

Stochastic model predictive (STOMP) glycemic control system [19] is another MPC system using the ICING model, which is an improvement of STAR by introducing MPC strategy, *i.e.* considering cost function consisting of BG errors from the desired range and the amounts of nutrition and insulin use. STOMP gave comparable results to STAR in an *in silico* trial (approximately 85% of BG measurements within the range 80–144 mg/dL (4.4–8.0 mmol/L) and 0.06% of BG measurements below 40 mg/dL (2.2 mmol/L), which indicated as good a performance and safety as STAR.

Enhanced model predictive control (eMPC) system for ICU patients [20, 21] uses a glucoregulatory model, a simplified model in the original eMPC system [40] which uses nonlinear MPC method to maintain normoglycemia for type 1 diabetes subjects during fasting conditions, and updates patients' specific parameters such as insulin sensitivity based on an incoming BG measurement and previously given insulin and glucose infusion rates. The target BG range of the system was 80–110 mg/dL (4.4–6.1 mmol/L), and the system has demonstrated that it can give tight glucose control safely and effectively. In a single-center trial [20], eMPC achieved 60.4% of BG measurements within the target range compared to only 27.5% based on a standard paper protocol. Although, no severe hypoglycemic event (BG $<$ 52 mg/dL (2.9 mmol/L)) was observed in both groups, 1.9% of the time under the target occurred by eMPC compared to 0.6% in paper group. In another trial that compared eMPC with two paper-based protocols (one is based on the absolute glucose value, and the other one is based on the relative glucose change) [21], eMPC showed significantly better glycemic control with 46.0% of the time within the target range compared to 39.7% and 38.2% for paper-based protocols, and 0% of BG below 52 mg/dL (2.9 mmol/L) compared to 0.4% and 0.4%. However, eMPC increased the time of BG in the range of 52–77 mg/dL (2.9–4.3 mmol/L) with 22.2% in eMPC compared to 10.9% and 13.1% in others.

The Glucosafe system for tight glucose control in critical care [22,23] is a model-based decision support system that uses the Glucosafe model [43] (see the next section). The system gives optimal insulin and nutrition use by minimizing the sum of four penalties based on errors between target BG and predicted BG, the total amount of nutrition, amount of enteral nutrition, and insulin use after identifying patient insulin sensitivity.

40% of BG measurements were maintained within the range of 80–110 mg/dL with no BG measurement under 63 mg/dL (3.5 mmol/L) when applied to ten neuro and trauma ICU patients [22]. In their subsequent study [23], they evaluated modifications by reducing the penalties on the amounts of insulin and nutrition and indicated that the time of BG in target band can reach to 54% with a minimal BG level at 59 mg/dL (3.3 mmol/L) when applied to 12 virtual patients *in silico*.

Table 2.1 gives the target BG range, the percentages of duration times within the respective target BG range, and below the hypoglycemic level in the trials for the above mentioned model-based glycemic control systems with the glycometabolism models. Although all of the MPC glycemic systems have demonstrated the safety and effectiveness of tight glucose control for ICU patients, the risk of hypoglycemic and severe hypoglycemic episodes still remains.

Table 2.1: The model-based BG control systems and their results of percentages of time in the respective target BG range and hypoglycemia in the trials

System	Target BG range	Trial	Time in target BG	Hypoglycemic events
LOGIC	80–110 mg/dL (4.4–6.1 mmol/L)	LOGIC-1 [15] (LOGIC vs paper*)	68.6% vs 60.1%	< 70 mg/dL: 2.3% vs 3.8% < 40 mg/dL: 0% vs 0.1%
		LOGIC-2 [16] (LOGIC vs paper)	67% vs 47.1%	< 70 mg/dL: 1.5% vs 1.8% < 40 mg/dL: 0.04% vs 0.05%
eMPC	80–110 mg/dL (4.4–6.1 mmol/L)	single-center [20] (eMPC vs paper)	60.4% vs 27.5%	< 80 mg/dL: 1.9% vs 0.6% < 52 mg/dL: 0 vs 0
		three protocols comparison (eMPC vs paper, paper) [21]	46.0% vs 38.2%, 39.7%	52–77 mg/dL: 22.2% vs 10.9%, 13.1% < 52 mg/dL: 0% vs 0.4%, 0.4%
STAR	80–145 mg/dL (4.4–8 mmol/L)	virtual trial [17] (STAR-2 hourly vs paper)	82.5% vs 78.5% (80–125 mg/dL)	< 80 mg/dL: 1.69% vs 7.83% < 40 mg/dL: 3 vs 14 patients
		mixed-medical ICU [18] (STAR vs paper)	82.6% vs 87.2% 43.9% vs 71.4% (72–110 mg/dL)	< 80 mg/dL: 1.4% vs 7.4%
STOMP	80–145 mg/dL (4.4–8 mmol/L)	virtual trial [19] (STOMP 4h vs STAR clinical)	86.2% vs 80.6% 73.5% vs 61.0% (80–126 mg/dL)	< 80 mg/dL: 2.8% vs 1.7% < 40 mg/dL: 0.06% vs 0.006%
Glucosafe	80–110 mg/dL (4.4–6.1 mmol/L)	in 10 ICU patients [22] (no comparison)†	40%	< 63 mg/dL: 0%
		virtual trial [23] (no comparison)	54%	minimal BG: 59 mg/dL

* paper-based insulin infusion protocol.

† no comparison with other protocols in the study.

2.5 Glucose-Insulin Dynamic Models of Critically Ill Patients

A glucose-insulin dynamic model of critically ill patients can be used in a controller of a model-based BG regulation system to predict the future BG response to insulin and to provide personalized glycemic control by identifying parameter(s) of the model from clinical data. In addition, a model can be used to create virtual patients or simulators to assess the safety and effectiveness of a new treatment *i.e.* insulin infusion protocol *in silico*. A virtual patient is a simulator that represents features in a critically ill patient *e.g.* insulin sensitivity and glucose utilization, and that can simulate glucose-insulin dynamics in a patient by giving personalized parameter(s) and glucose and insulin infusion rates to the model.

In this section, we introduce some glucose-insulin dynamic models including the well-known Bergman minimal model [44], and glycometabolism models of critically ill patients specifically:

- the ICU minimal model [27],
- the Intensive Control Insulin-Nutrition-Glucose model [41],
- the Hovorka model [42], and
- the Glucosafe model [43].

Note that except the Bergman minimal model that describes glucose-insulin dynamics in a healthy subject with minimum equations, the models have been utilized in glycemic control systems mentioned above.

There are two types of models of critically ill patients; one has less physiologically relevance with less number of parameters, and the other has high physiological relevance with a complex description. Representing glucose-insulin dynamics in ICU patients precisely is the main goal for all of the models.

2.5.1 The Bergman Minimal Model

Bergman *et al.* [44] developed a glycometabolism model from glucose and insulin concentration during an intravenous glucose tolerance test (IVGTT) to analyze glucose tolerance in lean and obese people. It is called "minimal model" because of its low complex description of glucose-insulin dynamics and has been widely used as a basic model for more complex models. The model shows an ability to describe glucose-insulin dynamics during

IVGTT with the simplest physiological representation including a single compartment of glucose action, a remote compartment of insulin that affects glucose uptake into the periphery and liver, and a compartment of insulin secretion. The equations of the minimal model are given in Eqs. (2.1)–(2.3).

$$\frac{dG(t)}{dt} = -(P_1 + X)G(t) + P_1 G_b, \tag{2.1}$$

$$\frac{dX(t)}{dt} = -P_2 X(t) + P_3 I(t), \tag{2.2}$$

$$\frac{dI(t)}{dt} = \gamma(G(t) - h)t - nI(t), \tag{2.3}$$

Here $G(t)$ and $I(t)$ are concentrations of blood glucose and plasma insulin, respectively, and $X(t)$ is the variable corresponding to insulin concentration in the remote compartment that affects glucose disappearance. G_b denotes basal glucose level. The secretion of insulin is proportional to the difference between BG and a threshold level of h with the proportionality factor γ. n is the rate of insulin disappearance, P_1 represents the rate of clearance of glucose from plasma, P_2 and P_3 denote the disappearance rate of remote insulin and the increase rate of that from plasma, respectively. The insulin sensitivity index is given by P_3/P_2.

2.5.2 The ICU Minimal Model

Based on the minimal model, Van Herpe *et al.* [27] proposed a simulation model of glycometabolism in critically ill patients for utilization of glycemic control called the ICU minimal model (ICUMM). The model is described as follows.

$$\frac{dG(t)}{dt} = (-P_1 - X(t))G(t) + P_1 G_b + \frac{F_{\mathrm{G}}}{V_{\mathrm{G}}}, \tag{2.4}$$

$$\frac{dX(t)}{dt} = -P_2 X(t) + P_3(I_1(t) - I_b), \tag{2.5}$$

$$\frac{dI_1(t)}{dt} = \alpha \max(0, I_2) - n(I_1(t) - I_b) + \frac{F_{\mathrm{I}}}{V_{\mathrm{I}}}, \tag{2.6}$$

$$\frac{dI_2(t)}{dt} = \beta\gamma(G(t) - h) - nI_2(t), \tag{2.7}$$

Here, $G(t)$ is glucose concentration, $X(t)$ is the variable corresponding to insulin concentration in the remote compartment that affects glucose uptakes, $I_1(t)$ represents plasma insulin concentration, and $I_2(t)$ is a purely mathematical variable corresponding to endogenous insulin secretion proportional to the BG level greater than the threshold level h.

Basal concentrations of blood glucose and plasma insulin are given by G_b and I_b, respectively. P_1 denotes the rate of clearance of glucose from plasma, P_2 and P_3 represent the disappearance rate of remote insulin and the increase rate of that, respectively, n is the rate of insulin disappearance, α and β are coefficients to keep the units correctly. There are two inputs of exogenous glucose F_{G} and insulin F_{I} in the model. V_{G} and V_{I} denote glucose and insulin distributed capacities, respectively.

2.5.3 The Intensive Control Insulin-Nutrition-Glucose Model

The Intensive Control Insulin-Nutrition-Glucose model (ICING model) [41], which is also developed from the minimal model, has more physiological relevance than ICUMM and contains dynamics of plasma glucose, plasma and interstitial insulin, and an absorption route of stomach and gut as well as an insulin sensitivity parameter. The model is used in simulations and BG controllers and is given as follows.

$$\frac{dG(t)}{dt} = -p_{\mathrm{G}}G(t) - \zeta G(t)\frac{Q(t)}{1+\alpha_{\mathrm{G}}Q(t)} + \frac{P(t)+\mathrm{EGP}_b - \mathrm{CNS}}{V_{\mathrm{G}}}, \tag{2.8}$$

$$\frac{dQ(t)}{dt} = n_{\mathrm{I}}(I(t)-Q(t)) - n_{\mathrm{C}}\frac{Q(t)}{1+\alpha_G Q(t)}, \tag{2.9}$$

$$\frac{dI(t)}{dt} = -n_{\mathrm{K}}I(t) - \frac{n_{\mathrm{L}}I(t)}{1+\alpha_{\mathrm{I}}I(t)} - n_{\mathrm{I}}(I(t)-Q(t)) + \frac{u_{\mathrm{ex}}(t)}{V_{\mathrm{I}}} + (1-\chi_{\mathrm{L}})\frac{u_{\mathrm{en}}(t)}{V_{\mathrm{I}}}, \tag{2.10}$$

$$\frac{dM_1(t)}{dt} = -d_1M_1(t) + D(t), \tag{2.11}$$

$$\frac{dM_2(t)}{dt} = -\min(d_2M_2(t), P_{\max}) + d_1M_1(t), \tag{2.12}$$

$$P(t) = \min(d_2M_2(t), P_{\max}) + \mathrm{PN}(t), \tag{2.13}$$

$$u_{\mathrm{en}}(t) = k_1 e^{-I(t)k_2/k_3}, \quad \text{when C-peptide data is not available,} \tag{2.14}$$

Here, $G(t)$ is blood glucose, $Q(t)$ and $I(t)$ represent interstitial insulin and plasma insulin, respectively, EGP_b denotes a constant basal endogenous glucose production, CNS means insulin-independent glucose uptake of centeral nervous system and p_{G} is endogenous glucose removal rate. ζ is the whole-body insulin sensitivity, n_{I}, n_{C}, n_{K} and n_{L} represent diffusion constant, cellular insulin clearance rate, kidney insulin clearance rate and liver insulin clearance rate, respectively. V_{G} and V_{I} are glucose and insulin distribution volumes, respectively. α_{I} denotes a saturation level of plasma insulin disappearance and α_{G} denotes a saturation level of insulin-stimulated glucose removal. Glucose appearance from exogenous input $P(t)$ contains a parenteral glucose intake $\mathrm{PN}(t)$ and a gastric absorption from an enteral glucose intake $D(t)$, which is saturated by a maximal flux $P_{\max}$. $M_1(t)$ and

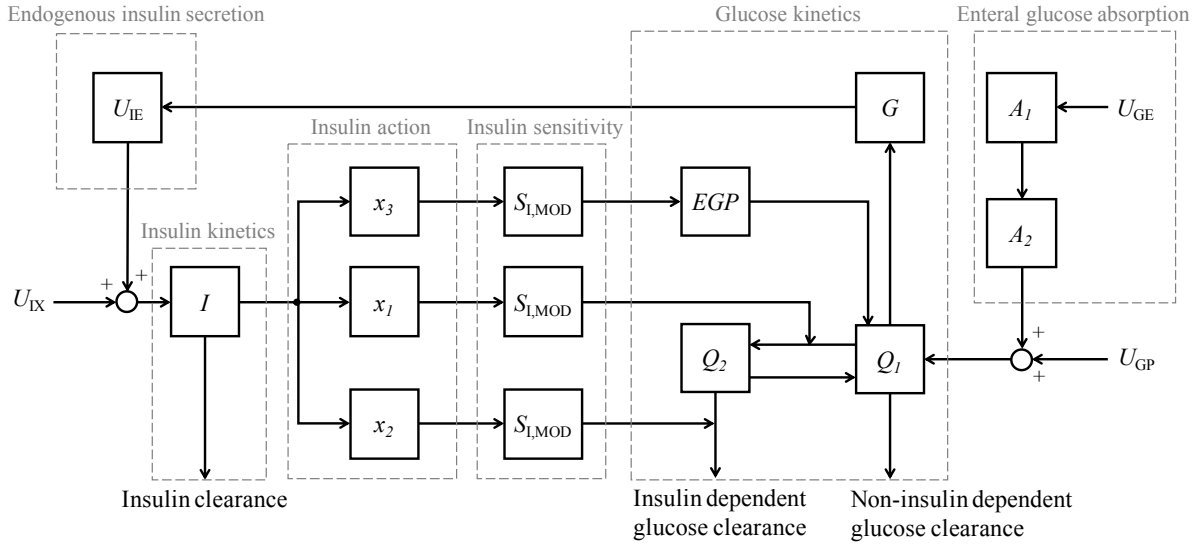


Figure 2.6: Diagram of the glycometabolism simulation model of critically ill patients by R. Hovorka *et al.* [42]

$M_2(t)$ are glucose amounts in stomach and gut, respectively. $u_{\mathrm{en}}(t)$ denotes endogenous insulin production with a basal rate k_1 and $u_{\mathrm{ex}}(t)$ represents exogenous insulin input. χ_{L}, k_2 and k_3 are parameters without any units.

2.5.4 The Hovorka Model

Hovorka *et al.* [42] also constructed a glycometabolism simulation model of critically ill patients, which was developed to create virtual patients for the purpose of testing glycemic controllers. The model is a large-scale model consisting of five submodels of endogenous insulin secretion, insulin kinetics, enteral glucose absorption, insulin action, and glucose kinetics (see Figure 2.6).

The exogenous input of insulin U_{IX} together with endogenous insulin secretion U_{IE} enter into plasma insulin I, which is related to three remote insulin x_1 (effect of insulin on glucose distribution and transport), x_2 (effect on glucose disposal) and x_3 (effect on endogenous glucose production EGP). $S_{\mathrm{I,MOD}}$ is a time-varying insulin sensitivity parameter. The glucose kinetics is described by two compartments of accessible glucose Q_1 and non-accessible glucose Q_2. The accessible glucose Q_1, which can be measured as blood glucose concentration G, includes the endogenous glucose production EGP, the absorption of enteral glucose U_{GE} through stomach A_1 and small intestine A_2, and the parenteral glucose input U_{GP}.

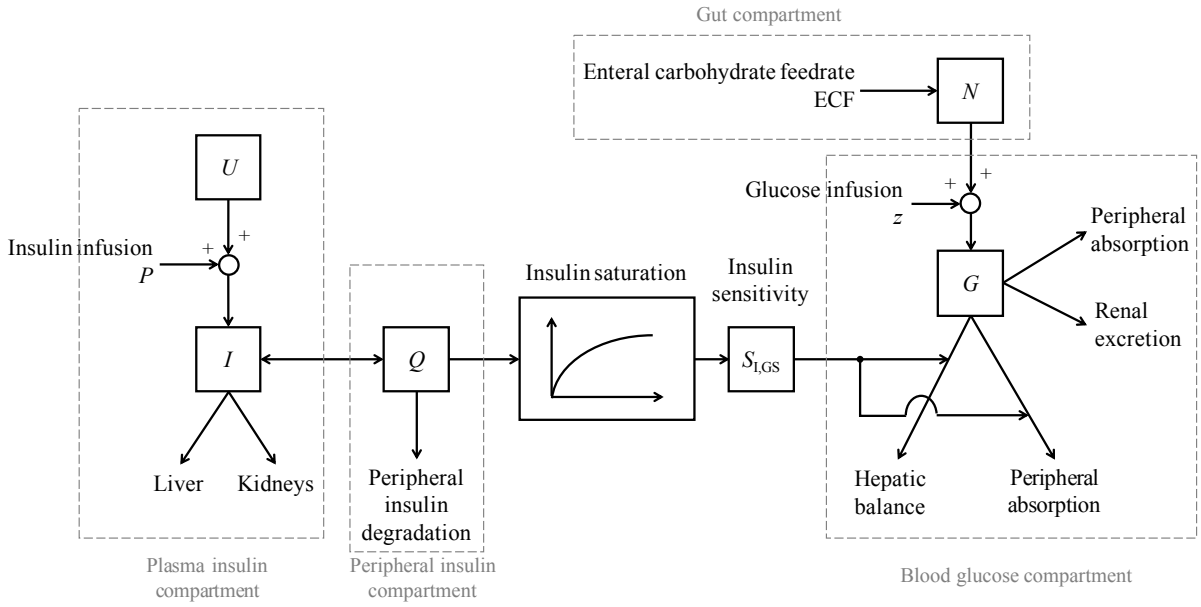


Figure 2.7: Diagram of the Glucosafe model [43]

The complete equations of the model are given in Appendix A.1.

2.5.5 The Glucosafe Model

The Glucosafe model [43] is a glycometabolism model of ICU patients with several physiological descriptions, which is used in simulations and the Glucosafe system. There are four compartments of plasma insulin, peripheral insulin instead of the remote insulin, blood glucose, and gut compartment where glucose is absorbed from an enteral feed. Unlike the other models, the Glucosafe model defines insulin sensitivity as a parameter with the maximal value of 1 (corresponding to the normal insulin sensitivity). The model is illustrated in Figure 2.7 and given in Appendix A.2.

In Figure 2.7, I and Q represent plasma insulin and peripheral insulin, respectively, U denotes post-hepatic endogenous insulin, G is blood glucose concentration, and N is carbohydrate gut content. $S_{\mathrm{I,GS}}$ is the insulin sensitivity parameter. Intravenous insulin P, enteral carbohydrate feed rate ECF, and glucose infusion rate z are inputs of the model.

Chapter 3

Glycemic Control Using a Time-Invariant Model

As mentioned in Chapter 2, computer-based insulin infusion protocols enable more complex algorithms and improve glucose control. Although some computer-based insulin infusion protocols for critically ill patients have been developed and have shown safety and effectiveness in glycemic control with 40%–70% of the time within the target BG range of 80–110 mg/dL [15, 16, 20, 22, 23, 36], most of them fail to prevent hypoglycemia and/or severe hypoglycemia (BG $<$ 40 mg/dL), specifically 1%–3% of BG measurements were below 80 mg/dL with several times of severe hypoglycemia [15–20].

Hypoglycemia, especially severe hypoglycemia, should be avoided. Setting a high target BG level in glycemic control in critically ill patients to prevent hypoglycemia, may not sufficiently reduce mortality nor morbidity as shown in Figure 2.3. Hypoglycemic events may be avoided by frequent measurements of blood glucose and an appropriate glycemic control strategy, *i.e.* a strategy providing personalized, patient-specific treatments considering illness state or other factors. Thus, we study the BG control strategy in the following.

Model predictive control (MPC) is one of the control strategies that can provide personalized control. It determines the manipulated input considering the future response of the controlled variable predicted by using a dynamic model of the controlled system. In the case of glycemic control, a good performance in BG control can be expected by predicting glucose response in a critically ill patient precisely by utilizing a glycometabolism model with patient-specific parameters. Hence, we use model predictive control to develop a blood glucose control system for ICU patients with effectiveness and safety.

Once a new insulin infusion protocol or glycemic control system has been developed, its effectiveness including safety has to be assessed before clinical tests. To this end, virtual

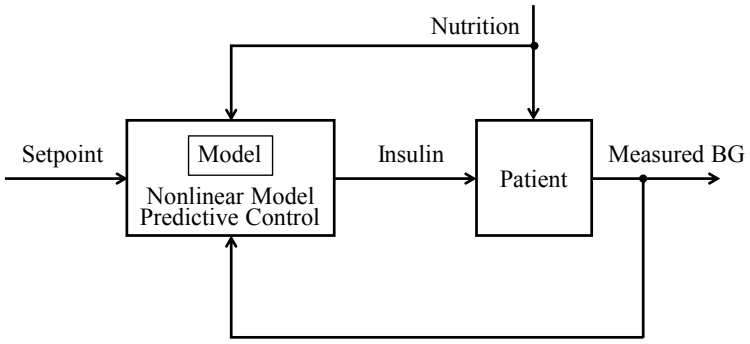


Figure 3.1: A closed-loop glycemic control system using nonlinear model predictive control

patients or patient simulators that can represent inter- and intra-individual features and simulate blood glucose response to glucose and insulin infusions accurately are necessary. Therefore, in this chapter, we not only develop a closed-loop BG control system but also create virtual patients considering inter- and intra-individual differences.

3.1 Closed-Loop Blood Glucose Control System

Patients admitted to ICU often suffer from hyperglycemia even if those have no history of diabetes. We aim at regulating BG levels of ICU patients into the range of 80–110 mg/dL (4.4–6.1 mmol/L) by administering insulin. We use model predictive control to regulate BG levels of ICU patients because it can provide personalized treatments as mentioned above and because BG prediction is crucially needed for precise BG control due to delayed appearance of insulin peak effect on BG. Considering that ICU patients receive continuous parenteral glucose infusion at a known rate, we treat the insulin infusion rate as the only manipulated input. In this section, we construct an automatic closed-loop blood glucose control system utilizing model predicted control based on an existing nonlinear glycometabolism model as shown in Figure 3.1.

3.1.1 Blood Glucose Prediction Model

A model predictive controller predicts the future outcomes from the current output and the inputs from past to future using a system model. In glycemic control, a model representing glucose-insulin dynamics is necessary. It is desirable that the prediction model can accurately predict the future BG response to insulin infusion in short calculation time. Therefore, we choose a simple but nonlinear model of critically ill patients, ICU minimal model (ICUMM) [27] introduced in Section 2.5.2. In this chapter, the parameters

Table 3.1: Parameters in the ICU Minimal Model [45]

Parameters	Values
G_{b}	95 mg/dL
I_{b}	10.7 μU/mL
V_{G}	116.8 dL
V_{I}	8760 mL
P_1	1.71×10^{-2} min^{-1}
P_2	2.24×10^{-2} min^{-1}
P_3	2.5×10^{-6} mL/(μU$\cdot$min^2)
h	107.4 mg/dL
n	0.2623 min^{-1}
α	0.35 min^{-1}
β	1 min
γ	1.4001×10^{-4} $\frac{\mu\mathrm{U}\cdot\mathrm{dL}}{\mathrm{mL}\cdot\mathrm{mg}\cdot\mathrm{min}^2}$

except P_1, P_2 and P_3 (*i.e.* the rate of clearance of glucose from plasma, disappearance rate and increase rate of remote insulin, respectively) are regarded as constants with no individual differences, and the parameter values are given in Table 3.1 [45]. P_1, P_2 and P_3 are considered as the parameters with inter-individual differences and identified for each patient.

3.1.2 Nonlinear Model Predictive Control

Since the ICUMM is nonlinear, we use nonlinear model predictive control without linearizing the model. The use of nonlinear MPC to regulate blood glucose levels in critically ill patients provides an advantage of accurate consideration of the effect of the glucose and insulin infusion on the future blood glucose levels in the patient.

In the glycemic control system, the controlled output is the BG level and the manipulated input is the insulin infusion rate (sometimes together with glucose infusion rate). In this study, we only consider the insulin infusion rate as the manipulated input.

Figure 3.2 illustrates the algorithm of nonlinear MPC in glycemic control. Suppose the output of the controlled system is measured and the input of the controlled system is changed at time $k\Delta t$ where Δt is the sampling period. First, the output is measured at the current time $k\Delta t$ (the measured output is denoted by $y(k)$). Second, the tentative input in the period of $[k\Delta t,\ (k+M)\Delta t)$ is given. Third, utilizing the model of the controlled system the output in the period of $(k\Delta t,\ (k+P)\Delta t]$ is predicted. Fourth, the input in the period of $[k\Delta t,\ (k+M)\Delta t)$ is determined so that the cost function to evaluate the performance of the control system is minimized. Fifth, the input in the period of [$k\Delta t$,

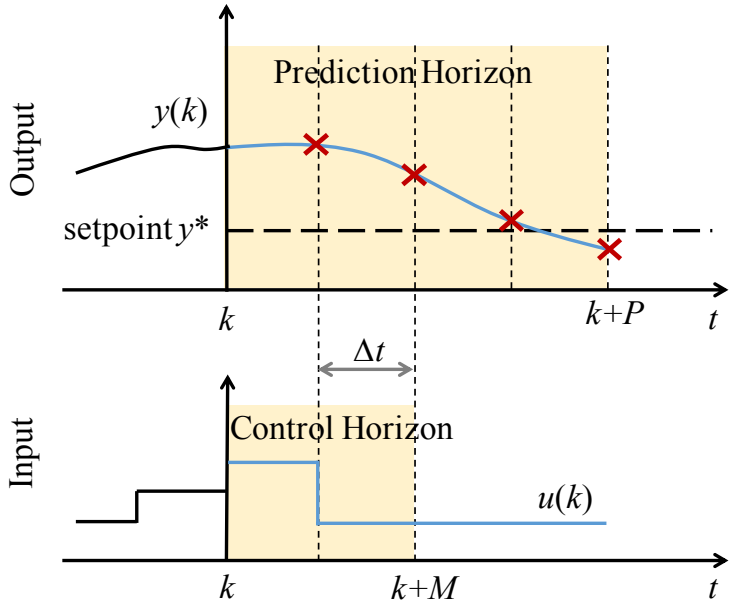


Figure 3.2: Model predictive control. y^* is setpoint. $y(k)$ is measured output at time $k\Delta t$. $u(k)$ is manipulated input at time $k\Delta t$. Δt is sampling time. P is the prediction horizon. M is the control horizons.

$(k+1)\Delta t)$ is given to the system until the next sampling. Here P is the prediction horizon (time steps of output prediction), and M is the control horizon (time steps of changing input).

In the following, we design the blood glucose control system for critically ill patients. For BG control for critically ill patients, the output is the blood glucose level, the input is the insulin infusion rate (glucose infusion rate is determined by doctors or nurses). The insulin infusion rate is obtained by solving the optimization problem. The cost function is given by

$$\begin{aligned} J_1 = {} & Q_1(G_p(k+P) - G^*)^2 + \sum_{i=1}^{P} Q_2(G_p(k+i) - G^*)^2 \\ & + \sum_{j=0}^{M-1} \left\{ R_1(u(k+j) - u(k+j-1))^2 + R_2 u^2(k+j) \right\}, \end{aligned} \tag{3.1}$$

where $G_p(k)$ is the predicted blood glucose level based on the model at time of $k\Delta t$, $u(k)$ is insulin infusion rate at the period $[k\Delta t,\ (k+1)\Delta t)$ and G^* is the target BG level. Q_1, Q_2, R_1 and R_2 are weighting coefficients of the cost function. The cost function J_1

includes a penalty of the difference between BG measurement and the target BG level (*i.e.* setpoint) to minimize the BG error, a penalty of the change of insulin infusion rates, and a penalty of the insulin infusion rates to prevent a sudden change of insulin infusion rate and suppress the total amount of insulin infusion. Insulin infusion rate sequence is obtained by solving the optimization problem:

$$\begin{aligned} &\min_{u} J_1, \\ &\text{subject to} \quad G(k+i) \geq 80 \text{ mg/dL}, (i = 1, 2, ..., P) \\ &\qquad\qquad 0 \leq u(k+j) \leq u_{\max}, (j = 0, 1, ..., M-1) \end{aligned} \tag{3.2}$$

Here, we add constraints to avoid hypoglycemia (*i.e.* $G(k+i) \geq 80$ mg/dL, $(i = 1, 2, ..., P)$) and excessive insulin infusion limited by a maximum infusion rate of $u_{\max}$ (*i.e.* $0 \leq u(k+j) \leq u_{\max}, (j = 0, 1, ..., M-1)$). If insulin infusion rate cannot be obtained under the constraint in Eq. (3.2), *i.e.* when the predicted BG $G(k+i)$ is smaller than 80 mg/dL for any insulin infusion rate satisfying $u(k+j) \geq 0$, the insulin infusion rate $u(k+j)$ is determined to 0. Then, insulin is administered at the rate of $u(k+j)$ of the first element of the obtained insulin infusion sequence until the next BG measurement becomes available. Every time the BG measurement is obtained, the above procedure is repeated.

The sampling time Δt for measuring BG and changing insulin infusion rate is set to 30 min considering that BG measurement in a period of 15–60 min in ICU is recommended for ICU patients by insulin infusion protocol [12] (see Figure 2.5). To maintain BG within the range of 80–110 mg/dL and prevent hypoglycemia, the prediction horizon P is 2 so that the system predicts BG levels for the future one hour considering time variability of insulin sensitivity, the control horizon M is set to 2, the values of weighting coefficients of Q_1, Q_2, R_1 and R_2 in the cost function J_1 in Eq. (3.2) are given by

$$\begin{aligned} Q_1 &= 6000, \quad Q_2 = 60, \\ R_1 &= R_2 = S_{\text{I,MM}}^2 \times 10^2, \end{aligned}$$

where $S_{\text{I,MM}}$ is the insulin sensitivity in the Bergman minimal model [44] defined by

$$S_{\text{I,MM}} = P_3/P_2 \text{ mL}/(\mu\text{U} \cdot \text{min}) \tag{3.3}$$

The weighting coefficient of Q_1 is set to be a large value than Q_2 to make $G(k+P)$ close to the target level, and R_1 and R_2 are dependent on the present insulin sensitivity $S_{\text{I,MM}}$ so that the weight for the insulin effect on BG is independent of the insulin sensitivity.

R_1 and R_2 related to $S^2_{\mathrm{I,MM}}$ gives a better performance of BG control that more insulin infusion rate is given to a patient with low insulin sensitivity to regulate BG within the desired range and less insulin infusion rate is given to a patient with high insulin sensitivity to prevent hypoglycemia.

3.2 Simulation

In this section, we apply the glycemic control system to various patients and situations to assess effectiveness and safety. First, we create virtual patients, a simulator of glucose-insulin dynamics in critically ill patients. Then, we do simulations of our glycemic control system designed in the preceding section and evaluate the performance of the system.

3.2.1 Virtual Patients Based on Clinical Data in a Paper of Hovorka (Virtual Patients H)

When a new infusion protocol or glycemic control system is developed, its performance especially safety must be ensured before clinical implementation. A virtual patient is a patient simulator that provides a way of assessing a new infusion protocol or control system *in silico*. Blood glucose response of a patient to glucose and insulin infusion can be obtained using a virtual patient. For an accurate assessment, a virtual patient must mimic glucose-insulin dynamics in critically ill patients as precisely as possible including patient specific-parameters representing inter-individual differences. In this thesis, we construct virtual patients based on the Glucosafe model [43], which is a glycometabolism model of critically ill patients integrating nonlinear functions based on physiological knowledge and saturation of insulin action with reduced insulin sensitivity. The Glucosafe model 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 including body weight, age, height, gender and diabetes state of the patient, and one time-varying parameter of insulin sensitivity. We use the Glucosafe model as a simulation model of ICU patients because it can precisely simulate glucose-insulin dynamics in ICU patients, and has been used as a simulator of ICU patients for calculating the value of insulin sensitivity in [23].

As mentioned above, the parameter of insulin sensitivity in the Glucosafe model is regarded as a time-varying patient-specific parameter. We construct ten profiles of insulin sensitivity of virtual patients with several typical changes, such as the increase of insulin sensitivity, as follows. First, from the clinical data of BG measurements, nutrition and

Table 3.2: Description of the ten insulin sensitivity profiles

Profile	Description
1	Identified from clinical data from [42] at one-hour intervals
2, 3	No. 1 profile + random value between −0.05 and 0.05 with uniform distribution
4, 5	No. 1 profile + random value between 0 and 0.1 with uniform distribution
6, 7	No. 1 profile + random value between 0.05 and 0.15 with uniform distribution
8	No. 1 profile + 0.05 increase at 10-hour intervals after 30 h
9	No. 4 profile + 0.05 increase at 10-hour intervals after 30 h
10	No. 6 profile + 0.05 increase at 10-hour intervals after 30 h

insulin infusion rates of a medical ICU patient given in [42], insulin sensitivity $S_{\mathrm{I,GS}}$ in Eq. (A.24) is identified at one-hour intervals based on the Glucosafe model. The obtained insulin sensitivity profile is illustrated in Figure 3.3 and assigned as insulin sensitivity profile No. 1. Second, Profiles No. 2–No. 7 are constructed by adding random values with uniform distribution in the range of [−0.05, 0.05], [0, 1], and [0.05, 0.15] to Profile No. 1. Then, Profiles No. 8–No. 10 are constructed by adding 0.05 at 10-hour intervals after 30 hours to Profile No. 1, 4 and 6 to represent the increase of insulin sensitivity in the recovery of patients from illness as demonstrated in [49]. Table 3.2 shows all of the profiles of insulin sensitivity and Figure 3.4 gives two examples of the profiles No. 6 and No. 8.

In the simulation, we consider 30 virtual female patients of 48 years old with a height of 1.7 m and no history of diabetes by combining the ten insulin sensitivity profiles and body weights of 50, 60 and 70 kg due to less influence of age, gender and height. The created set of virtual patients is called “virtual patients H”.

3.2.2 Method

We assess the performance of our BG control system using virtual patients. As an early stage of the development of the BG control system in this thesis, the purpose is to assess the performance of the nonlinear MPC control system when the averaged insulin sensitivity is known and when it is unknown. To this end, we divide each insulin sensitivity profile given in Table 3.2 into two parts. The first part is the profile in the period of 0–34 hours (part (a)) and the second part is the profile in the period of 34–68 hours (part (b)). We

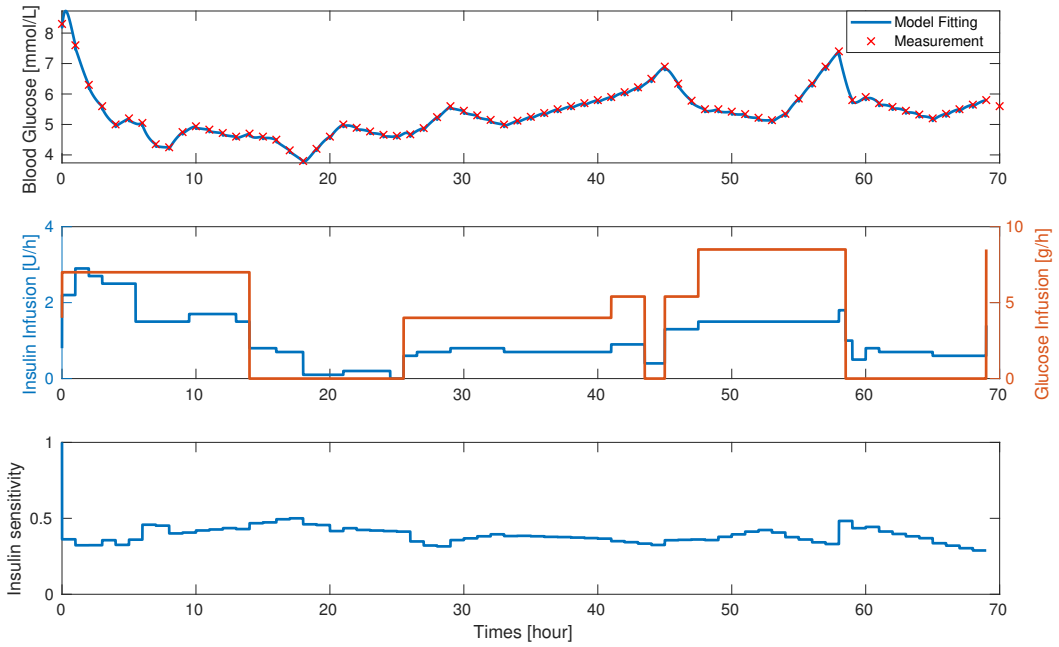
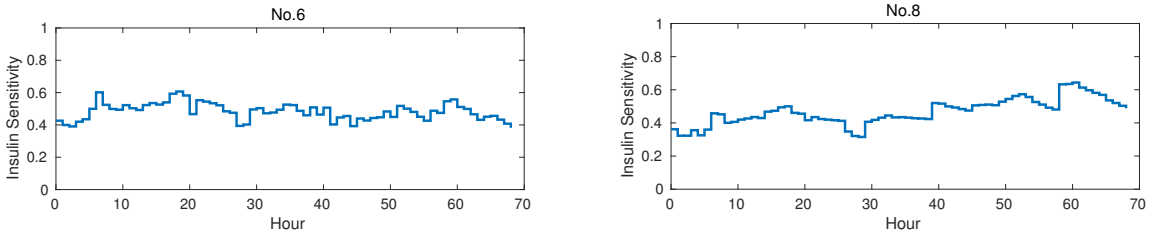


Figure 3.3: Insulin sensitivity profile No.1 identified from clinical data of BG, insulin and glucose infusions described in [42]. The top panel shows the clinical BG and simulation results. The second panel shows the clinical glucose and insulin infusion rates. The bottom panel shows the identified insulin sensitivity values at one-hour intervals.



(a) Insulin sensitivity profile No. 6

(b) Insulin sensitivity profile No. 8

Figure 3.4: Examples of insulin sensitivity profiles

denote the first and the second parts of insulin sensitivity profile No. X as No. X(a) and No. X(b), respectively. As mentioned in Section 3.1.1, the ICUMM is used for prediction of the future blood glucose, and the parameters values of P_1, P_2 and P_3 are considered to be different for each patient. We use the part (a) of each insulin sensitivity profile to identify the parameters of P_1, P_2 and P_3 in ICUMM of each virtual patient assuming that the parameters are constant. The parameters P_1, P_2 and P_3 of each patient are identified from the response of the Glucosafe model with the insulin sensitivity of part (a) by solving the optimization problem with the initial values in Table 3.1

$$\min_{P_1,P_2,P_3} \sum_{k=1}^{k_{\text{end}}} (G(k) - G_{\text{model}}(k))^2,$$

where $G(k)$ is the measured blood glucose at time k, G_{model} is the estimated BG at time k from the model, and k_{end} is the number of time steps in part (a). The problem is solved by the sequential quadratic programming method using the MATLAB function 'fmincon'.

The simulation of the BG control system is performed as follows. The initial BG level is set to 200 mg/dL (11.1 mmol/L) assuming no BG management is done before admission to ICU. The setpoint BG level is 100 mg/dL (5.5 mmol/L). All patients receive continuous parenteral glucose infusion at a rate of 2.86 mg/min/kg, which is determined by doctors or nurses. The maximum insulin infusion rate is set to 200 mU/min to avoid hyperinsulinemia. The parameters P_1, P_2 and P_3 of ICUMM in the controller is set to the respective identified values for each patient, and the BG control is applied to each patient with insulin sensitivity profiles (a) and (b). Furthermore, to assess the performance of the control system against measurement errors of blood glucose and disturbance of a changing glucose infusion rate, BG control simulation is performed when adding the Gaussian noise with zero mean and standard deviation $\sigma = 7.5$ mg/dL to BG measurements considering the permissible range of measurement error is 15 mg/dL at 100 mg/dL and when glucose infusion rate decreased from 2.86 mg/min/kg to 1.43 mg/min/kg.

3.2.3 Results

The identification results of P_1, P_2 and P_3 in the 30 virtual patients H are given in Table 3.3. The value of insulin sensitivity $S_{\text{I,MM}} = P_3/P_2$ is within the range from 3.89×10^{-4} to 9.57×10^{-4} mL/(μU·min).

The simulation results of mean BG levels, the minimal BG levels, the percentages of duration time within the range of 80–110 mg/dL (4.4–6.1 mmol/L), 80–125 mg/dL (4.4–7 mmol/L), 80–144 mg/dL (4.4–8 mmol/L) and below 80 mg/dL (4.4 mmol/L) for

parts (a) and (b) of each insulin sensitivity profile are listed in Table 3.4. Note that the simulation results of the mean BG levels, the percentage duration time within the ranges, and below 80 mg/dL are those after two hours from the start of the BG control considering hyperglycemia at the time of admission to the ICU. From the simulation results, the control system maintains 67% and 58% of BG measurements within the range of 80–110 mg/dL for parts (a) and (b) of the insulin sensitivity profiles, respectively. The minimal BG level for all profiles is 74 mg/dL with only 0.4% of BG measurements below 80 mg/dL. No severe hypoglycemic episodes (BG $<$ 40 mg/dL (2.2 mmol/L) [11]) is observed.

Figure 3.5 and Figure 3.6 show glycemic control results in a virtual patient of 60 kg with the insulin sensitivity profiles No. 1(a) and No. 1(b), respectively, whose insulin sensitivity profile is identified from the clinical data. Figure 3.7 and Figure 3.8 illustrate simulation results in a virtual patient of 60 kg with the insulin sensitivity profiles No. 9(a) and No. 9(b), respectively, whose insulin sensitivity profile is constructed by adding random values and considering the increase of insulin sensitivity. Although insulin sensitivity in ICU patients is time-varying and even increasing in the case of No. 9, our glycemic control system based on the time-invariant model has an ability to regulate BG of the patients. However, it seems to be insufficient to maintain BG below 110 mg/dL when the insulin sensitivity of the patients becomes low, *e.g.* from about 200 to 900 minutes and after 1800 minutes in Figure 3.6 as well as from 1400 to 1800 minutes in Figure 3.7.

Figure 3.9 shows simulation results of BG control in the virtual patient of 60 kg with the insulin sensitivity profile No. 1(a) with and without BG measurement noise. The results show that the system has an ability to regulate BG against the measurement noise. Figure 3.10 shows a simulation result on the virtual patient of 70 kg with the insulin sensitivity profile No. 7(b) when the glucose infusion rate is decreased from 2.86 mg/min/kg to 1.43 mg/min/kg at 800 minutes. The system reduces the insulin infusion rate immediately according to the decrease of the glucose infusion rate, and appropriately regulates BG of the patient.

3.3 Discussion

In the present chapter, we construct a glycemic control system to regulate BG in critically ill patients utilizing nonlinear model predictive control based on a time-invariant model. The system maintains 62% of BG measurements within the range of 80–110 mg/dL, 84% within 80–125 mg/dL and 95% within 80–144 mg/dL. The percentage of duration time below 80 mg/dL of the system is 0.4% with the minimal BG measurement of 74 mg/dL.

Table 3.3: Means and standard deviations of the identified parameter values of P_1, P_2 and P_3 of the 30 virtual patients H.

Parameter	Mean value (mean ± std)	[Min Max]
P_1 min^{-1}	$(0.45 \pm 0.21) \times 10^{-2}$	$[0.35 \times 10^{-10}\ 0.80 \times 10^{-2}]$
P_2 min^{-1}	$(0.36 \pm 0.06) \times 10^{-2}$	$[0.27 \times 10^{-2}\ 0.57 \times 10^{-2}]$
P_3 mL/(μU·min^2)	$(2.34 \pm 0.75) \times 10^{-6}$	$[1.21 \times 10^{-6}\ 3.87 \times 10^{-6}]$
$S_{\mathrm{I,MM}}$ mL/(μU·min)	$(6.44 \pm 1.61) \times 10^{-4}$	$[3.89 \times 10^{-4}\ 9.57 \times 10^{-4}]$

Table 3.4: Results of the glycemic control in the 30 virtual patients H grouped in 10 insulin sensitivity profiles

Profile No.	Mean BG (mg/dL)	Min BG (mg/dL)	80–110 mg/dL (%)	80–125 mg/dL (%)	80–144 mg/dL (%)	< 80 mg/dL (%)
1 (a)	117	91	59	74	85	0.0
2 (a)	119	75	55	68	76	1.0
3 (a)	115	83	57	78	88	0.0
4 (a)	108	78	66	88	96	0.5
5 (a)	108	77	68	87	94	1.0
6 (a)	105	76	74	90	97	1.0
7 (a)	104	78	82	93	99	0.5
8 (a)	116	89	67	77	85	0.0
9 (a)	108	77	68	88	96	0.5
10 (a)	105	77	76	90	97	1.0
mean (a)	110	75†	67	83	91	0.6
1 (b)	123	90	25	50	95	0.0
2 (b)	119	94	25	72	99	0.0
3 (b)	124	94	22	53	90	0.0
4 (b)	110	79	49	95	99	0.5
5 (b)	112	84	47	88	100	0.0
6 (b)	105	88	76	100	100	0.0
7 (b)	104	86	78	100	100	0.0
8 (b)	103	80	78	95	100	0.0
9 (b)	101	74	88	99	99	1.0
10 (b)	100	79	87	99	99	0.5
mean (b)	110	74†	58	85	98	0.2
mean all	110	74†	62	84	95	0.4

† is the minimal value.

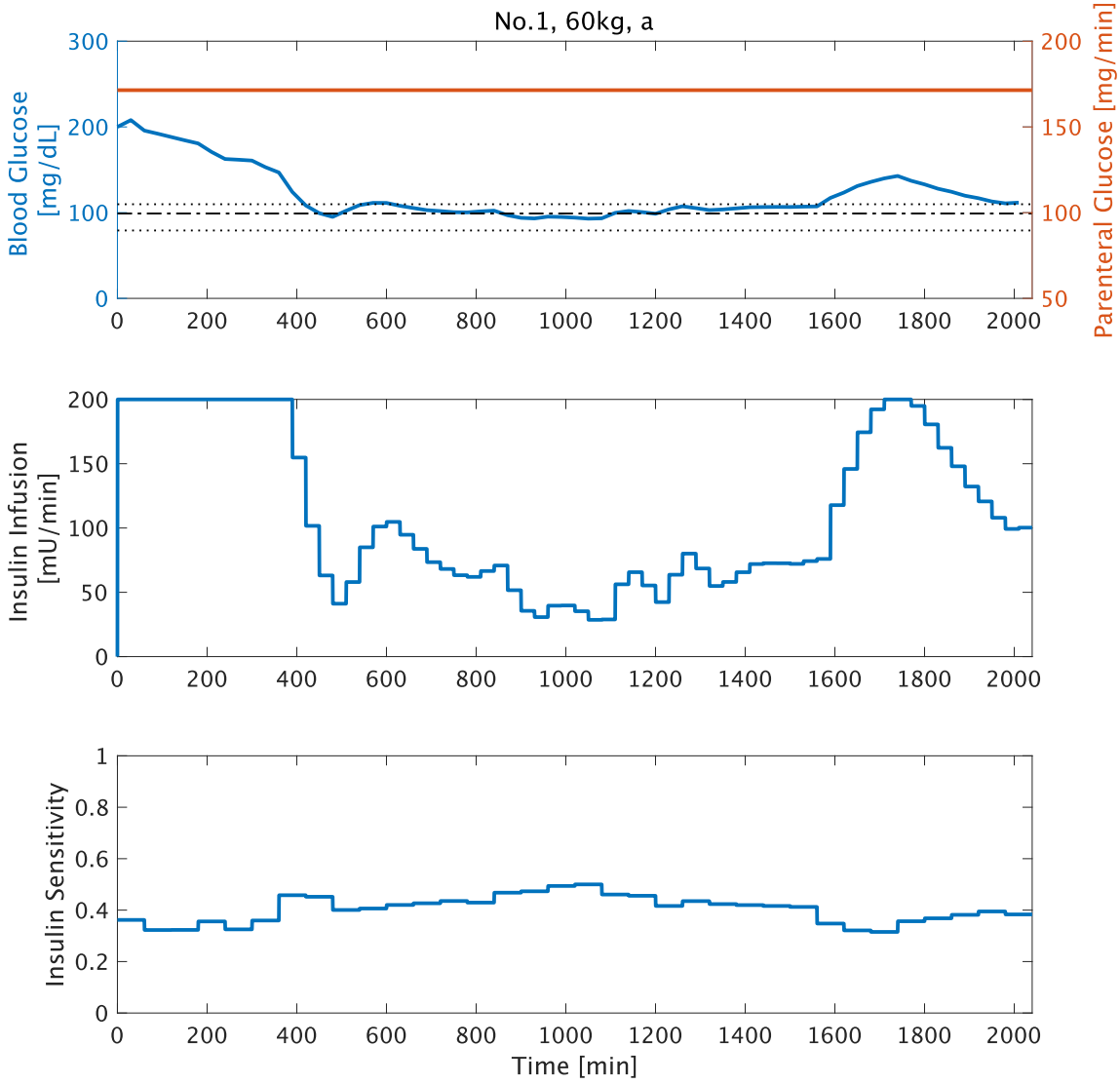


Figure 3.5: Simulation result in a virtual patient of 60 kg with insulin sensitivity profile No. 1(a). Top panel: BG levels (solid line), desired BG levels (dotted line), target BG level (dot-dashed line) and glucose infusion rate (red solid line). Middle panel: insulin infusion rate. Bottom panel: insulin sensitivity profile.

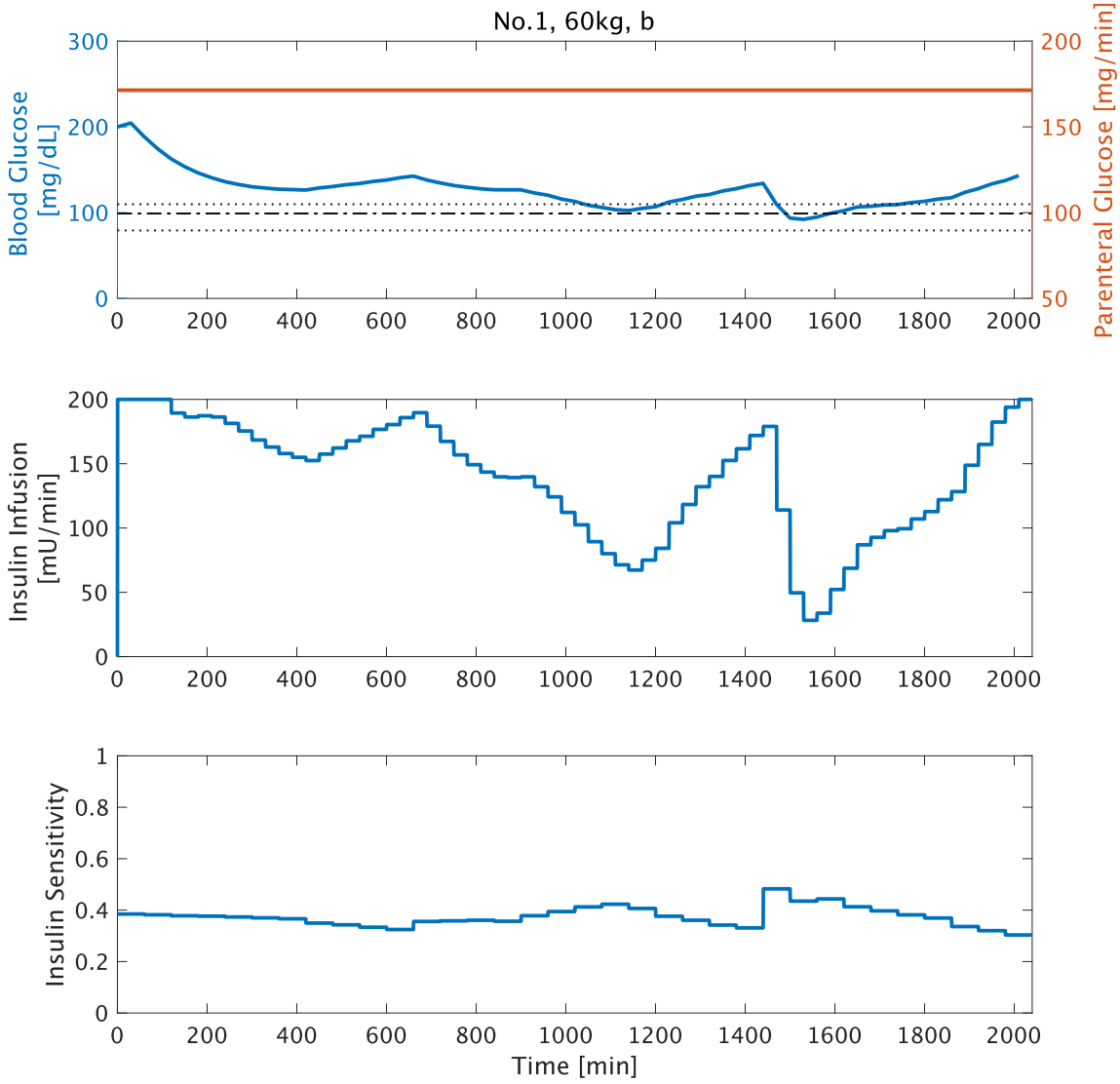


Figure 3.6: Simulation result in a virtual patient of 60 kg with insulin sensitivity profile No. 1(b). Top panel: BG levels (solid line), desired BG levels (dotted line), target BG level (dot-dashed line) and glucose infusion rate (red solid line). Middle panel: insulin infusion rate. Bottom panel: insulin sensitivity profile.

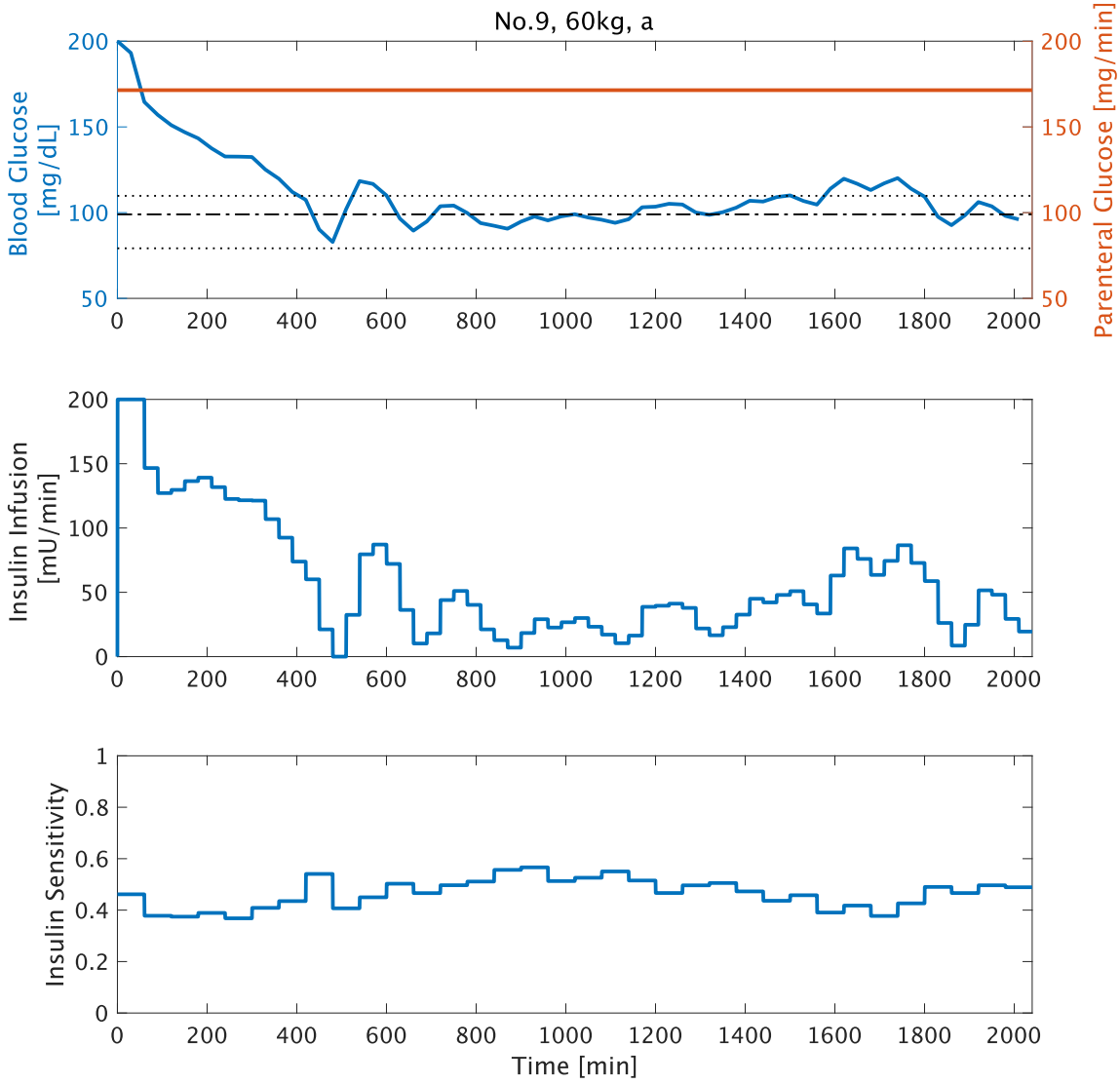


Figure 3.7: Simulation result in a virtual patient of 60 kg with insulin sensitivity profile No. 9(a). Top panel: BG levels (solid line), desired BG levels (dotted line), target BG level (dot-dashed line) and glucose infusion rate (red solid line). Middle panel: insulin infusion rate. Bottom panel: insulin sensitivity profile.

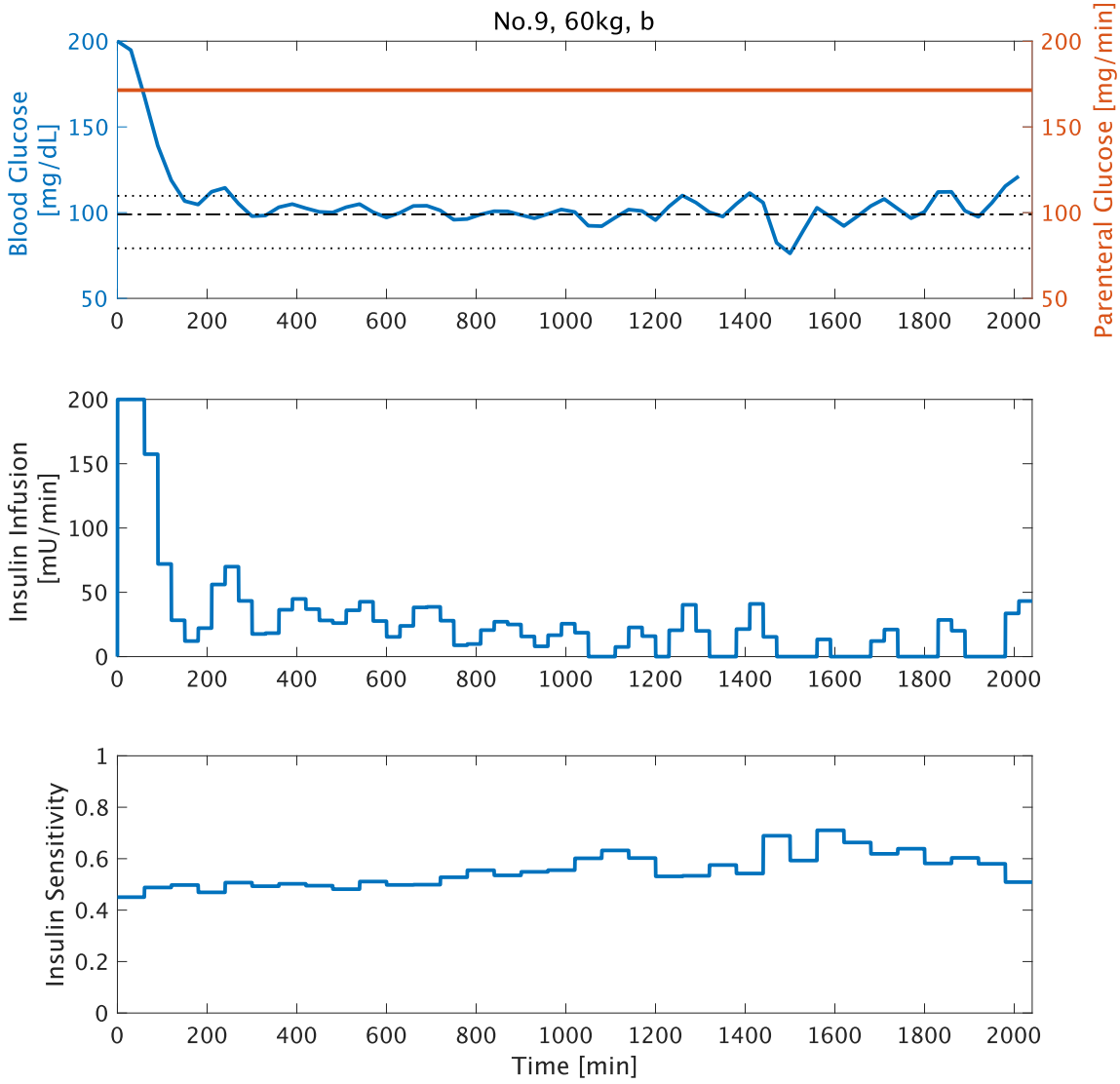


Figure 3.8: Simulation result in a virtual patient of 60 kg with insulin sensitivity profile No. 9(b). Top panel: BG levels (solid line), desired BG levels (dotted line), target BG level (dot-dashed line) and glucose infusion rate (red solid line). Middle panel: insulin infusion rate. Bottom panel: insulin sensitivity profile.

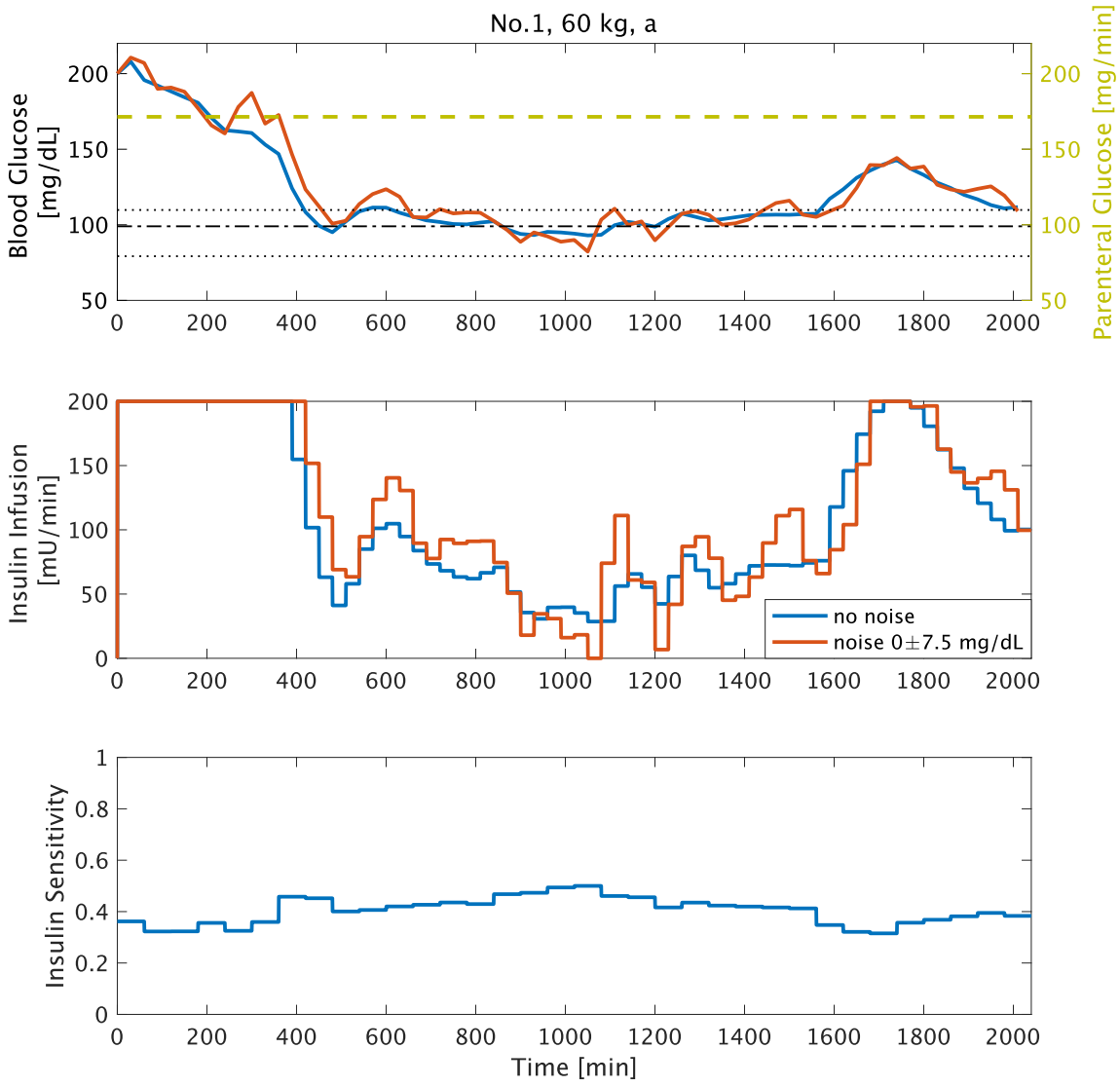


Figure 3.9: Simulation result in a virtual patient of 60 kg with insulin sensitivity profile No. 1(a) with measurement noise of a Gaussian distribution of zero mean and standard deviation of $\sigma = 7.5$ mg/dL. Top panel: BG levels without measurement noise (blue solid line), BG levels with measurement noise of 0 ± 7.5 mg/dL (red solid line) desired BG levels (dotted line), target BG level (dot-dashed line) and glucose infusion rate (dashed line). Middle panel: insulin infusion rates without measurement noise (blue line), with measurement noise of 0 ± 7.5 mg/dL (red line). Bottom panel: insulin sensitivity profile

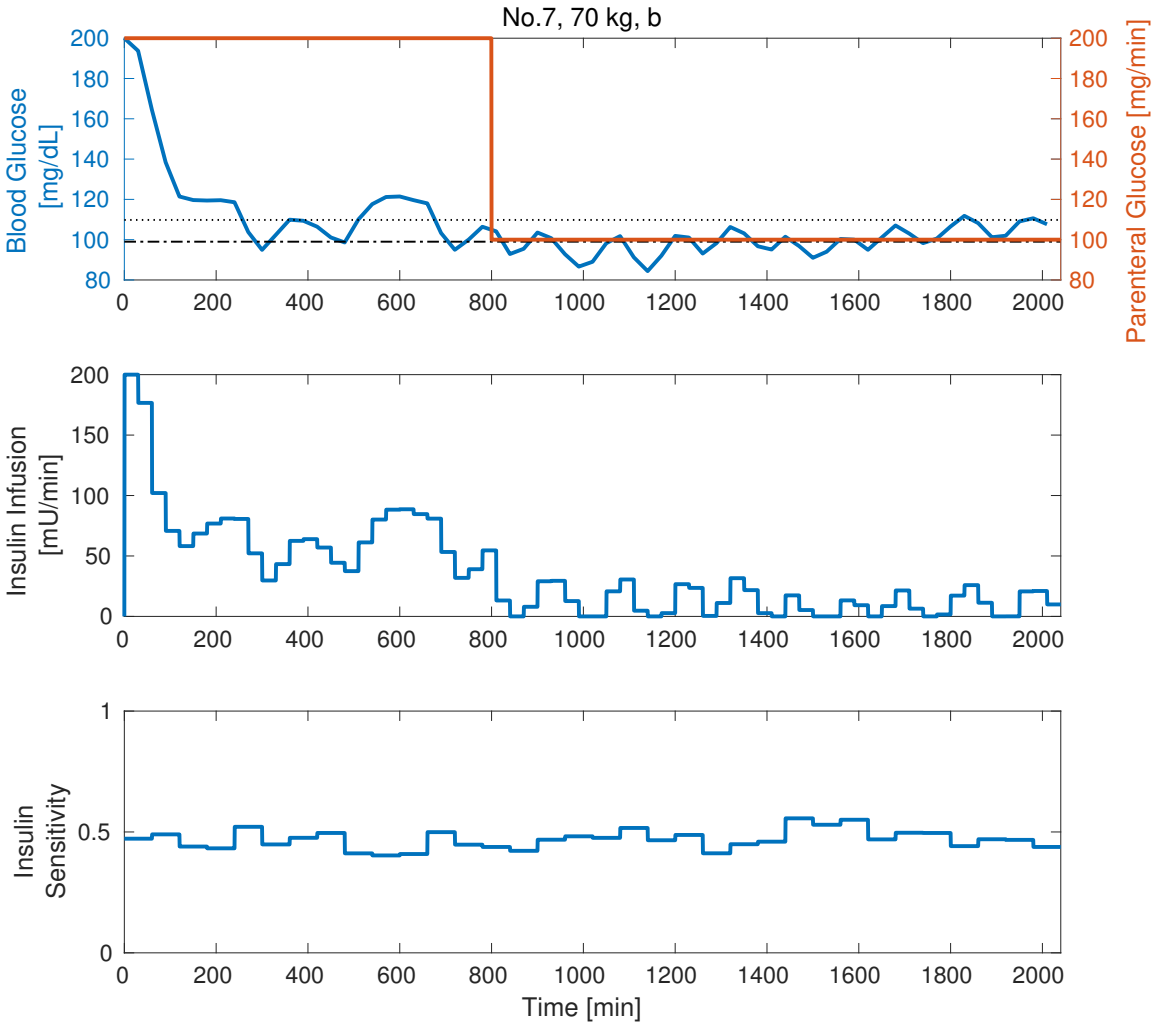


Figure 3.10: Simulation result in a virtual patient of 70 kg with insulin sensitivity profile No. 7(b). Top panel: BG levels (solid line), desired BG levels (dotted line), target BG level (dot-dashed line) and glucose infusion rate (red solid line). Middle panel: insulin infusion rate. Bottom panel: insulin sensitivity profile.

The existing systems maintain 40% in [22], 54% in [23], 69% in [15] and 67% in [16] of BG measurements are within the range 80–110 mg/dL, 74% of BG measurements are within 80–126 mg/dL and 86% in [19] of BG measurements are within 80–145 mg/dL (see Table 2.1). Furthermore, the minimal BG measurements of the existing systems are 59 mg/dL in [23], 45 mg/dL in [15] and 26 mg/dL in [16]. The results suggest the safety of our glycemic control system. However, it is hard to compare our results with other studies [15, 16, 19, 22, 23] due to the difference in BG control conditions and patients.

We use the ICU minimal model [38] for BG prediction in our MPC system. The model has an ability to simulate BG change in critically ill patients although it consists of only four simple ordinary differential equations. Since there is no single parameter describing insulin sensitivity in the ICUMM, we calculate the insulin sensitivity $S_{\mathrm{I,MM}}$ from the parameters P_2 and P_3 according to the definition of the insulin sensitivity in the Bergman minimal model. The parameter values of P_1, P_2 and P_3 are identified from the first half part (part (a)) of the data of BG measurements, insulin and glucose infusions rates of each virtual patient assuming that the parameters are time-invariant. Note that the insulin sensitivity $S_{\mathrm{I,MM}}$ in Eq. (3.3) used in the cost function Eq. (3.2) is different from the insulin sensitivity $S_{\mathrm{I,GS}}$ in Eq. (A.24) used in Glucosafe model, which is utilized to simulate glucose-insulin dynamics in critically ill patients. The values of the identified insulin sensitivity $S_{\mathrm{I,MM}}$ are within the range of 3.89×10^{-4}–9.57×10^{-4} mL/(μU·min). It demonstrates an ability to represent insulin sensitivity by Eq. (3.3) in the ICUMM.

Although we use a time-invariant model to predict BG in our glycemic control system, the simulation results show a good performance in the regulation of BG of critically ill patients with time-varying insulin sensitivity. The system reduces insulin infusion rates imminently when BG measurement decreases below 80 mg/dL, the lower bound of the desired BG range, due to increased insulin sensitivity value in a patient as shown in Figure 3.7 and Figure 3.8. However, when insulin sensitivity value in a patient decreases, the system shows an insufficient performance on increasing the insulin infusion rate to regulate BG below 110 mg/dL, the upper bound of the desired BG range.

Since the value of insulin sensitivity $S_{\mathrm{I,MM}}$ of the model in the controller are identified from the insulin sensitivity profiles part (a), averaged insulin sensitivity $S_{\mathrm{I,MM}}$ of each virtual patient is known during the glycemic control for the patient with insulin sensitivity profile part (a). On the other hand, averaged insulin sensitivity $S_{\mathrm{I,MM}}$ is uncertain in glycemic control for patients with insulin sensitivity profile part (b). The mean values of the percentages of duration time within the desired range of 80–110 mg/dL for parts (a) and (b) of the insulin sensitivity profile No. 1–No. 7 (no consideration of increasing insulin sensitivity) are 66% and 46% respectively as shown in Table 3.4, which suggests

that the system provides a higher BG control performance when insulin sensitivity of the patient is known. It is important to grasp insulin sensitivity to improve glycemic control in critically ill patients.

In Figures 3.9 and 3.10, the system gives good performances on regulating BG against measurement noise of Gaussian distribution with zero mean and standard deviation $\sigma =$ 7.5 mg/dL and against a change of glucose infusion rate, which indicates the effectiveness of the closed-loop glycemic control system with nonlinear model predictive control based on a time-invariant glycometabolism model.

3.4 Concluding Remarks

In this chapter, we construct a closed-loop glycemic control system using nonlinear model predictive control. As an early stage of developing the glycemic control system, we use an existing time-invariant glycometabolism model to predict BG levels in ICU patients. We aim at regulating BG levels in ICU patients within the range of 80–110 mg/dL (4.4–6.1 mmol/L). The system is assessed with virtual patients of body weight of 50 kg, 60 kg and 70 kg with ten insulin sensitivity profiles. Although the system utilizes a time-invariant insulin sensitivity and shows an insufficient performance in BG control when insulin sensitivity of the patient is small, it gives less than 1% duration time of BG below 80 mg/dL, which demonstrates the safety of the system. From the result that the percentage of duration time within the desired range for patients with unknown insulin sensitivity is smaller than that for patients with known insulin sensitivity, insulin sensitivity may be the key in glycemic control in critically ill patients.

Chapter 4

Prediction Model of Glycometabolism in ICU Patients

In the previous chapter, we develop a closed-loop glycemic control system using nonlinear model predictive control. As an early stage of developing the glycemic control system, we use the ICUMM, an existing time-invariant glycometaboslim model. We identify several parameters of each patient to cope with inter-individual differences and regulate BG of the patients treating the model parameters including the identified parameters as a constant, *i.e.* neglecting intra-individual differences in the patients during BG control. Although the simulation results show the safety of the BG control system, the system does not have sufficient performance when regulating the BG of the patients with unknown insulin sensitivity. It suggests that grasping insulin sensitivity in ICU patients improves BG control.

However, the ICUMM, the glycometabolism model used in the previous chapter, cannot easily deal with insulin sensitivity due to no single parameter corresponding to it. Moreover, it does not consider several nonlinear properties of glucose-insulin dynamics, nor enteral glucose infusion. Therefore, in this chapter, we construct a novel prediction model of glucose-insulin dynamics in ICU patients by introducing an insulin sensitivity parameter, nonlinear functions of glucose uptakes, and adding input of enteral glucose infusion into the ICUMM. Then, we assess the accuracy of the glycometabolism model by comparing simulation results with clinical data of ICU patients. Furthermore, we study time variability of insulin sensitivity in ICU patients because insulin sensitivity is important for glycemic control as shown in Chapter 3, and good performance of BG control can be expected if the change of insulin sensitivity in the patients is known.

4.1 Modification of Glycometabolism Model

ICU minimal model [38] is a simple glycometabolism model based on the Bergman minimal model [44]. The advantage of the model is to have fewer parameters compared with other models [41–43], while the disadvantage is no single parameter corresponding to the insulin sensitivity. In the previous chapter, we identify three parameters of P_1 (the rate of clearance of glucose from plasma), P_2 (disappearance rate of remote insulin), and P_3 (increase rate of remote insulin) for each patient and estimate insulin sensitivity. However, it is not easy to deal with time variability of insulin sensitivity by identifying three parameters during glycemic control. Therefore, we modify the controller model, *i.e.* the ICU minimal model, by introducing a parameter of insulin sensitivity. We also introduce several nonlinear functions of glucose uptakes and a compartment of glucose absorption through the small intestine to improve the accuracy of the model.

In addition, the parameters of the modified model are identified from clinical data of BG measurements, insulin, and glucose infusion rates obtained from patients in the ICU of Kagawa University Hospital with the ethical approval (No. 2018-147) of the Ethics Committee of Kagawa University Hospital.

4.1.1 Model Equations

Critically ill patients often suffer from peripheral insulin resistance that results in diminished insulin-dependent glucose uptakes into cells as well as hepatic insulin resistance that increases glucose production from the liver [29]. Both peripheral and hepatic insulin sensitivity causes the patients hyperglycemia. Therefore, insulin sensitivity is quite important in glucose-insulin dynamics. Since there is no parameter of insulin sensitivity in the ICUMM, we introduce an insulin sensitivity parameter that has nonlinear effects on insulin-dependent glucose uptake [43,46] and hepatic glucose balance considering previous studies [41,43,47]. The insulin sensitivity parameter should be time-varying to deal with intra-individual differences in critically ill patients. In addition, we consider the nonlinearity of the insulin-independent glucose uptake [42,43]. Furthermore, a compartment of glucose absorption from the small intestine is added to enable an enteral glucose infusion through the intestine, which is not included in the ICUMM.

The complete model is illustrated in Figure 4.1 and given by Eqs. (4.1)–(4.6), consisting of five compartments of blood glucose concentration $G(t)$, interstitial insulin concentration $I_i(t)$, plasma insulin concentration $I_p(t)$, pancreas insulin $I_s(t)$ and small intestinal glucose content $E(t)$, a time-varying insulin sensitivity parameter S_{I}, and three inputs of parenteral glucose infusion rate F_{G}, enteral glucose infusion rate F_{E} and intravenous

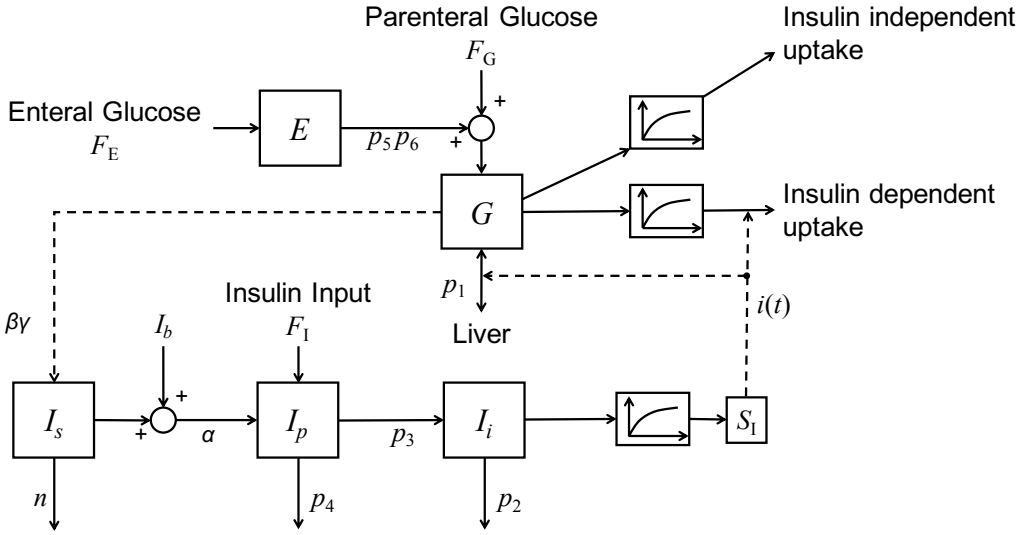


Figure 4.1: The structure of the modified glycometabolism model

insulin infusion rate F_{I}.

$$\frac{dG(t)}{dt} = -i(t)\frac{k_{a2}G(t)}{k_{b2}+G(t)} - (p_1 i(t)G(t) - H) - \frac{k_{a3}G(t)}{k_{b3}+G(t)} + \frac{F_{\mathrm{G}} + p_6p_5E(t)}{V_{\mathrm{G}}}, \quad (4.1)$$

$$\frac{dI_i(t)}{dt} = p_3I_p(t) - p_2I_i(t), \quad (4.2)$$

$$\frac{dI_p(t)}{dt} = \alpha\{\max(0, I_s(t)) + I_b\} - p_3I_p(t) - p_4I_p(t) + \frac{F_{\mathrm{I}}}{V_{\mathrm{I}}}, \quad (4.3)$$

$$\frac{dI_s(t)}{dt} = \beta\gamma(G(t) - h) - nI_s(t), \quad (4.4)$$

$$\frac{dE(t)}{dt} = F_{\mathrm{E}} - p_5E(t), \quad (4.5)$$

$$i(t) = S_{\mathrm{I}}\frac{k_{a1}I_i(t)}{k_{b1}+I_i(t)}. \quad (4.6)$$

In Eq. (4.1), blood glucose is determined by nonlinear insulin dependent glucose utilization $i(t)\frac{k_{a2}G(t)}{k_{b2}+G(t)}$, nonlinear insulin independent glucose uptake $\frac{k_{a3}G(t)}{k_{b3}+G(t)}$, hepatic glucose balance $(p_1i(t)G(t) - H)$ and exogenous glucose $\frac{F_{\mathrm{G}}+p_6p_5E(t)}{V_{\mathrm{G}}}$ from parenteral glucose infusion and glucose absorption from the small intestine. Eq. (4.2) represents interstitial insulin action that increases by transferring from plasma to interstitial compartment $p_3I_p(t)$ and disappears by interstitial insulin clearance $p_2I_i(t)$. Plasma insulin increases by secretion from pancreas including basal insulin $\alpha\{\max(0, I_s(t)) + I_b\}$, insulin transfer from plasma to interstitial compartment $p_3I_p(t)$, insulin clearance $p_4I_p(t)$ and exogenous

Table 4.1: Details of the 26 ICU patients collected from the ICU of Kagawa University Hospital from June 2016 to August 2018

Gender	Male/Famale	15/11
Stay (days)	mean ± std	5 ± 3
	median [IQR]	4 [3 5]
Age (years)	mean ± std	64 ± 17
Weight (kg)	mean ± std	58 ± 17
Height (cm)	mean ± std	160 ± 7
Disease		N
Pancreatic cancer		10
Bile duct cancer		5
Infective endocarditis		1
Major duodenal papilla cancer		2
Renal failure and type 1 diabetes		2
Cecum cancer		1
Pneumonia		1
Insulinoma		2
Unknown		2

insulin $\frac{F_{\mathrm{I}}}{V_{\mathrm{I}}}$ given in Eq. (4.3). Eq. (4.4) is taken from [27], which is a function of pancreas insulin secretion released proportionally to blood glucose level above a threshold level h. In Eq. (4.5), small intestinal glucose increases by enteral glucose delivery F_{E} and diminishes by absorption of the small intestine $p_5 E(t)$. $i(t)$ is insulin effect defined by insulin sensitivity S_{I} and saturation effect of interstitial insulin $\frac{k_{a1} I_i(t)}{k_{b1} + I_i(t)}$.

4.1.2 Identification of Model Parameters

With the ethical approval (No. 2018-147) of the Ethics Committee of Kagawa University Hospital, we have collected clinical data of BG measurements, parenteral and enteral glucose infusion rates and insulin infusion rates from 26 ICU patients in the ICU of Kagawa University Hospital from June 2016 to August 2018 including diseases of pancreatic cancer, bile duct cancer, infective endocarditis, major duodenal papilla cancer, renal failure, cecum cancer, pneumonia, and insulinoma (see Table 4.1 for more details). The numbers of the patients range from 16-0003 to 16-0016, from 17-0001 to 17-0007, and from 18-0001 to 18-0005.

To obtain typical parameter values of ICU patients, we identify the values of the parameters except for h, γ, V_{G} and V_{I}, whose parameter values are given in [38] or [46],

Table 4.2: Details of the 9 ICU patients for the identifications of the model parameters

Diseases	Pancreas/Bile duct	5/4
Gender	Male/Female	5/4
Stay (days)	mean ± std	3 ± 1
Age (years)	mean ± std	66 ± 5
Weight (kg)	mean ± std	58 ± 13
Height (cm)	mean ± std	163 ± 8

using the clinical data from the ICU patients after surgeries of pancreatic cancer or bile duct cancer and stayed three or four days in the ICU from 2016 to 2017, excluding two patients due to the lack of BG measurements. Hence, the model parameters are identified from the nine ICU patients whose demographic data are given in Table 4.2. We estimate the parameter values of the model for each patient utilizing the MATLAB R2015 function 'lsqnonlin' based on the nonlinear least squares method for solving the problem

$$\min_{p_1,p_2,p_3,p_4,p_5,p_6,k_{a2},k_{a3},k_{b1},k_{b2},k_{b3},H,n,\alpha,\gamma,I_b,S_{\mathrm{I}}} \sum (G_{\mathrm{clinical}}(k) - G_{\mathrm{model}}(k))^2, \tag{4.7}$$

where $G_{\mathrm{clinical}}(k)$ is the BG measurements from the ICU patient and $G_{\mathrm{model}}(k)$ is the BG obtained from the model. We use mean values of the identified parameters listed in Table 4.3 as the parameter values of the model of ICU patients except the insulin sensitivity S_{I} which is treated as a time-varying parameter.

4.2 Evaluation of Model Accuracy

In this section, to evaluate the accuracy of the modified model we simulate BG responses of the model with the identified parameter values. We assume that only insulin sensitivity is varying with time and identified from BG measurements, insulin, and glucose infusion rates of the clinical data of each patient and treat the other parameters as constant parameters listed in Table 4.3. Figure 4.2 illustrates the usage of BG measurements in the identification of insulin sensitivity and the usage of 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 insulin sensitivity identified from the first four successive BG measurements. After the third BG measurement, BG response between k-th and $(k+1)$-th ($k \geq 3$) measurements is estimated from the model with the insulin sensitivity identified from $(k-1)$-th to

Table 4.3: Parameters of the model

Patient features	Values	Patient features	Values
S_{I}	To be identified	V_{G} (dL)	1.88 BW [46]
BW (kg)	Body weight	V_{I} (mL)	120 BW [38]
Parameters	Values	Parameters	Values
h (mg/dL)	107.4 [38]	β (min)	1 [38]
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} (μU/mL)	171.0552
k_{b2} (mg/dL)	94.4972	k_{b3} (mg/dL)	8.0479
H (mg/dL/min)	0.7686	n (min^{-1})	5.9027
α (min^{-1})	0.5417	γ ($\frac{\mu\mathrm{U}\cdot\mathrm{dL}}{\mathrm{mL}\cdot\mathrm{mg}\cdot\mathrm{min}^2}$)	0.1457
I_b (μU/mL)	13.3909	p_5 (min^{-1})	0.5719
p_6	0.2872		

$(k+2)$-th BG measurements.

An example of the simulation result on ICU patient No. 16-0009, whose clinical data is used to identify the model, together with the clinical data (BG measurements, glucose, and insulin infusions) is shown in Figure 4.3. Figure 4.4 illustrates another example of the simulation result on ICU patient No. 16-0006, whose clinical data is not used for the identification.

To evaluate the accuracy of the model, we calculate the mean percentage error (MPE) of the simulated BG and the clinical BG measurements for each patient. The MPE value is calculated by

$$\mathrm{MPE} = \frac{\sum_i^N \frac{|G(i)-G_p(i)|}{G(i)}}{N} \times 100\%, \tag{4.8}$$

where G_p is simulated BG, G is the clinical BG measurements, N is the number of measurement BG. The MPE of the 26 ICU patients is small with a mean value of 8.85% with a standard deviation of 4.37%. We also compare the simulation results of the modified model with ICUMM with six patients who only receive parenteral glucose infusion because there is no enteral glucose input in ICUMM. We identify the parameter of P_1, P_2 and P_3 in ICUMM with the other parameter values given in Table 3.1. Our model gives a comparable result of MPE value to ICUMM that the mean MPE value for the six patients of the modified model is 7.63% with a standard deviation of 5.79% compared with 8.25%

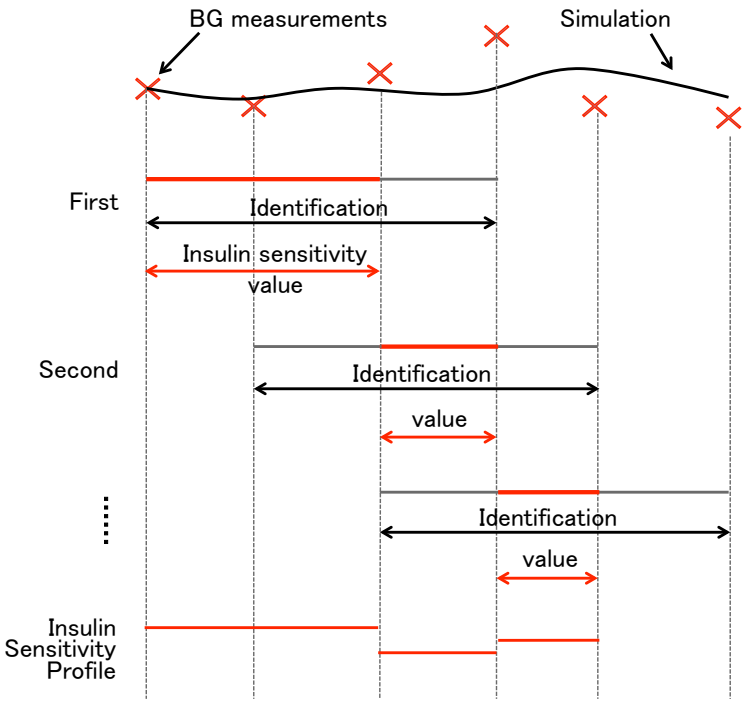


Figure 4.2: The usage of BG measurements for insulin sensitivity identification and insulin sensitivity values for estimation in each period. BG response between the first and third measurements is estimated from the model with the insulin sensitivity identified from the first four successive BG measurements. After the third BG measurement, BG response between k-th and $(k+1)$-th $(k \geq 3)$ measurements is estimated from the model with the insulin sensitivity identified from $(k-1)$-th to $(k+2)$-th BG measurements.

with a standard deviation of 5.30% for ICUMM ($p = 0.43$).

As shown in Figure 4.3 and Figure 4.4, the model represents BG change well in the ICU patients whether the clinical data is used for identifying the model parameter values or not. Although we treat the parameters except for insulin sensitivity S_{I} as constants during the simulations, the MPE values are small, which indicates that the model can deal with inter- and intra-individual differences in ICU patients only by changing the insulin sensitivity parameter.

4.3 Analysis of Time Variability of Insulin Sensitivity in ICU Patients

As mentioned in Chapter 3, insulin sensitivity is important for effective BG regulation. To improve the performance of the BG control system, insulin sensitivity should be known as precisely as possible. In addition, it is desired that the future change of insulin sensitivity can be predicted especially when using MPC. In this section, to investigate the variation of insulin sensitivity with time and diseases, we analyze the differences of insulin sensitivity between diseases and the changes in insulin sensitivity of the ICU patients from the ICU of Kagawa University Hospital.

The median values of identified insulin sensitivity S_{I} of patients grouped by diseases are shown in Figure 4.5. There is no significant difference in insulin sensitivity values between pancreatic cancer, the bile duct cancer patients, and the other patients analyzed by t-test.

Figure 4.6 illustrates the median insulin sensitivity of four-hour blocks for each disease from the admission to ICU (0-hour) to 60 hours. In bile duct cancer patients, there is a significant increase in insulin sensitivity during 16–36 hours, as well as during 12–28 hours in pancreatic cancer patients. In addition, the changes of median insulin sensitivity (ΔS_{I}) of every four-hour block are analyzed for each disease by

$$\Delta S_{\mathrm{I}} = \frac{S_{\mathrm{I}n+1} - S_{\mathrm{I}n}}{S_{\mathrm{I}n}} \times 100\%. \tag{4.9}$$

The results of median insulin sensitivity change for respective diseases in a period of 12–36 hours are listed in Table 4.4. For all the patients, the change of median insulin sensitivity from the blocks of 12–15 hours to 16–19 hours is -6.08%, from the blocks of 16–19 hours to 20–23 hours is 11.55%, from the blocks of 20–23 hours to 24–27 hours is 20.33%, from the blocks of 24–27 hours to 28–31 hours is 3.77% and from the blocks of 28–31 hours to

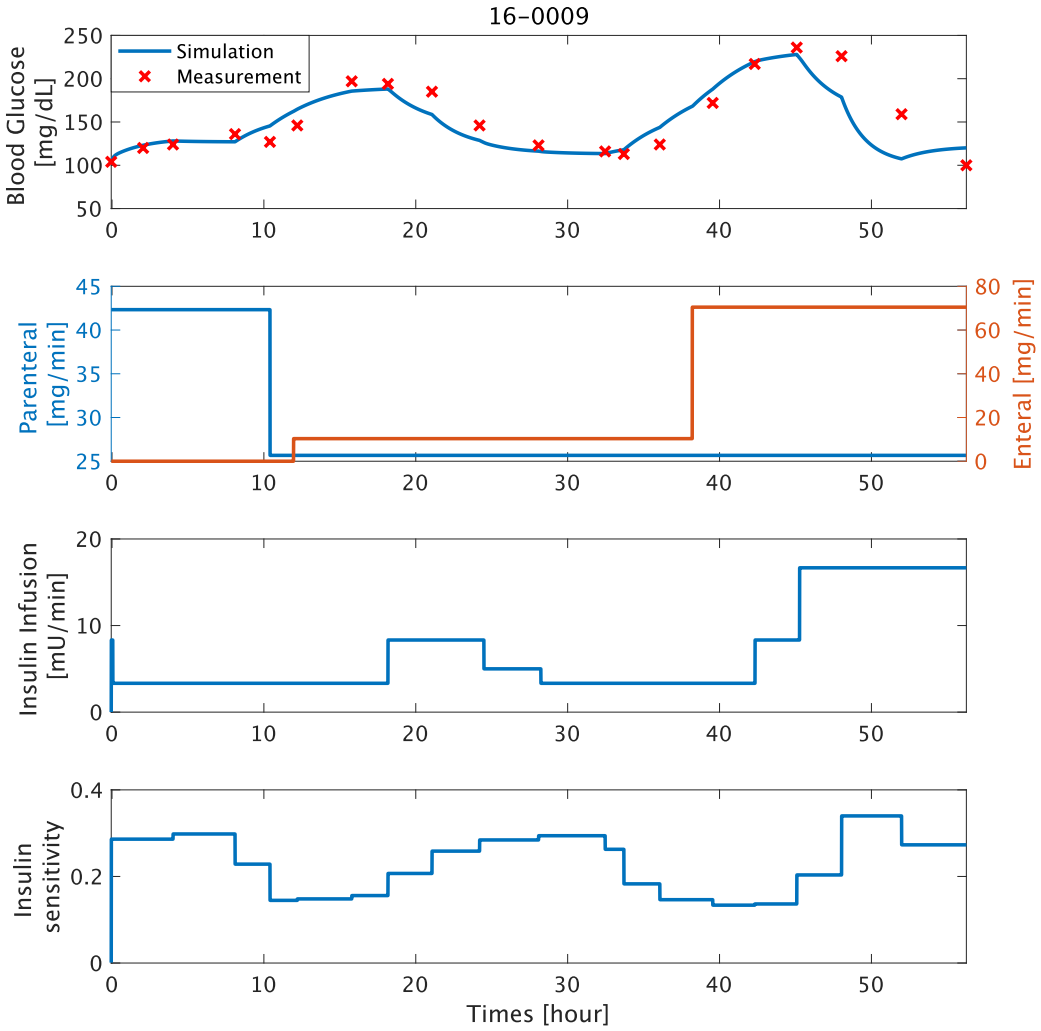


Figure 4.3: Simulation result of the modified model with the identified insulin sensitivity on ICU patient No. 16-0009. The top panel shows the clinical BG measurements and simulation results. The second panel shows the clinical parenteral and enteral glucose infusions. The third panel shows the clinical insulin infusion. The bottom panel shows the identified insulin sensitivity of the patient using the model.

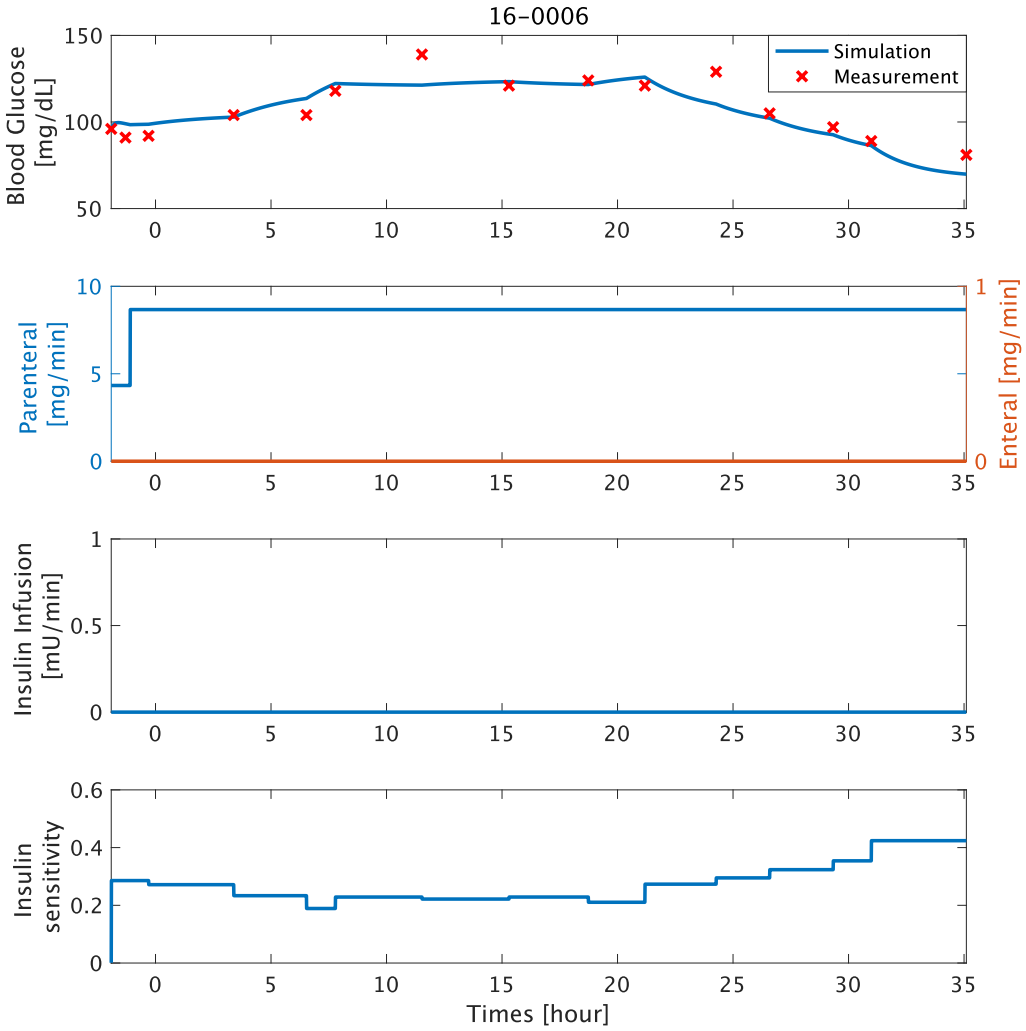


Figure 4.4: Simulation result of the modified model with the identified insulin sensitivity on ICU patient No. 16-0006. The top panel shows the clinical BG measurements and simulation results. The second panel shows the clinical parenteral and enteral glucose infusions. The third panel shows the clinical insulin infusion. The bottom panel shows the identified insulin sensitivity of the patient using the model.

Table 4.4: Changes of median insulin sensitivity ($\Delta S_{\mathrm{I}}\%$) for patients grouped by diseases in the period of 12–36 hours

blocks	Pancreatic cancer	Bile duct cancer	Others	All
16–19 h vs 12–15 h	26.50	−10.79	−19.73	−6.08
20–23 h vs 16–19 h	5.10	5.60	36.72	11.55
24–27 h vs 20–23 h	45.87	22.81	−1.54	20.23
28–31 h vs 24–27 h	−8.71	26.25	1.44	3.77
32–35 h vs 28–31 h	−20.06	12.21	−15.25	−15.26

32–35 hours is −15.26%.

Table 4.5 lists the median insulin sensitivity in the blocks of 12–15 hours and 24–27 hours and the change of that for each patient. Note that there is no BG measurement data for identifying insulin sensitivity in the block of 12–15 hours in patients No. 16-0016 and No. 18-0001, and in the block of 24–27 hours in the patient No. 16-0015. Figure 4.7 illustrates the median insulin sensitivity of blocks 12–15 hours and 24–27 hours of 23 patients except for patients No. 16-0015, No. 16-0016 and No. 18-0001 due to their absence of BG measurement data for identifying insulin sensitivity. Median insulin sensitivity in 24–27 h significantly increases from 12–15 h ($p = 0.02$ by one-tailed paired t-test). However, it is very difficult to construct a method of insulin sensitivity prediction due to its large variation. We will analyze the change of insulin sensitivity from more clinical data.

4.4 Discussion

As mentioned in the previous chapter, it is important to grasp insulin sensitivity for a good performance of regulating BG within the desired range. However, the ICUMM cannot easily deal with intra-individual difference or time variability of insulin sensitivity due to lack of a single parameter corresponding to the insulin sensitivity. Therefore, in this chapter, we modify the ICUMM by introducing an insulin sensitivity parameter. In addition, to more accurately represent glucose-insulin dynamics in critically ill patients we also introduce nonlinear insulin-dependent and independent glucose uptakes, and saturation of interstitial insulin effect. The model parameters are identified from nine ICU patients with pancreatic and bile duct cancer collected from the ICU of Kagawa University Hospital. To assess the accuracy of the model, we simulate BG responses of the model with the identified parameter values only by changing the insulin sensitivity parameter

Table 4.5: Median insulin sensitivity in the blocks of 12–15 h and 24–27 h and the changes of median insulin sensitivity Δ for each patient.

Block	16-0003	16-0004	16-0005	16-0006	16-0007	16-0008	16-0009
12–15 h	0.31	0.25	0.13	0.24	0.25	0.24	0.14
24–27 h	0.29	0.40	0.29	0.31	0.30	0.35	0.27
Δ (%)	−7.55	59.47	125.15	29.71	22.17	45.30	99.92
Block	16-0010	16-0011	16-0012	16-0013	16-0014	16-0015	16-0016
12–15 h	0.15	0.38	0.31	0.11	0.17	0.30	
24–27 h	0.28	0.56	0.35	0.22	0.08		0.32
Δ (%)	86.02	49.14	12.43	89.54	−52.73		
Block	17-0001	17-0002	17-0003	17-0004	17-0005	17-0006	17-0007
12–15 h	0.76	0.12	0.27	0.25	0.18	0.22	0.29
24–27 h	0.33	0.21	0.34	0.28	0.21	0.55	0.30
Δ (%)	−56.84	70.46	26.18	12.16	21.07	155.06	2.78
Block	18-0001	18-0002	18-0003	18-0004	18-0005		
12–15 h		0.45	0.31	0.38	0.12		
24–27 h	0.40	0.58	0.37	0.27	0.39		
Δ (%)		26.94	20.58	−28.27	217.87		

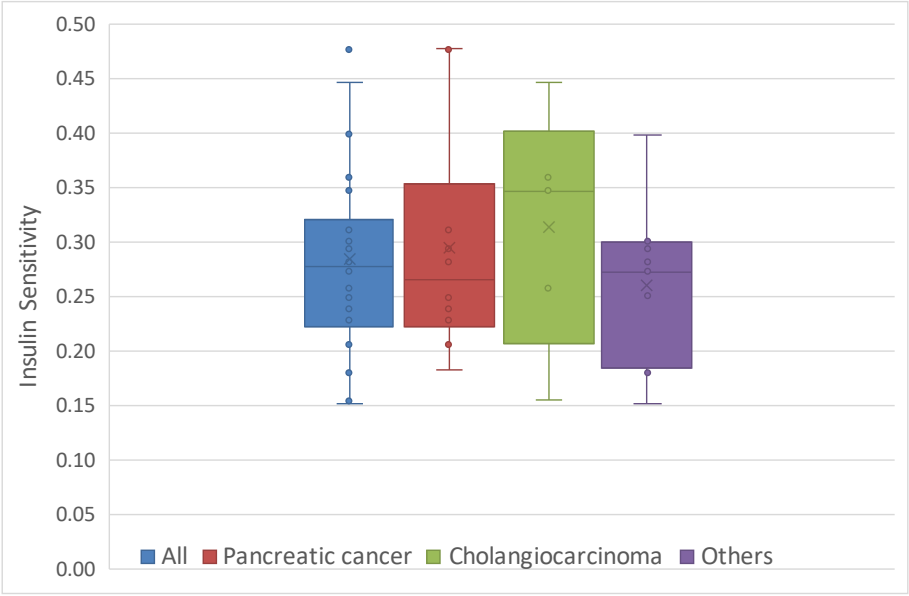


Figure 4.5: Median and IQR of the median insulin sensitivity for patients grouped by diseases. All: 0.28 [IQR 0.23, 0.31]. Pancreatic cancer: 0.27[IQR 0.23, 0.31]. Bile duct cancer: 0.35 [IQR 0.26, 0.36]. Others: 0.27 [IQR 0.22, 0.30].

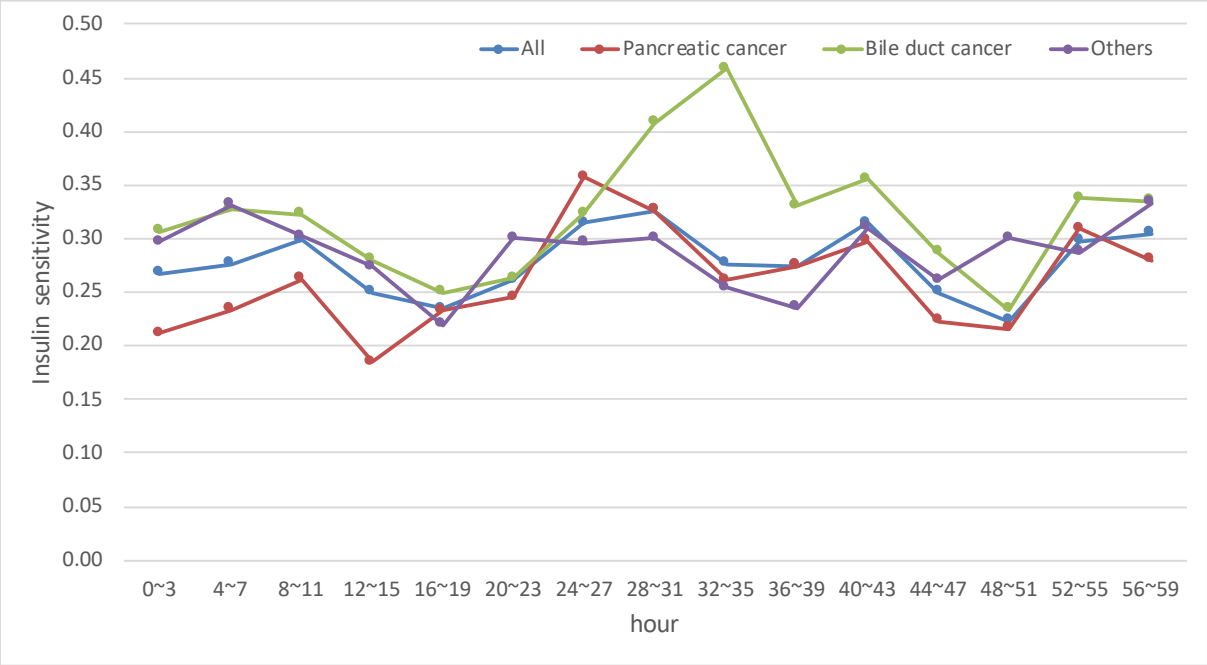


Figure 4.6: Median insulin sensitivity of four-hour blocks for patients grouped by diseases in the period of 0 to 60 hours.

and compare the results with clinical data of BG. The mean MPE value of simulation results on 26 ICU patients is fairly small, which demonstrates the ability to deal with inter- and intra-individual differences in ICU patients only by changing the insulin sensitivity parameter. Our model gives a comparable result of MPE values with ICUMM that indicates as accurate as ICUMM and the ability to represent insulin sensitivity by identifying only one parameter instead of identifying three.

The model also contains a new compartment of the small intestinal glucose absorption, which allows enteral glucose infusion through the intestine. We obtain the small intestinal glucose absorption rate p_6 in Eq. (4.1) of 0.2872 (Table 4.3) from the identification based on the ICU data, which means that about 30% of enteral glucose can be absorbed from the intestine. The result demonstrates a reduced small intestinal glucose absorption in critically ill patients as pointed out in a previous study [48]. However, we believe that the small intestinal glucose absorption rate in critically ill patients may be time-varying, especially on the way of recovery from illness. Therefore, we still need to improve the small intestinal glucose absorption model in critically ill patients.

In this chapter, we also study the differences in insulin sensitivity in diseases and the changes in insulin sensitivity among the patients because insulin sensitivity is important

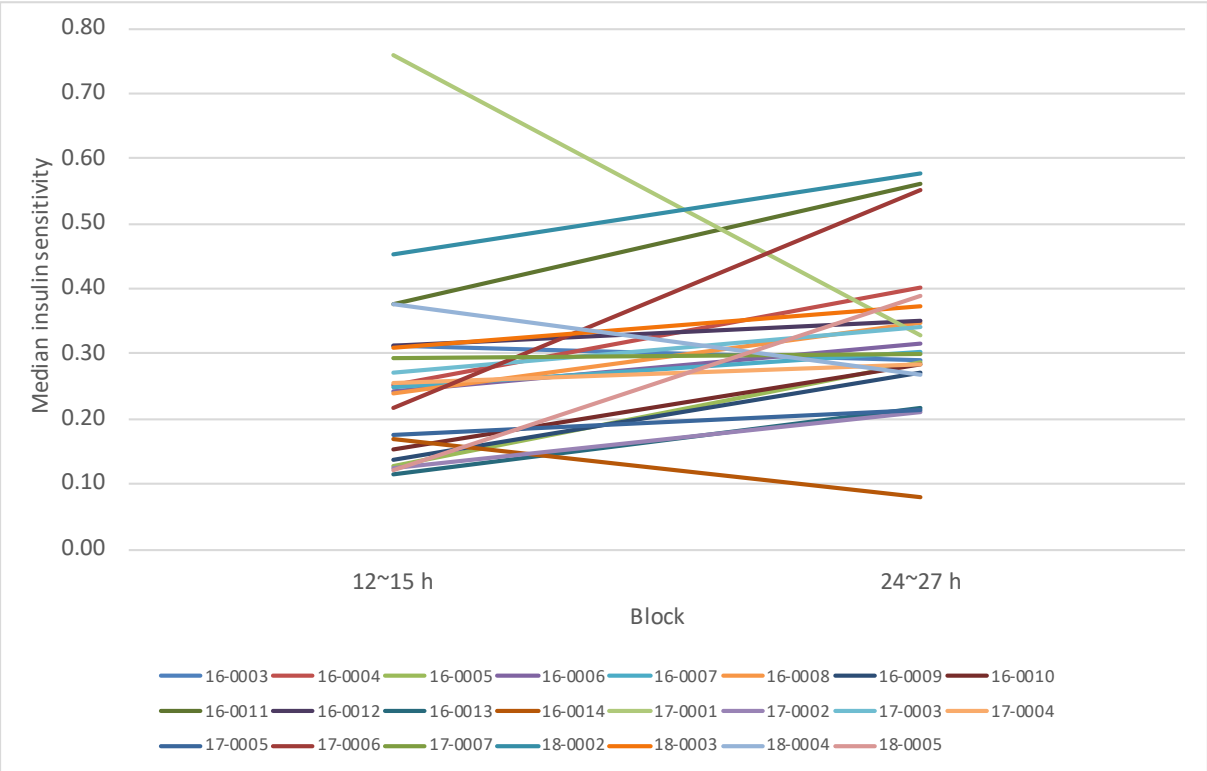


Figure 4.7: Median insulin sensitivity of blocks of 12–15 h and 24–27 h for each patient.

for a good performance of BG control. The analysis of insulin sensitivity in critically ill patients suggests that there is no significant difference in insulin sensitivity between diseases. Table 4.5 and Figure 4.7 show a significant increase of insulin sensitivity value during 12–27 hours in most of the patients ($p < 0.05$ by t-test). To confirm the increase of insulin sensitivity in ICU patients within the period, we will analyze insulin sensitivity profiles from more clinical data.

4.5 Concluding Remarks

In this chapter, we improve the glycometabolism model of ICU patients by introducing a parameter of insulin sensitivity, nonlinear effects of glucose utilization, a saturation of interstitial insulin effect and a route of enteral glucose infusion, and identify the parameters using clinical data of ICU patients in the ICU of Kagawa University Hospital. Although the model has the fixed parameter values except the parameter of insulin sensitivity, simulation results demonstrate that the model can represent BG responses of ICU patients well only by changing the insulin sensitivity parameter. Future works include improvement of the small intestinal glucose absorption model in critically ill patients, which may be time-varying, and analysis of insulin sensitivity in ICU patients in a large population to study the difference of insulin sensitivity between diseases and the change of that in ICU patients.

Chapter 5

Nonlinear Model Predictive Glycemic Control with Online Identification of Insulin Sensitivity

As mentioned in Chapter 3, the simulation result suggests that the developed nonlinear MPC system using a prediction model with fixed parameter values provides more appropriate BG control when the insulin sensitivity of an ICU patient is known. However, it is not easy to normalize BG in ICU patients by the system due to the time variability and unmeasurability of insulin sensitivity. As shown in Chapter 4, insulin sensitivity may largely vary with time during ICU stay. Since the variability of insulin sensitivity has a 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.

If the current or delayed insulin sensitivity in a patient is known, it is expected that MPC can predict the future BG in a patient more precisely. Therefore, in this chapter, to cope with the time variability of insulin sensitivity, we first develop an online identification algorithm of insulin sensitivity that updates insulin sensitivity parameter value in the prediction model during the glycemic control. Then, we construct a new glycemic control system based on the modified model using nonlinear MPC method with the online identification of insulin sensitivity. Furthermore, to more appropriately evaluate practical effectiveness and safety of the BG control system a new set of virtual patients are created from clinical data collected in the ICU of Kagawa University Hospital. Finally, we apply the system to the virtual patients H created in Chapter 3 and the new set of virtual patients created in this chapter.

5.1 Online Identification of Insulin Sensitivity

As shown in Chapter 4, insulin sensitivity largely varies with time. To always grasp insulin sensitivity and predict BG as accurately as possible, online identification of insulin sensitivity may be effective. Because we have modified the ICUMM used in our previous system by introducing an insulin sensitivity parameter, identification of the insulin sensitivity is no longer difficult. Therefore, we construct an online identification algorithm of insulin sensitivity from BG measurements, glucose and insulin infusion rates.

We estimate the insulin sensitivity parameter S_{I} in Eq. (4.6) at every sampling. During the online identification of insulin sensitivity, the other parameters are treated as constants of the values in Table 4.3. The value of insulin sensitivity S_{I} is estimated by solving the optimization problem Eq. (5.1) based on the preceding 30 min data of BG measurements of a patient, glucose and insulin infusion rates.

$$\begin{aligned} &\min_{S_{\mathrm{I}}} J_{\mathrm{S}}, \\ &J_{\mathrm{S}} = \sum_{n=0}^{1} (G_{\mathrm{clinical}}(k-n) - G_{\mathrm{model}}(k-n))^2 + W(S_{\mathrm{I}}(k) - S_{\mathrm{I}}(k-1))^2, \qquad (5.1) \\ &\text{subject to} \quad S_{\mathrm{I}} > 0, \end{aligned}$$

Here, $G_{\mathrm{clinical}}(k)$ and $G_{\mathrm{model}}(k)$ represent measured BG and simulated BG at time $k\Delta t$, respectively. Δt is the sampling time and set to 30 minutes. $S_{\mathrm{I}}(k)$ denotes the value of insulin sensitivity in Eq. (4.6) at time $k\Delta t$. W is the weight of the penalty of insulin sensitivity change and which is fixed to 500 $\mathrm{mg}^2/\mathrm{dL}^2$. The cost function consists of errors between measured BG and simulated BG, and a difference between the present and the previous insulin sensitivity. The second term in the cost function avoids a sudden change of insulin sensitivity during the online identification to prevent a rapid increase and decrease of insulin infusion rate. The minimization problem is solved by nonlinear least squares method using the MATLAB function 'lsqnonlin'.

The estimated value of insulin sensitivity S_{I} is regarded as that of the patient at present and is used for prediction of the future BG in the patient for the following hours. The identification is repeated at 30-minute intervals. Hence, there are three steps in online identification of insulin sensitivity as illustrated in Figure 5.1.

Step 1 Collect clinical data of BG measurements, glucose and insulin infusion rates from the preceding 30 minutes from a patient.

Step 2 Identify insulin sensitivity parameter value S_{I} in Eq. (4.6) based on the collected

clinical data by solving the problem Eq. (5.1).

Step 3 Repeat step 1–2 every time a new BG measurement becomes available from the patient.

The initial value of insulin sensitivity parameter S_{I} is set to 0.3 considering that conditions of ICU patients are unknown at admission to ICU and insulin sensitivity may be small (see Figure 4.6).

5.2 Nonlinear Model Predictive Control with Online Identification of Insulin Sensitivity

In this section, we develop a new closed-loop glycemic control system based on nonlinear model predictive control with the online identification algorithm of insulin sensitivity proposed in the previous section, where the continuous-time glycometabolism model with a time-varying insulin sensitivity parameter constructed in Section 4.1 is used for predicting the future BG in ICU patients. The new closed-loop glycemic control system is illustrated in Figure 5.2.

We design the nonlinear MPC system to keep BG within the desired range by a smaller amount of insulin infusion to avoid hypoglycemia. Considering that an ICU patient receives continuous exogenous glucose at a known rate, the insulin infusion rate is needed to be determined by the system and then insulin is administered at the determined rate to the patient until a new BG measurement from the patient is available. The insulin infusion rate is determined by solving the optimization problem

$$
\begin{aligned}
&\min_{u} J_{\mathrm{U}}, \\
&J_{\mathrm{U}} = Q_1(G_p(k+P) - G^*)^2 + \sum_{i=1}^{P} Q_2(G_p(k+i) - G^*)^2 \\
&\qquad + \sum_{j=0}^{M-1} \{R_1(u(k+j) - u(k+j-1))^2 + R_2 u^2(k+j)\}, \\
&\text{subject to} \quad G_p(k+i) \geq 80 \text{ mg/dL } (i = 1, 2, ..., P), \\
&\qquad\qquad 0 \leq u(k+j) \leq u_{\max} \ (j = 0, 1, ..., M-1).
\end{aligned}
\tag{5.2}
$$

Here, P and M denote the prediction and control horizons, respectively. $G_p(k)$ represents the predicted BG level by the glycometabolism model at time $k\Delta t$ with the sampling time Δt. G^* is the setpoint BG level. $u(k)$ is the insulin infusion rate at time $k\Delta t$. $u_{\max}$

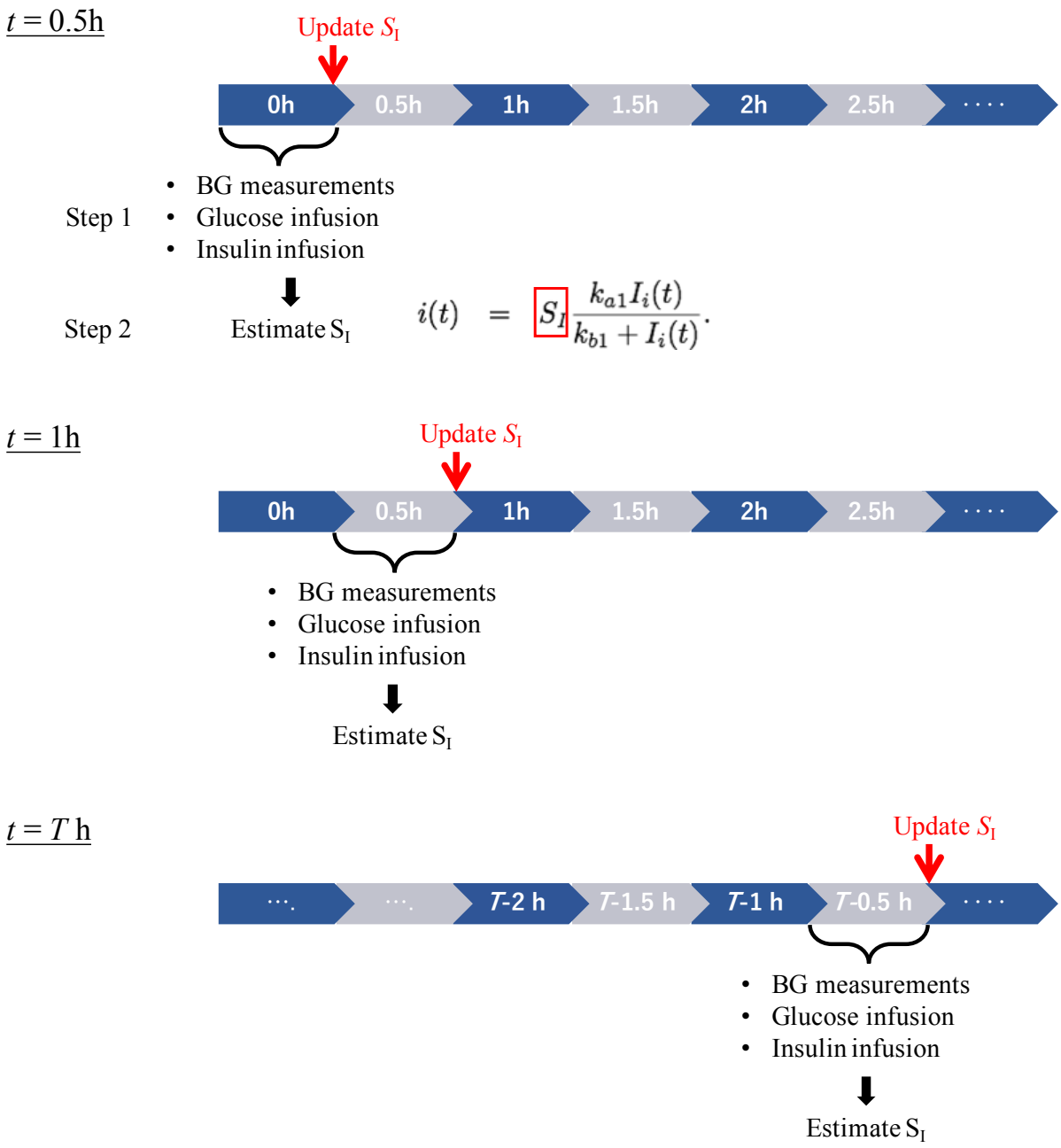


Figure 5.1: Online identification algorithm of insulin sensitivity. The insulin sensitivity parameter S_I is estimated at 30-minute intervals based on the preceding 30 minutes data. Step 1: Collect data of BG measurements, glucose and insulin infusions rates in the preceding 30 minutes. Step 2: Identify insulin sensitivity parameter value in Eq. (4.6) based on the collected 30 minutes data. Update insulin sensitivity in the model and predict the future BG for the following hours. The online identification of insulin sensitivity repeats at an interval of 30 minutes.

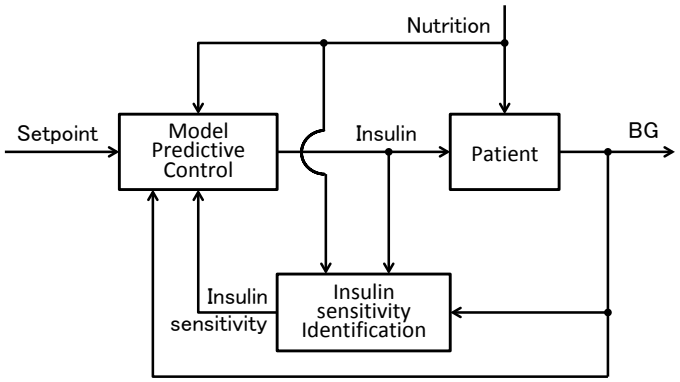


Figure 5.2: A new closed-loop glycemic control system with online identification of insulin sensitivity

denotes the maximum insulin infusion rate. Q_1, Q_2, R_1 and R_2 are weighting coefficients. The cost function J_{U} consists of errors between BG levels predicted by the model and the desired BG level, a difference between the present and the previous insulin infusion rates as well as an amount of the present insulin infusion, and allows a less change and smaller amount of insulin infusion rate during regulation of BG. The weighting coefficients Q_1, Q_2, R_1 and R_2 are adjusted considering robustness and time variability of insulin sensitivity and given by

$$
\begin{aligned}
Q_1 &= \begin{cases} 1000\ \mathrm{dL}^2/\mathrm{mg}^2, & G(k) \geq 110\ \mathrm{mg/dL} \\ 400\ \mathrm{dL}^2/\mathrm{mg}^2, & 95 \leq G(k) < 110\ \mathrm{mg/dL} \\ 10\ \mathrm{dL}^2/\mathrm{mg}^2, & 80 \leq G(k) < 95\ \mathrm{mg/dL} \\ 1000\ \mathrm{dL}^2/\mathrm{mg}^2, & G(k) < 80\ \mathrm{mg/dL} \end{cases}, \\
Q_2 &= Q_1/4, \\
R_1 &= \begin{cases} 10^{-7}\ \mathrm{min}^2/\mu\mathrm{U}^2, & S_{\mathrm{I}} > 0.3 \\ 10^{-5}\ \mathrm{min}^2/\mu\mathrm{U}^2, & S_{\mathrm{I}} \leq 0.3 \end{cases}, \\
R_2 &= \begin{cases} 1.19 \times 10^{-3}/\mathrm{BW\ kg} \cdot \mathrm{min}^2/\mu\mathrm{U}^2, & S_{\mathrm{I}} > 0.3 \\ 2.8 \times 10^{-4}/\mathrm{BW\ kg} \cdot \mathrm{min}^2/\mu\mathrm{U}^2, & S_{\mathrm{I}} \leq 0.3 \end{cases},
\end{aligned}
$$

where G is the BG measurement of the patient at time $k\Delta t$ and BW is the body-weight of the patient. The weighting coefficients of 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. R_1 and R_2 are dependent on not only the present insulin sensitivity S_{I} value identified by the online identification algorithm to avoid hypoglycemia due to a large insulin infusion rate for small insulin sensitivity, but also the weight for the insulin effect on BG to give less insulin to the

patient with a small weight.

The sampling time Δt of BG measurement is set to 30 minutes (see Section 3.2.2). To give greater importance to the robustness of the system, we set $P = 4$ so that BG in the ICU patient approaches the target in the future two hours, more slowly than in Chapter 3, and $M = 1$ because better robustness is obtained for $M = 1$ than $M > 1$. The problem is solved by the sequential quadratic programming method using the MATLAB function 'fmincon'. If insulin infusion rate cannot be obtained under the constraint in Eq. (5.2), *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.

5.3 Simulation

When a new glycemic control system is developed, it is necessary to assess its safety and effectiveness in virtual trials, *i.e.* using virtual patients that mimic glucose-insulin behaviors in clinical patients, as [17], [19] and [23] used virtual patients constructed from clinical data directly. In Chapter 3, we have generated the 30 virtual patients H from one set of clinical data by adding random fluctuations with uniform distribution considering as ICU patients with several typical changes of insulin sensitivity. In this section, we construct another new set of virtual patients from clinical data collected in the ICU of Kagawa University Hospital as virtual patients with more appropriate changes in insulin sensitivity.

To assess the effectiveness and safety of the new glycemic control system with online identification of insulin sensitivity, we do two types of simulations. First, to evaluate the performance of the control system under the condition of several typical changes of insulin sensitivity, we apply it to the virtual patients H created in Chapter 3 for comparison with the previous system. Here we make simulations of the system under parenteral glucose infusion, and both parenteral and enteral glucose infusions, and under the conditions of without and with considering BG measurements noise to assess the robustness of the system. Second, to more appropriately evaluate the practical performance of the control system, we apply the system to virtual patients created from clinical data collected in the ICU of Kagawa University Hospital and compare the results with the existing systems.

5.3.1 Virtual Patients Created from Clinical Data of Patients in the ICU of Kagawa University Hospital (Virtual Patients K)

In Section 4.1.2, we have constructed a new glycometabolism model based on the 26 ICU patients collected in the ICU of Kagawa University Hospital from June 2016 to August 2018 (see Table 4.1). The patients received continuous parenteral and/or enteral glucose and intravenous insulin according to their condition. BG measurement was taken approximately every four-hours.

In this section, we create a new set of virtual patients from the 26 ICU patients that mimic glucose-insulin behavior (*i.e.* insulin sensitivity) of these patients using the Glucosafe model [43] as we do in Section 3.2.1. As mentioned before, the reason for using the Glucosafe model is that it integrates nonlinear functions based on physiological knowledge and saturation of insulin action with reduced insulin sensitivity and consists 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 including body weight, age, height, gender and diabetes state of the patient, and one time-varying parameter of insulin sensitivity. We identify the insulin sensitivity value of the ICU patients during each interval between BG measurements based on the Glucosafe model from two successive BG measurements, insulin and glucose infusion rates. Since a bolus input cannot be treated in the Glucosafe model, we treat bolus injection as a continuous infusion at a constant rate over 1 minute with the same amount. The glucose-insulin dynamics of the virtual patients are simulated by the Glucosafe model with the identified insulin sensitivity profiles.

For the simulations, we exclude two patients who are insulinoma because we regulate BG of the patients suffering from hyperglycemia. Furthermore, we remove the period of 2 hours after bolus glucose infusion with more than 10 g because BG may rapidly change by such a large bolus glucose infusion and insulin sensitivity may not be identified accurately. As a result, we obtain 24 virtual patients of Kagawa with different insulin sensitivity profiles. Because these virtual patients are created from clinical data of ICU patients collected in the ICU of Kagawa University Hospital, we call them "virtual patients K".

5.3.2 Setting

Here, the simulation settings are given. Glycemic control starts at an initial BG level of 200 mg/dL (11.1 mmol/L) considering that the patients admitted to ICU have hy-

perglycemia with no BG management. The maximum insulin infusion rate is set to 200 mU/min which are the same as in Chapter 3. The setpoint BG level is set to 95 mg/dL (5.25 mmol/L) to regulate BG within the range of 80–110 mg/dL. To evaluate simulation results we calculate mean BG, the minimal BG, percentages of duration time within the range of 80–110 mg/dL, 80–125 mg/dL, 80–144 mg/dL and below 80 mg/dL after two hours from the start of BG control considering hyperglycemia at the time of admission.

First, to evaluate the performance of the control system under the condition of several typical changes of insulin sensitivity, we apply the glycemic control system with online identification of insulin sensitivity to the 30 virtual patients H constructed in Chapter 3. A continuous parenteral glucose infusion is administered at a known rate of 2.86 mg/min/kg to all the patients. Furthermore, we make simulations with BG measurement error of Gaussian noise with zero mean and standard deviation of $\sigma = 7.5$ mg/dL, and with the parenteral glucose infusion rate decreased from 2.86 mg/min/kg to 0.94 mg/min/kg and the enteral glucose infusion rate increase from 0 mg/min/kg to 1.43 mg/min/kg at 20 hours considering that an ICU patient receives decreased parenteral glucose and increased enteral glucose infusion in ICU as shown in Figure 4.3 to assess the robustness of the system. We also compare the developed system using nonlinear MPC with a linear MPC system with online identification of insulin sensitivity to confirm that the nonlinear MPC is necessary to regulate BG level in ICU patients. The linear MPC system uses the glycometabolism model linearized around $G = 95$ mg/dL, and the performance index and the prediction and control horizons are the same as in the nonlinear MPC system.

Second, to evaluate the performance of the control system under more appropriate clinical condition, we apply the glycemic control system to the virtual patients of K developed in Section 5.3.1 with parenteral and enteral glucose infusion at the rates in the clinical data.

5.3.3 Results on the Virtual Patients H

Figure 5.3 illustrates the simulation result on a virtual patient with 60 kg and the insulin sensitivity profile No. 8. In the figure, the top panel shows BG levels of the patient (blue line), the target BG level at 95 mg/dL (dot-dashed line) and the desired BG range of 80–110 mg/dL (between dotted line), and the bottom panel shows the identified insulin sensitivity by the online identification algorithm (blue line) and insulin sensitivity of the virtual patient (magenta line). From the figure, although BG becomes above 110 mg/dL when insulin sensitivity is very low, BG is almost always kept above 80 mg/dL even when insulin sensitivity increases rapidly. Moreover, we observe that the insulin sensitivity of the patient can be identified appropriately from the fourth panel of the figure. The system

regulates BG in the patient well by changing the insulin sensitivity of the prediction model in the controller.

Figure 5.4 compares simulation results on the virtual patient with 60 kg and the insulin sensitivity profile No. 8 without and with BG measurement error of Gaussian noise with zero mean and standard deviation of $\sigma = 7.5$ mg/dL. Figure 5.5 shows simulation result on a virtual patient with 70 kg and the insulin sensitivity profile No. 1 when the parenteral glucose infusion rate decreases from 2.86 mg/min/kg to 0.94 mg/min/kg while the enteral glucose infusion rate rises from 0 mg/min/kg to 1.43 mg/min/kg at 20 hours. The simulation results show that the system can regulate the BG of the patient against BG measurement noise and the change of both parenteral and enteral glucose infusion rates.

Table 5.1 shows the simulation results on the 30 virtual patients H of mean BG levels, the minimal BG levels, percentages of the duration times within the range of 80–110 mg/dL, 80–125 mg/dL, 80–144 mg/dL and below 80 mg/dL for the respective insulin sensitivity profiles. Note that the mean BG and the percentage values of BG within the range of 80–110 mg/dL, 80–125 mg/dL, 80–144 mg/dL, and below 80 mg/dL are those after two hours from the start of the glycemic control. The percentage of duration time within the desired range of 80–110 mg/dL is 71%. 1.5% of BG measurements are below 80 mg/dL with a minimal BG level of 60 mg/dL. No severe hypoglycemic events (BG $<$ 40 mg/dL) is observed.

Table 5.2 shows the mean BG levels, minimal BG levels, percentages of duration time within the range of 80–110 mg/dL, 80–125 mg/dL, 80–144 mg/dL and below 80 mg/dL of the nonlinear model predictive glycemic control system with the online identification algorithm of insulin sensitivity and a linear model predictive glycemic control system with the online identification algorithm of insulin sensitivity. The results are analyzed by two-tailed paired t-test. Although the linear MPC achieves only 0.1% of BG measurements below 80 mg/dL, the percentage of the duration time of BG measurements within the range of 80–110 mg/dL for the linear MPC is 20%. It suggests that the linear MPC system provides a safe but quite insufficient control.

5.3.4 Results on the Virtual Patients K

Figure 5.6 and Figure 5.7 are examples of the simulation results of the control system for the ICU patient No. 16-0005 and No. 16-0007, respectively. The percentages of the duration times within the range of 80–110 mg/dL and below 80 mg/dL for No. 16-0005 are 76% and 2.5%, respectively, with the minimal BG level of 69 mg/dL (3.8 mmol/L). On the other hand, the percentage of the duration time within the range of 80–110 mg/dL for

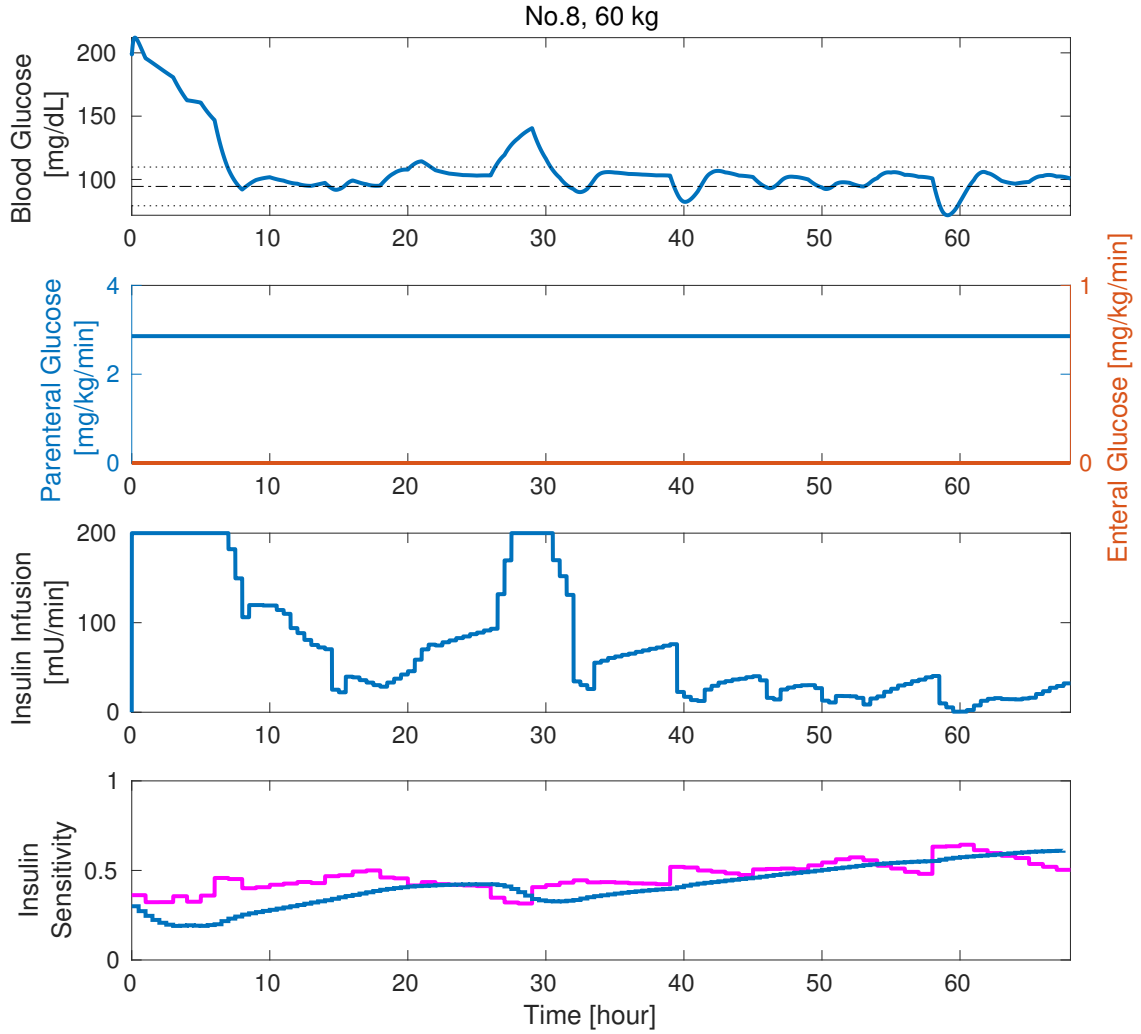


Figure 5.3: Simulation result in a virtual patient with 60 kg and insulin sensitivity profile No. 8. The top panel: BG levels (blue line), the desired BG range of 80–110 mg/dL (dotted line), target BG level at 95 mg/dL (dot-dashed line). The second panel: parenteral (blue line) and enteral (red line) glucose infusions. The third panel: insulin infusion obtained by the system. The bottom panel: patient's insulin sensitivity (magenta line, the Glucosafe model simulation), insulin sensitivity identified by online identification algorithm (blue line).

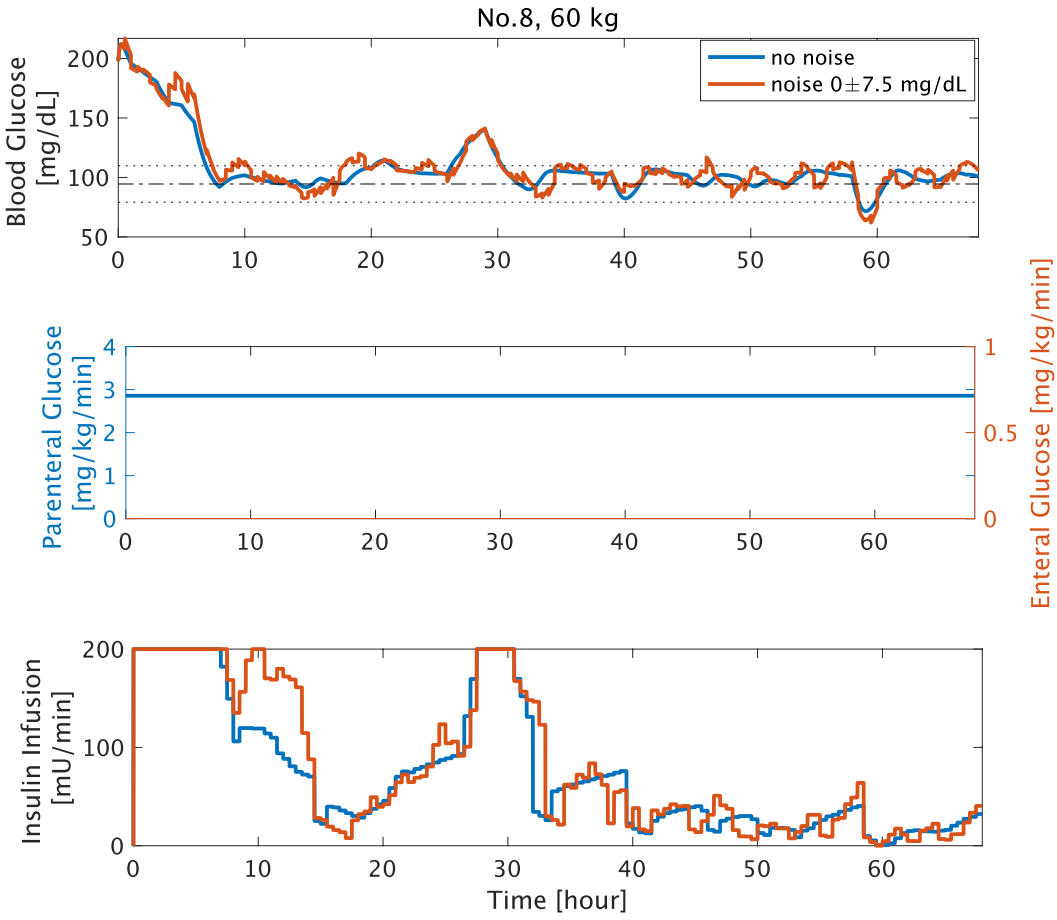


Figure 5.4: Simulation result in a virtual patient with 60 kg and insulin sensitivity profile No. 8 with BG measurement error of Gaussian noise with zero mean and standard deviation $\sigma = 7.5$ mg/dL. The top panel: BG levels (blue line), BG levels with measurement noise of Gaussian noise with zero mean and standard deviation $\sigma = 7.5$ mg/dL (red line), the desired BG range of 80–110 mg/dL (dotted line), target BG level at 95 mg/dL (dot-dashed line). The second panel: parenteral (blue line) and enteral (red line) glucose infusions. The third panel: insulin infusion obtained by the system without measurement noise (blue line), with Gaussian noise with zero mean and standard deviation $\sigma = 7.5$ mg/dL (red line).

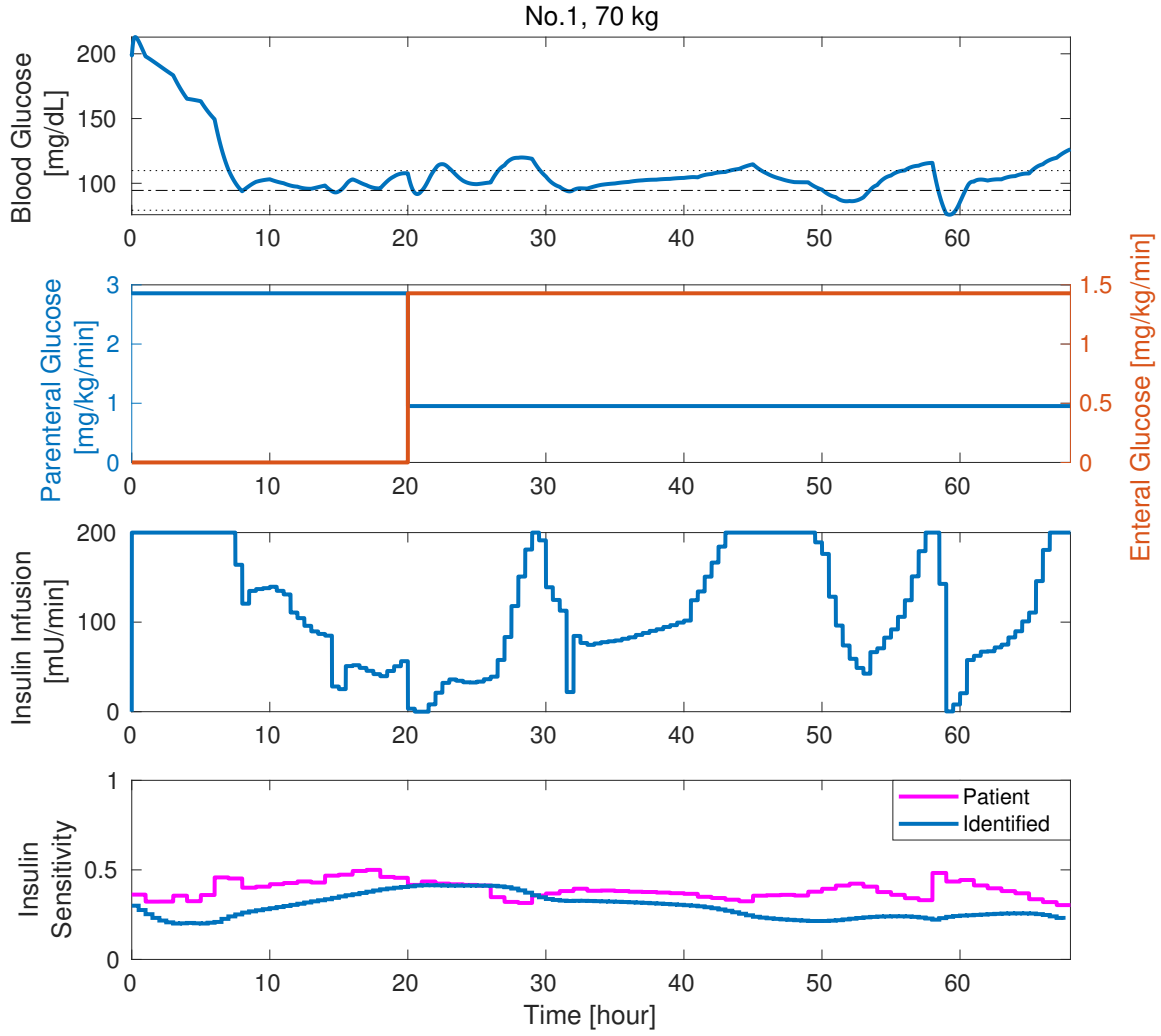


Figure 5.5: Simulation result in a virtual patient with 70 kg and insulin sensitivity profile No. 1 with the parenteral glucose infusion rate decrease from 2.86 mg/min/kg to 0.94 mg/min/kg and the enteral glucose infusion rate increase from 0 to 1.43 mg/min/kg at 20 hours.. The top panel: BG levels (blue line), the desired BG range of 80–110 mg/dL (dotted line), target BG level at 95 mg/dL (dot-dashed line). The second panel: parenteral (blue line) and enteral (red line) glucose infusions. The third panel: insulin infusion obtained by the system. The bottom panel: patient's insulin sensitivity (magenta line, the Glucosafe model simulation), insulin sensitivity identified by online identification algorithm (blue line).

Table 5.1: Simulation results of glycemic control system with online identification algorithm of insulin sensitivity for each insulin sensitivity profile of the virtual patients H

No.	Mean BG (mg/dL)	Min BG (mg/dL)	80–110 mg/dL (%)	80–125 mg/dL (%)	80–144 mg/dL (%)	< 80 mg/dL (%)
1	115	85	50	77	92	0.0
2	116	82	50	76	88	0.0
3	115	89	50	76	91	0.0
4	105	68	74	92	97	2.0
5	107	70	64	90	95	2.3
6	101	60	85	95	97	2.3
7	101	72	86	96	99	1.3
8	106	71	83	88	92	1.5
9	101	68	87	93	97	1.5
10	99	60	85	93	95	4.5
mean	106	60 †	71	88	94	1.5

† is the minimal BG level.

Table 5.2: Comparison of simulation results of glycemic control system with online identification algorithm of insulin sensitivity using nonlinear MPC and linear MPC on the 30 virtual patients H

	Nonlinear MPC	Linear MPC	p-value
Mean BG (mg/dL)	106	125	–
Min BG (mg/dL)	60	79	–
80–110 mg/dL (%)	71	20	6.84×10^{-17}
80–125 mg/dL (%)	88	60	2.57×10^{-7}
80–144 mg/dL (%)	94	88	8.18×10^{-4}
< 80 mg/dL (%)	1.5	0.1	1.52×10^{-6}

No. 16-0007 is only 27%. The reason for this low percentage of the duration time within the desired range is that the maximal insulin infusion rate is insufficient for lowering BG levels during approximate 10–27 hours and 40–50 hours due to small insulin sensitivity of the ICU patient. Figure 5.8 shows an example of ICU patient No. 16-0014 who stayed in ICU in a long duration time. From the figure, we find that insulin sensitivity is increasing after approximately 150 hours. The percentage of duration time within the range of 80–110 mg/dL is only 38% but after 150 hours it is 50%, which shows that the system can regulate BG when insulin sensitivity is not too small.

Table 5.3 shows mean BG levels, the minimal BG levels, percentages of duration time within the range of 80–110 mg/dL, 80–125 mg/dL, 80–144 mg/dL and below 80 mg/dL for each patient. The minimal BG level for each patient ranges from 49 mg/dL (2.7 mmol/L) to 105 mg/dL (5.8 mmol/L) and the percentage of duration time of BG measurements within the range of 80–110 mg/dL ranges from 27% to 100%. The mean BG level of the 24 ICU patients is 106 mg/dL (5.9 mmol/L), the minimal BG level is 49 mg/dL (2.7 mmol/L), and the averaged percentages of the duration times within the range of 80–110 mg/dL and below 80 mg/dL are 68% and 2.3%, respectively.

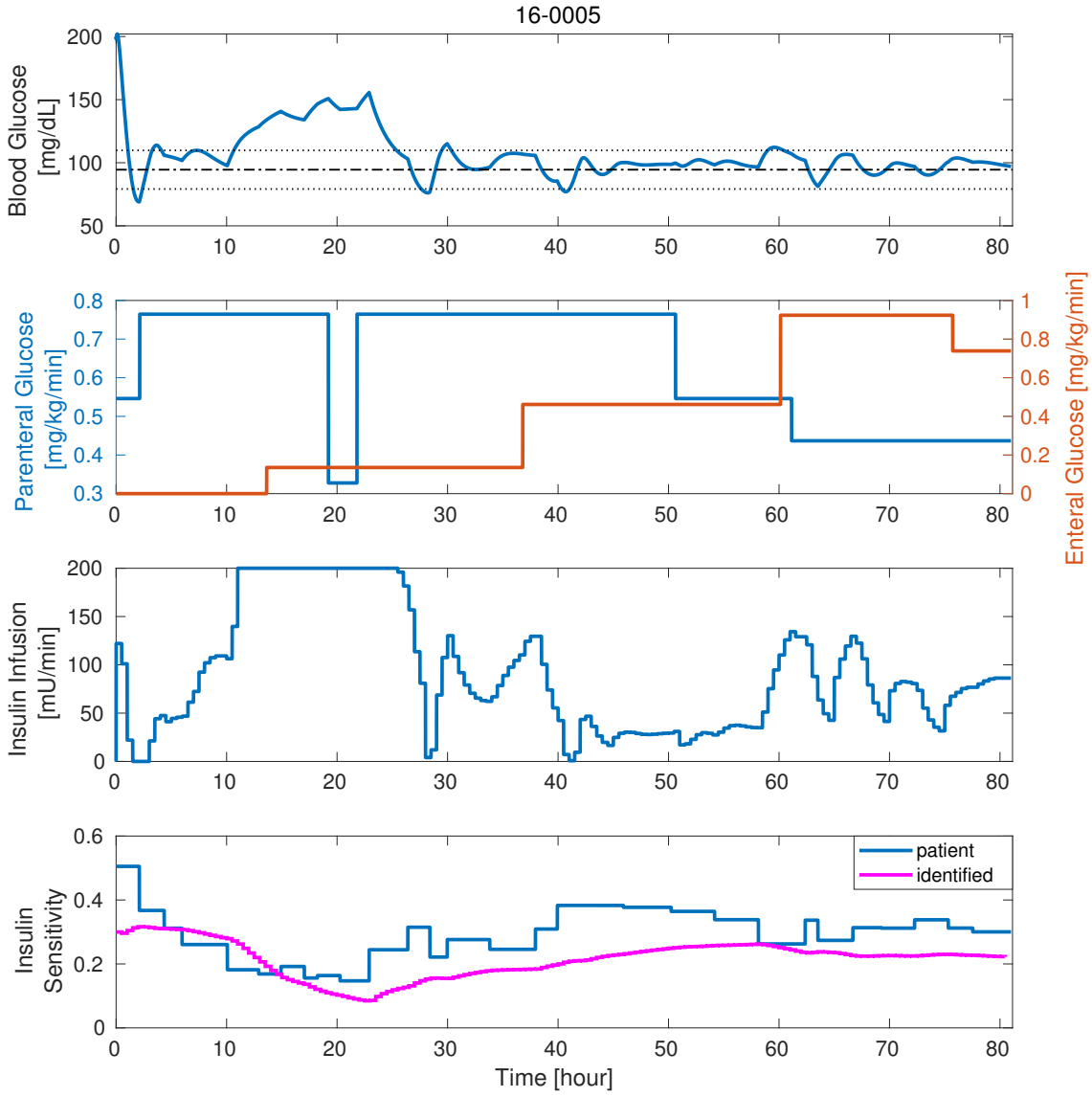


Figure 5.6: Simulation result for the virtual patient K No. 16-0005. The top panel: BG levels, the desired BG range of 80–110 mg/dL (dotted line), BG level at 95 mg/dL (dot-dashed line). The second panel: clinical parenteral (blue line) and enteral (red line) glucose infusions. The third panel: insulin infusion. The bottom panel: insulin sensitivity of the patient (blue line) and insulin sensitivity identified by online identification algorithm (magenta line).

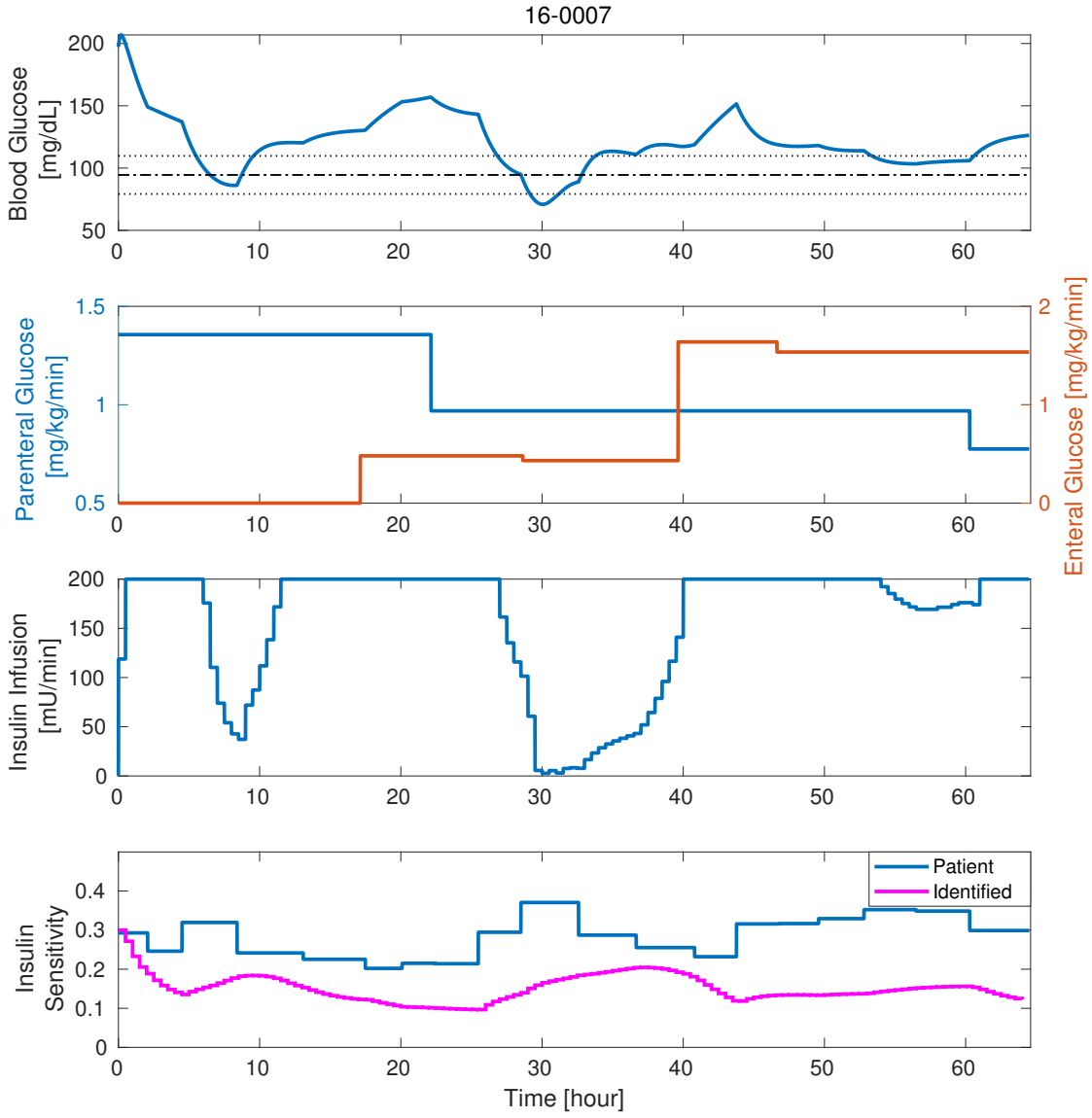


Figure 5.7: Simulation result for the virtual patient K No. 16-0007. The top panel: BG levels, the desired BG range of 80–110 mg/dL (dotted line), BG level at 95 mg/dL (dot-dashed line). The second panel: clinical parenteral (blue line) and enteral (red line) glucose infusions. The third panel: insulin infusion. The bottom panel: insulin sensitivity of the patient (blue line) and insulin sensitivity identified by online identification algorithm (magenta line).

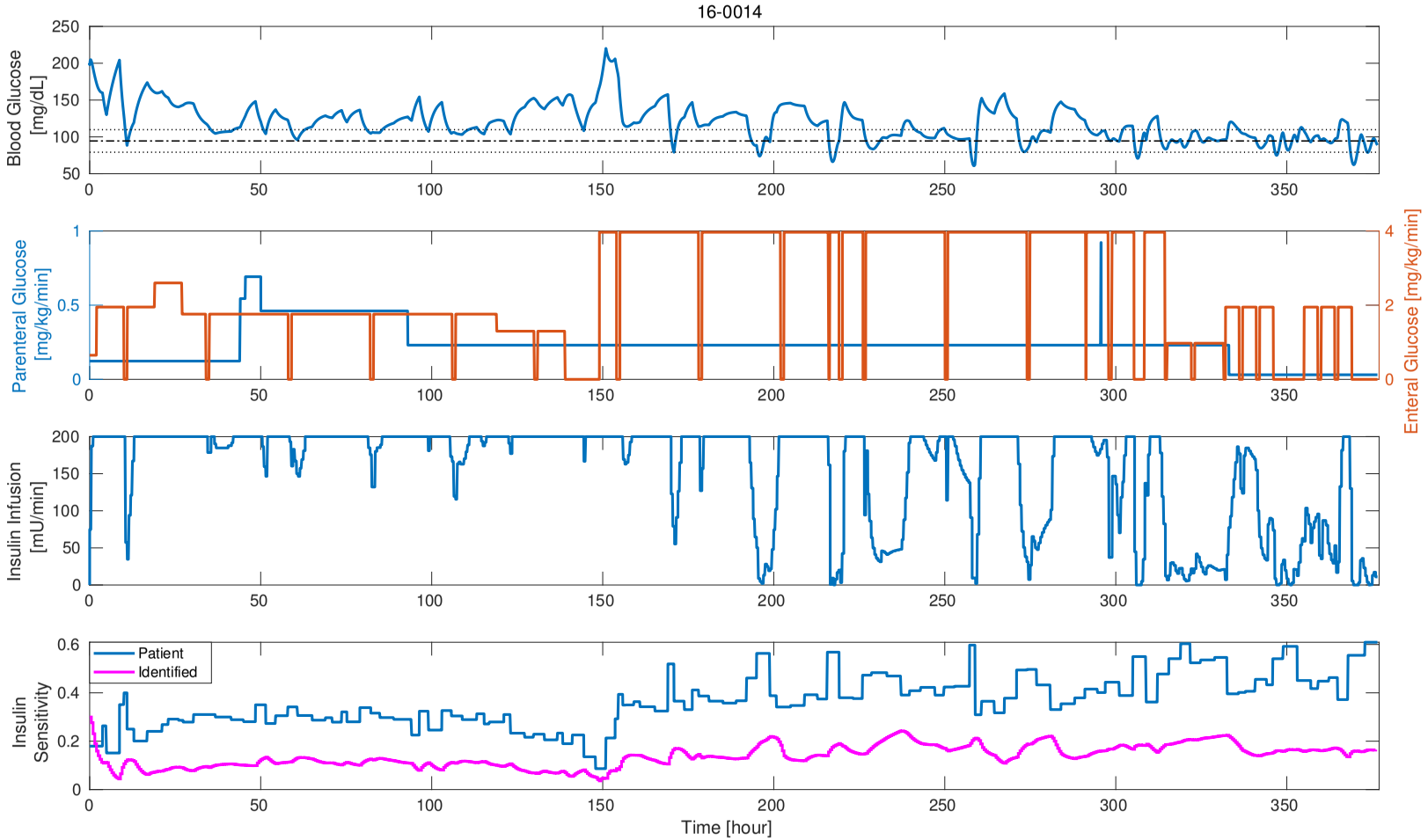


Figure 5.8: Simulation result for the virtual patient K No. 16-0014. The top panel: BG levels, the desired BG range of 80–110 mg/dL (dotted line), BG level at 95 mg/dL (dot-dashed line). The second panel: clinical parenteral (blue line) and enteral (red line) glucose infusions. The third panel: insulin infusion. The bottom panel: insulin sensitivity of the patient (blue line) and insulin sensitivity identified by online identification algorithm (magenta line).

5.4 Discussion

As mentioned in the previous chapter, grasping insulin sensitivity improves glycemic control in critically ill patients. We develop an online identification algorithm of insulin sensitivity to deal with the time variability of insulin sensitivity in critically ill patients. As shown in Figure 5.3 the identified insulin sensitivity has a trend corresponding to the insulin sensitivity profile No. 8, which indicates the good performance and precision in the online identification of insulin sensitivity.

We develop a new glycemic control system with the online identification of insulin sensitivity using nonlinear model predictive control. For the BG predictive control problem, we set the prediction horizon to 4, which is set to 2 in Chapter 3, because insulin sensitivity in the past 30 minutes is known to the controller by the online identification algorithm of insulin sensitivity that the new control system can provide more precise BG prediction.

To evaluate the new control system under several typical changes of insulin sensitivity and compare its performance with that in Chapter 3, we apply the control system to the 30 virtual patients H. The new glycemic control system with the online identification of insulin sensitivity achieves 71% of BG measurements within the range of 80–110 mg/dL, which is improved from 62% of the glycemic control system in Chapter 3. However, 1.5% of BG measurements below 80 mg/dL and the minimal BG of 60 mg/dL are worse than 0.4% of BG measurements below 80 mg/dL and the minimal BG of 74 mg/dL in Chapter 3, respectively. No severe hypoglycemic event of BG under 40 mg/dL is observed. The insufficient safety of the system indicates that the ability of hypoglycemia prevention needs to be improved.

In this chapter, we also apply the glycemic control system with online identification of insulin sensitivity to the virtual patients K created from clinical data collected in the ICU of Kagawa University Hospital to more appropriately evaluate the performance of the control system in clinical condition. Insulin sensitivity profiles of the virtual patients of Kagawa are identified based on two successive BG measurements, parenteral and enteral glucose infusion rates and insulin infusion rates.

Our glycemic control system achieves 68% of BG measurements within the range of 80–110 mg/dL (4.4–6.1 mmol/L), 83% of BG within the range of 80–125 mg/dL (4.4–7 mmol/L) and 92% of BG measurements within the range of 80–144 mg/dL (4.4–8 mmol/L). For comparison, the LOGIC-Insulin algorithm regulated 69% [15] and 67% [16] of BG within the range of 80–110 mg/dL in two trials. The eMPC system achieved 60% [20] and 46% [21] of BG measurements within the range of 80–110 mg/dL in two

Table 5.3: Simulation results of the glycemic control system using nonlinear MPC on the virtual patients K for parenteral and enteral glucose infusion in the clinical data

No.	Mean BG (mg/dL)	Min BG (mg/dL)	80–110 mg/dL (%)	80–125 mg/dL (%)	80–144 mg/dL (%)	< 80 mg/dL (%)
160003	108	64	48	76	89	6.7
160004	103	77	73	89	96	1.2
160005	106	69	76	82	93	2.5
160006	94	78	94	97	97	2.8
160007	119	71	27	65	84	3.2
160008	92	49	92	93	93	6.6
160009	106	73	59	74	94	5.5
160010	104	80	79	91	98	0.0
160011	94	62	96	96	96	3.9
160012	97	76	96	99	99	0.8
160013	110	89	66	86	96	0.0
160014	119	61	38	60	83	2.5
160015	94	87	100	100	100	0.0
160016	109	92	52	90	100	0.0
170001	111	64	56	84	93	2.1
170002	125	94	27	60	84	0.0
170003	96	54	98	99	99	1.2
170004	104	82	67	97	100	0.0
170006	121	72	34	52	63	8.3
170007	96	82	98	99	100	0.0
180002	97	82	97	100	100	0.0
180003	118	70	45	56	82	4.3
180004	100	77	89	91	96	1.5
180005	131	79	30	48	68	0.9
mean	106	49 †	68	83	92	2.3

† is the minimal BG level.

different trials respectively. The STAR achieved 83% [17] of BG within the range of 4.4–7 mmol/L in a virtual trial and 83% [18] of BG within the target range of 4.4–8 mmol/L in a clinical trial. The STOMP regulated 74% [19] of BG within the range of 4.4–7 mmol/L and 86% [19] of BG within the target range 4.4–8 mmol/L. Our glycemic system gives comparable results of percentages of the duration times within the range of 80–110 mg/dL (4.4–6.1 mmol/L) with the LOGIC, 80–125 mg/dL (4.4–7 mmol/L) and 80–144 mg/dL (4.4–8 mmol/L) with STAR and STOMP, which indicates the effectiveness of our glycemic control system.

There is no severe hypoglycemic event observed. The hypoglycemic episode is 2.3% of BG measurements below 80 mg/dL in our system. For comparison, 2.3% [15] and 1.5% [16] of BG below 70 mg/dL were observed by LOGIC-Insulin algorithm, 1.9% [20] of BG below 80 mg/dL was observed in eMPC system, 1.7% [17] and 1.4% [18] of BG below 80 mg/dL were observed by STAR system and 2.8% [19] hypoglycemia (BG $<$ 80 mg/dL) was observed by STOMP. In addition, severe hypoglycemic episodes (BG $<$ 40 mg/dL) were 0.04% in [16], 3 patients in [17] and 0.06% in [19]. No severe hypoglycemic event in our system indicates the safety of the glycemic control system with the online identification algorithm of insulin sensitivity.

We also compare the performance of the control system using nonlinear MPC with a BG control system using linear MPC. The linear model predictive control with online identification of insulin sensitivity maintains only 20% of BG within the range of 80–110 mg/dL with 0.1% of BG measurements below 80 mg/dL, which shows an insufficient performance of BG control. It confirms that the utilization of nonlinear model predictive control provides a more precise prediction of BG than linear MPC.

The BG control system appropriately regulates BG even if there is a measurement error of Gaussian noise with zero mean and standard deviation of $\sigma = 7.5$ mg/dL as shown in Figure 5.4. Moreover, the system can maintain BG within the desired range when parenteral glucose infusion rate decreases while enteral glucose infusion rate increases as shown in Figure 5.5. The results indicate the robustness of the system against the BG measurement noise and the change of glucose infusion rate.

5.5 Concluding Remarks

In this chapter, an online identification algorithm of insulin sensitivity is developed to deal with the time-varying insulin sensitivity in critically ill patients during glycemic control because the glycemic control results in the previous chapter suggest that insulin sensitivity is the key of BG control. Using the online identification of insulin sensitivity,

a new control system based on the modified model is constructed. We also construct a new set of virtual patients from ICU clinical data collected from the ICU of Kagawa University Hospital. We apply the developed control system to the virtual patients H and the virtual patients K to assess the effectiveness and safety of the control system. Although our system achieves sufficient BG control, several BG measurements under 80 mg/dL indicate that the safety of the present BG control system should be improved.

Chapter 6

Glycemic Control Using Zone Model Predictive Control

In the previous chapter, to capture insulin sensitivity in ICU patients during glycemic control we developed an online identification algorithm of insulin sensitivity that updates the insulin sensitivity parameter value in the prediction model from the BG measurements, insulin and glucose infusion rates and constructed a new glycemic control system for ICU patients. The simulation results show a better performance of maintaining BG within the desired range. However, it does not have a sufficient performance of hypoglycemia prevention. In this chapter, we adopt zone model predictive control into our glycemic control system to reduce hypoglycemic events.

Zone model predictive control (zone MPC) is a control method that keeps the controlled variable within a target zone instead of a target level. It has been applied to type 1 diabetes mellitus (T1DM) to avoid both hyperglycemia and hypoglycemia [50, 51] and in [50] safer insulin delivery was demonstrated in comparison with an ordinary MPC system. Hence, zone MPC may be suitable for maintaining BG of ICU patients above a certain level or within a desired range. Therefore, we apply zone MPC to BG control of ICU patients to improve the ability to prevent hypoglycemia.

In this chapter, we first develop a glycemic control system with online identification of insulin sensitivity for ICU patients utilizing zone MPC. Then, we apply the new system to the 30 virtual patients H created in Chapter 3 for comparison with the previous system using MPC. We also apply the developed system to the virtual patients K constructed in the previous chapter with glucose infusion at the rate in clinical data to assess the effectiveness and safety of the system and compare the simulation results with the previous system.

6.1 Zone Model Predictive BG Control

In the previous chapter, we developed a glycemic control system using nonlinear MPC with online identification of insulin sensitivity, which shows the effectiveness of maintaining BG within the desirable range. However, its ability to prevent hypoglycemia may not be sufficient. Since nonlinear MPC determines insulin infusion rate to reduce the error between the predicted BG and the target BG level, the insulin infusion rate increases for the predicted BG above the target level (*i.e.* 95 mg/dL) even if it is within the desirable range (*i.e.* 80–110 mg/dL). This may be one of the causes of excessive insulin infusion. To avoid such an increase of insulin infusion, zone MPC, which keeps the controlled variable within a specified range, may be effective because the insulin infusion rate is determined from the error between the predicted BG and the nearer bound of the target zone only when BG is outside the zone. BG control using zone MPC can be expected to avoid excessive insulin infusion and hypoglycemia.

Instead of a target level (setpoint), zone MPC sets a target zone defined by upper and lower bounds as shown in Figure 6.1. The target zone divides BG into three parts of the upper zone (BG $>$ upper bound), the lower zone (BG $<$ lower bound), and the target zone (lower bound $\leq$ BG $\leq$ upper bound).

We construct a new glycemic control of critically ill patients using zone MPC with online identification of insulin sensitivity illustrated in Figure 6.2. To predict BG level in ICU patients the glycometabolism model Eqs. (4.1)–(4.6) with parameter values in Table 4.3 is used. The online identification algorithm of insulin sensitivity updates insulin sensitivity value in the model at every sampling time as developed in Chapter 5. The change in the glycemic control system from that developed in Chapter 5 is the use of zone MPC method instead of MPC method.

Considering that ICU patients receive continuous glucose infusion at a known rate adjusted by medical staff, the insulin infusion rate is determined by solving the optimization problem:

$$
\begin{aligned}
&\min_{u} J_{\mathrm{zmpc}}, \\
&J_{\mathrm{zmpc}} = Q\sum_{i=1}^{P} z_i + \sum_{j=0}^{M-1}\{R_1(u(k+j)-u(k+j-1))^2 + R_2u^2(k+j)\}, \qquad (6.1)\\
&\text{subject to}\ \ G_p(k+i) \geq 80\ \text{mg/dL}\ (i=1,2,...,P), \\
&\qquad\qquad 0 \leq u(k+j) \leq u_{\max}\ (j=0,1,...,M-1).
\end{aligned}
$$

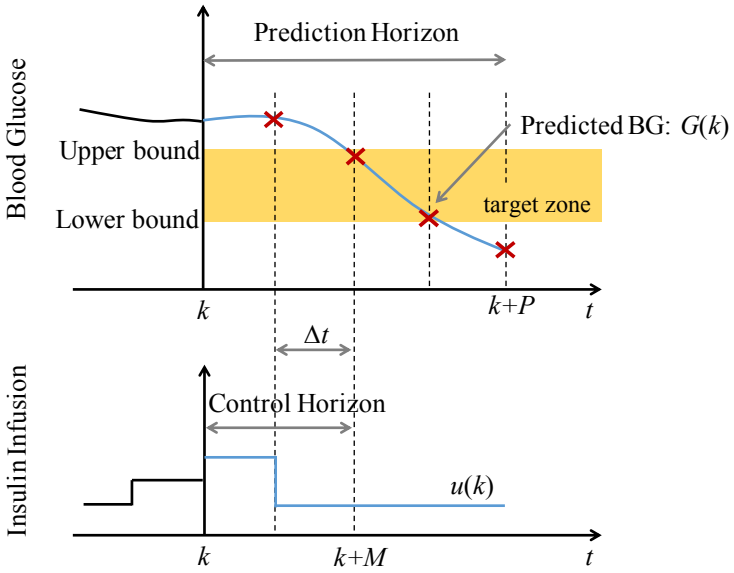


Figure 6.1: Zone model predictive control in glycemic control. The yellow area denotes the target zone defined by upper and lower bounds for the zone MPC. $G(k)$ is the predicted blood glucose level at time $k\Delta t$. $u(k)$ is the insulin infusion rate at time $k\Delta t$. Δt is the sampling time. P is the prediction horizon. M is the control horizon.

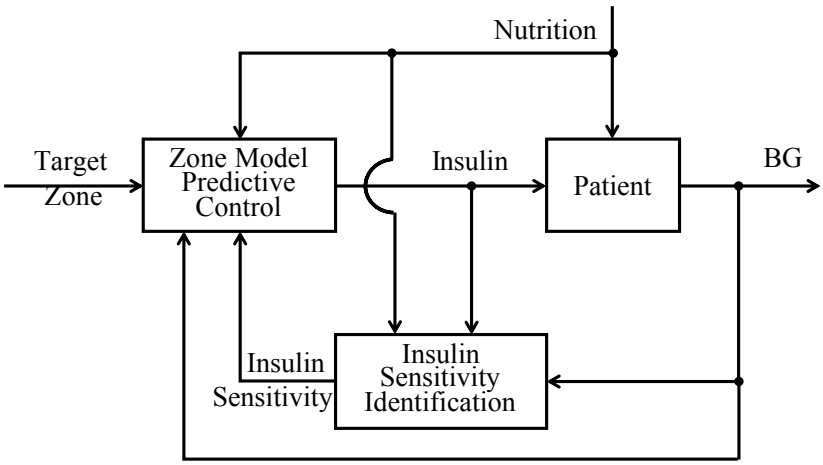


Figure 6.2: Glycemic control with online identification of insulin sensitivity based on zone model predictive control.

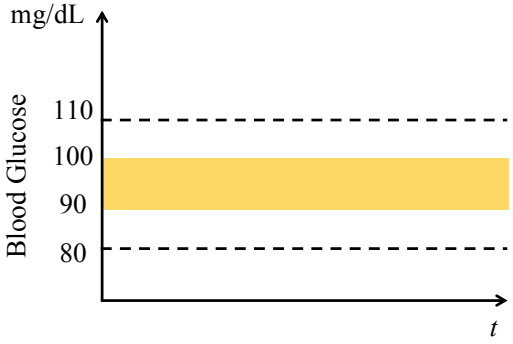


Figure 6.3: The target zone of 90–100 mg/dL (yellow area) and the desired range of 80–110 mg/dL (between the dashed line) in glycemic control utilizing zone MPC.

Here, z_i is the distance between the predicted BG and the target zone of BG defined by

$$z_i = \begin{cases} G_p(k+i) - G_{\text{upper}}, & G_p(k+i) > G_{\text{upper}} \\ 0, & G_{\text{lower}} \leq G_p(k+i) \leq G_{\text{upper}} \\ G_{\text{lower}} - G_p(k+i), & G_p(k+i) < G_{\text{lower}} \end{cases}, \tag{6.2}$$

where $G_p(k+i)$ is the predicted BG at time $(k+i)\Delta t$ (Δt: sampling period), G_{upper} and G_{lower} represent the upper and lower bounds of the zone MPC, respectively, P and M denote the prediction and control horizons, respectively, $u(k)$ is the insulin infusion rate at time $k\Delta t$ limited by the maximum infusion rate $u_{\max}$. In the cost function, we set the distance between the predicted BG and the target zone to z_i instead of z_i^2 because it shows better performance of preventing hypoglycemia and keeping BG within the range of 80–110 mg/dL than the use of z_i^2.

The control parameters are determined as follows. To regulate BG in critically ill patients within the range of 80–110 mg/dL against measurement errors and sudden changes in patients, we set the target zone to 90–100 mg/dL (*i.e.* the upper bound G_{upper} is 100 mg/dL and the lower bound G_{lower} is 90 mg/dL; see Figure 6.3 that illustrates the target zone with the yellow area and the desired range of BG of 80–110 mg/dL between the dashed lines). The sampling time is set to 30 min as in the previous chapters. The prediction horizon P and the control horizon M are set to 4 and 1, respectively, and the

weighting coefficients Q, R_1 and R_2 are set as

$$\begin{aligned} Q &= \begin{cases} 12000 \text{ dL/mg}, & G(k) \geq 110 \text{ mg/dL} \\ 2800 \text{ dL/mg}, & 95 \text{ mg/dL} \leq G(k) < 110 \text{ mg/dL} \\ 160 \text{ dL/mg}, & 80 \text{ mg/dL} \leq G(k) < 95 \text{ mg/dL} \\ 12000 \text{ dL/mg}, & G(k) < 80 \text{ mg/dL} \end{cases}, \\ R_1 &= 10^{-7} \text{ min}^2/\mu\text{U}^2, \\ R_2 &= 3.85 \times 10^{-4}/\text{BW kg} \cdot \text{min}^2/\mu\text{U}^2, \end{aligned} \tag{6.3}$$

where $G(k)$ denotes the BG measurement at time $k\Delta t$, BW is the body-weight of the patient. Note that G is different from G_p in Eq. (6.2) which is predicted using the model from the present BG measurement G. To solve the optimization problem, we utilize the Matlab function 'fmincon' based on the sequential quadratic programming method. Note that if insulin infusion rate cannot be obtained under the constraints in Eq. (6.1), insulin infusion rate $u(k)$ is determined to 0.

6.2 Simulation

In this section, we assess the performance of the developed glycemic control system using zone MPC. To compare the present system with the system developed in the previous chapter which is based on regular MPC, we make simulations under the same conditions as is Chapter 5, *i.e.* under the conditions of parenteral glucose infusion, and both parenteral and enteral glucose infusions and under the condition without and with considering BG measurements noise to assess the robustness of the system for the virtual patients H and under the condition with parenteral and enteral glucose infusion at the rates in the clinical data for the virtual patients K.

6.2.1 Setting

Here, the simulation settings are given. Glycemic control starts at an initial BG level at 200 mg/dL (11.1 mmol/L) considering that the patients admitted to ICU have hyperglycemia with no BG management. The maximum insulin infusion rate is set to 200 mU/min which are the same as in the previous chapter. The target zone of BG is set to 90–100 mg/dL to regulate BG within the range of 80–110 mg/dL. To evaluate simulation results we calculate mean BG, the minimal BG, percentages of duration time within the range of 80–110 mg/dL, 80–125 mg/dL, 80–144 mg/dL and below 80 mg/dL after two hours from the start of BG control considering hyperglycemia at the time of admission.

First, we apply the glycemic control system to the 30 virtual patients H to evaluate the performance of the control system under the condition of several changes of insulin sensitivity. A continuous parenteral glucose infusion is administered at a known rate of 2.86 mg/min/kg to all the patients. Furthermore, to assess the robustness of the control system, we make simulations with BG measurement error of Gaussian noise with zero mean and standard deviation of $\sigma = 7.5$ mg/dL, and with the parenteral glucose infusion rate decrease from 2.86 mg/min/kg to 0.94 mg/min/kg and the enteral glucose infusion rate increase from 0 mg/min/kg to 1.43 mg/min/kg at 20 hours considering that the ICU patient receives decreased parenteral glucose and increased enteral glucose infusion rates in ICU as shown in Figure 4.3.

Second, we apply the glycemic control system to the virtual patients K developed in Chapter 5 with parenteral and enteral glucose infusion at the rates in the clinical data to evaluate the performance of the control system under more appropriate clinical condition.

6.2.2 Results on the Virtual Patients H

Figure 6.4 illustrates the simulation results of the glycemic control system using zone MPC and MPC for the virtual patient with 70 kg and insulin sensitivity profile No. 10. The top panel in the figure shows BG level regulated by the glycemic control system using zone MPC (red line) and that regulated by the MPC system (blue line), the third panel shows the insulin infusion rates of the zone MPC system (red line) and MPC system (blue line), respectively. We find that the zone MPC system has a better performance of hypoglycemia prevention from BG at approximately 7 hours and 30 hours. Furthermore, the minimal BG level is 72 mg/dL for the zone MPC system compared with 60 mg/dL for the MPC system. Three BG measurements below 80 mg/dL are observed in zone MPC system, while five BG measurements are observed in MPC system. Zone MPC reduces 43% hypoglycemic episodes (2.3% vs 3.8%) and improves 6% of BG within the desired range (89% vs 84%) for the virtual patient. Table 6.1 summarizes the results for the patient.

Figure 6.5 shows another example of the simulation results of the zone MPC and MPC systems for the virtual patient with 60 kg and insulin sensitivity No. 6. Although the zone MPC system gives a comparable result of the percentage of duration time of BG below 80 mg/dL to the MPC system, the minimal BG level is improved from 64 mg/dL to 68 mg/dL and the percentage of duration time of BG within the desired range is also improved from 86% to 88% (see Table 6.2).

The simulation results on the 30 virtual patients H of mean BG levels, the minimal BG levels, percentages of duration time within the range of 80–110 mg/dL (4.4–6.1 mmol/L),

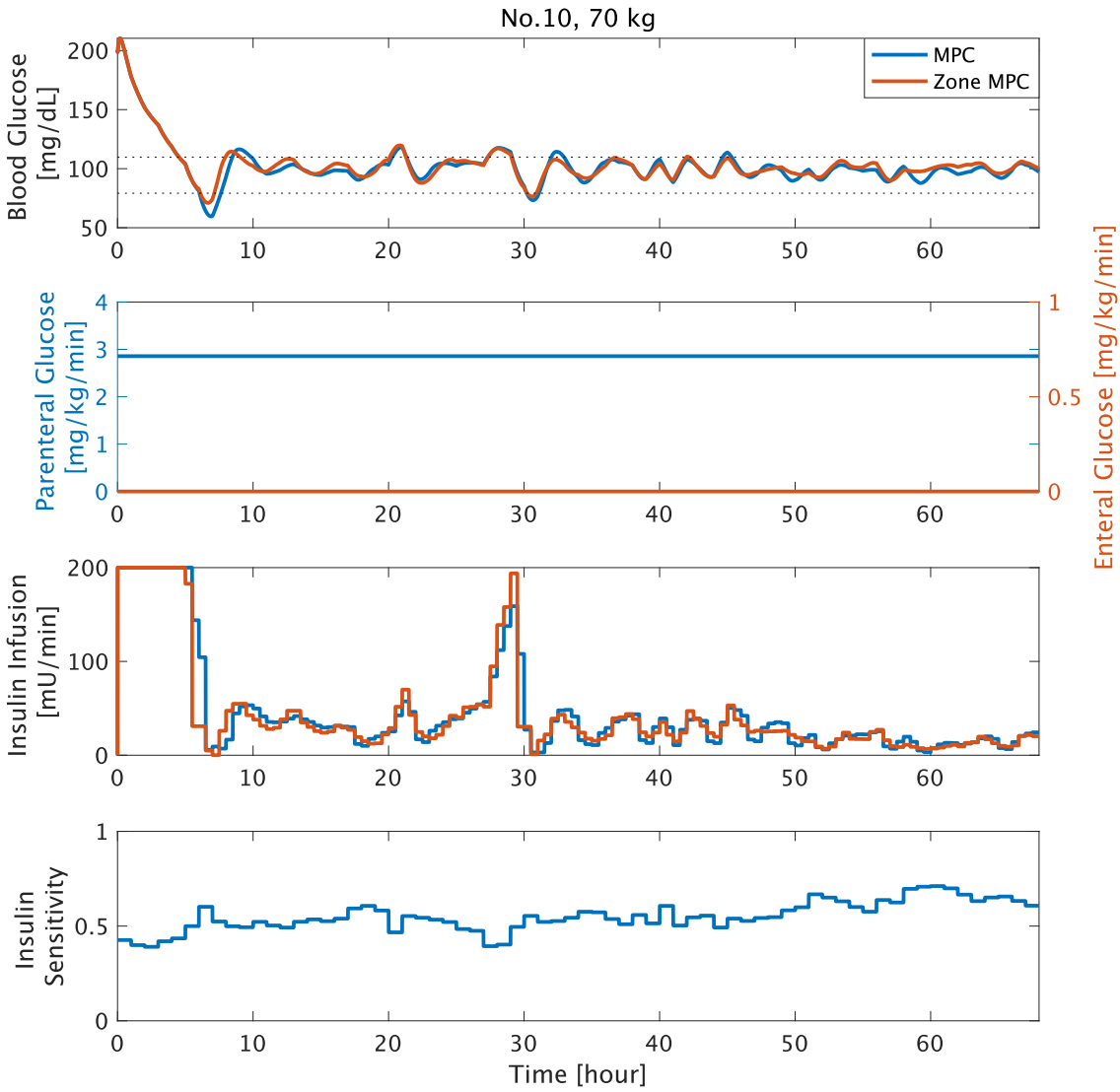


Figure 6.4: Simulation result for the virtual patient with 70 kg and insulin sensitivity profile No. 10. The top panel: BG levels of zone MPC system (red line), BG levels of the MPC system (blue line), the desired BG range of 80–110 mg/dL (dotted line). The second panel: parenteral (blue line) and enteral (red line) glucose infusions. The third panel: insulin infusion of the zone MPC system (red line), and the MPC system (blue line). The bottom panel: insulin sensitivity of the patient

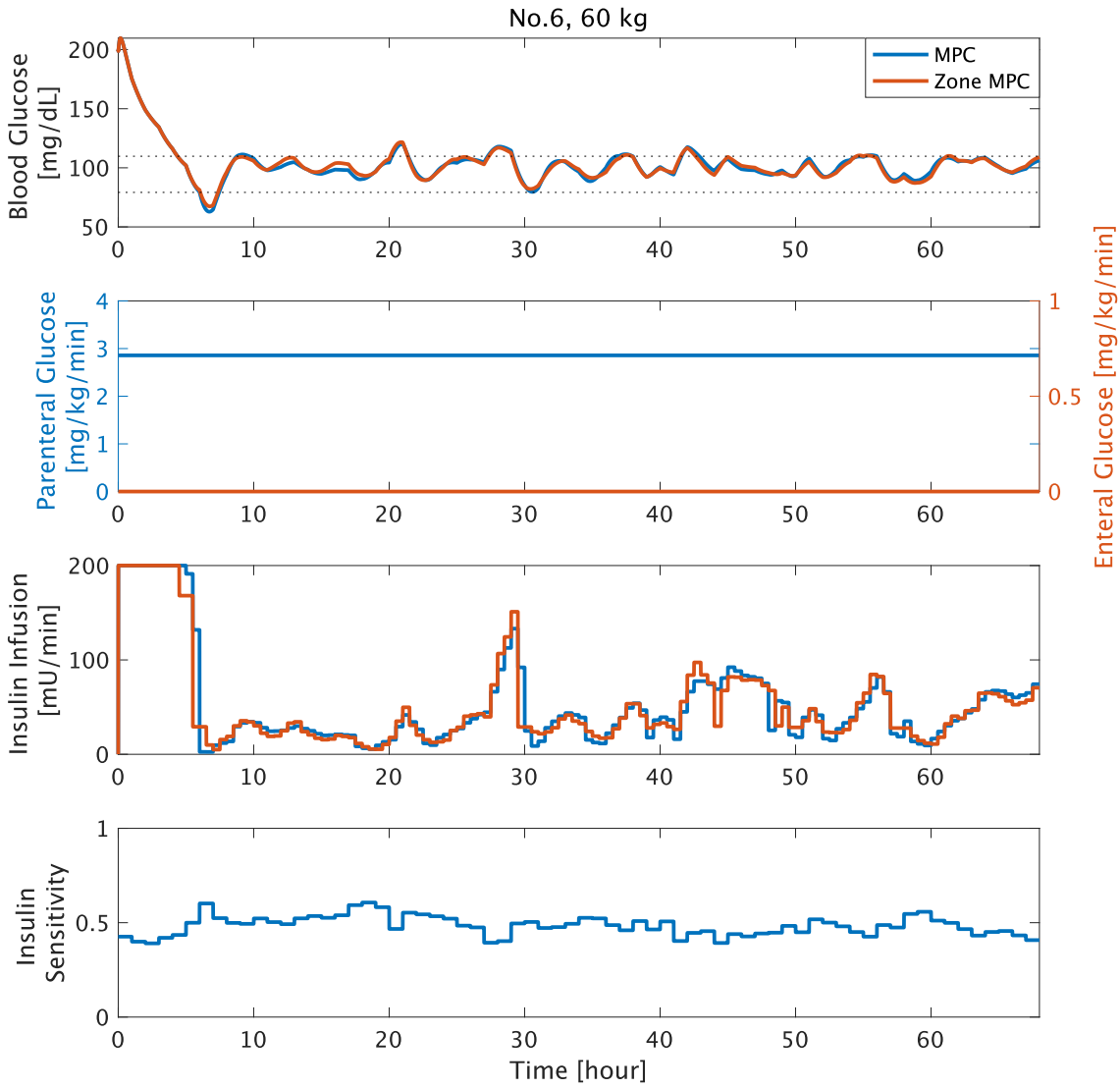


Figure 6.5: Simulation result for the virtual patient with 60 kg and insulin sensitivity profile No. 6. The top panel: BG levels of zone MPC system (red line), BG levels of the MPC system (blue line), the desired BG range of 80–110 mg/dL (dotted line). The second panel: parenteral (blue line) and enteral (red line) glucose infusions. The third panel: insulin infusion of the zone MPC system (red line), and the MPC system (blue line). The bottom panel: insulin sensitivity of the patient

Table 6.1: Simulation results of the zone MPC system and the MPC system for the virtual patient with 70 kg and insulin sensitivity profile No. 10

	Zone MPC	MPC
Mean BG (mg/dL)	101	100
Min BG (mg/dL)	72	60
80–110 mg/dL (%)	89	84
< 80 mg/dL (%)	2.3	3.8
< 80 mg/dL (times)	3	5

Table 6.2: Simulation results of the zone MPC system and the MPC system for the virtual patient with 60 kg and insulin sensitivity profile No. 6

	Zone MPC	MPC
Mean BG (mg/dL)	102	101
Min BG (mg/dL)	68	64
80–110 mg/dL (%)	88	86
< 80 mg/dL (%)	1.5	1.5
< 80 mg/dL (times)	2	2

80–125 mg/dL (4.4–7 mmol/L), 80–144 mg/dL (4.4–8 mmol/L) and below 80 mg/dL for the respective insulin sensitivity profiles are shown in Table 6.3. The percentage of duration time within the desired range of 80–110 mg/dL is 71%. 1.3% of BG measurements are below 80 mg/dL with a minimal BG level of 67 mg/dL. No severe hypoglycemic events (BG < 40 mg/dL) is observed. Table 6.4 compares the present system using zone MPC and the previous system using nonlinear MPC of the 30 virtual patients H analyzed by two-tailed paired t-test. The two systems give comparable results on the percentage of duration time within the range of 80–110 mg/dL ($p > 0.05$), 80–125 mg/dL ($p > 0.05$) and below 80 mg/dL (from 1.5% in the ordinary MPC system to 1.3% in the zone MPC system ($p > 0.05$)), while the percentage of duration time within the range of 80–144 mg/dL is significantly improved in the zone MPC system ($p < 0.05$).

Figure 6.6 shows the simulation results of the zone MPC system and the MPC system for the virtual patient with 60 kg and insulin sensitivity No. 5 when parenteral glucose infusion rate decreases from 2.86 to 0.94 mg/min/kg and enteral glucose infusion rate increases from 0 to 1.43 mg/min/kg at 20 hours. The zone MPC system obtains 80% of BG measurements within the range of 80–110 mg/dL, only one BG measurement below 80 mg/dL with the minimal BG of 73 mg/dL. On the other hand, the MPC system gives

Table 6.3: Simulation results of glycemic control system with online identification algorithm of insulin sensitivity utilizing zone MPC for each insulin sensitivity profile of the virtual patients H

No.	Mean BG (mg/dL)	Min BG (mg/dL)	80–110 mg/dL (%)	80–125 mg/dL (%)	80–144 mg/dL (%)	< 80 mg/dL (%)
1	116	88	49	77	93	0.0
2	116	80	48	76	88	0.0
3	116	89	49	76	92	0.0
4	105	69	75	92	97	2.0
5	107	71	65	91	96	1.5
6	102	67	87	96	98	1.5
7	101	76	87	96	99	1.5
8	107	73	83	88	92	1.8
9	102	69	85	94	97	1.5
10	100	67	88	94	96	3.5
mean	107	67 †	71	88	95	1.3

† is the minimal BG level.

Table 6.4: Simulation results of the glycemic control system utilizing zone MPC and MPC for the 30 virtual patients H.

	Zone MPC	MPC	p-value
Mean BG (mg/dL)	107	106	–
Min BG (mg/dL)	67	60	–
80–110 mg/dL (%)	71	71	0.7090
80–125 mg/dL (%)	88	88	0.0539
80–144 mg/dL (%)	95	94	0.0116
< 80 mg/dL (%)	1.3	1.5	0.0729
< 80 mg/dL (patients)	21	21	–

Table 6.5: Simulation results of the zone MPC system and the MPC system for the ICU virtual patient No. 16-0005 .

	Zone MPC	MPC
Mean BG (mg/dL)	108	106
Min BG (mg/dL)	69	69
80–110 mg/dL (%)	75	76
$<$ 80 mg/dL (%)	0.6	2.5
$<$ 80 mg/dL (times)	1	4

79% of BG measurements within the range of 80–110 mg/dL, four BG measurements below 80 mg/dL with the minimal BG of 71 mg/dL in MPC system.

Figure 6.7 shows simulation result on the virtual patient with 60 kg and insulin sensitivity No. 5 under BG measurement noise of Gaussian distribution with zero mean and standard deviation of $\sigma = 7.5$ mg/dL. 62% of BG measurements within the range of 80–110 mg/dL, four BG measurements below 80 mg/dL with the minimal BG of 73 mg/dL is achieved.

6.2.3 Results on the Virtual Patients K

Figure 6.8 illustrates the simulation results on patient No. 16-0005 who shows good performance of BG control and prevention of hypoglycemia when parenteral and enteral glucose is infused at the rates given in the clinical data. In the top panel, the red line shows BG level regulated by the glycemic control system using zone MPC and the blue line illustrates that regulated by the MPC system. In the third panel, the red line and the blue line show insulin infusion rates computed by the zone MPC system and MPC system, respectively. From the figure, BG becomes lower than 80 mg/dL at approximate 29 hours, 40 hours and 64 hours when applying the MPC system, while BG is kept above 80 mg/dL at these times by rapidly reducing insulin infusion rate for the sudden decrease of BG in the zone MPC system. Table 6.5 gives the simulation results on the patient. Although the two systems give comparable results of the mean BG, the minimal BG levels and the percentage of duration time within the range of 80–110 mg/dL, BG measurements below 80 mg/dL is reduced from 2.5% (four BG measurements) to 0.6% (one BG measurement) by utilizing zone MPC.

We calculate mean BG levels, the minimal BG levels, percentages of duration time of BG within the ranges of 80–110 mg/dL, 80–125 mg/dL, 80–144 mg/dL and below 80 mg/dL for each virtual patient and list them in Table 6.6. The mean BG level of all the

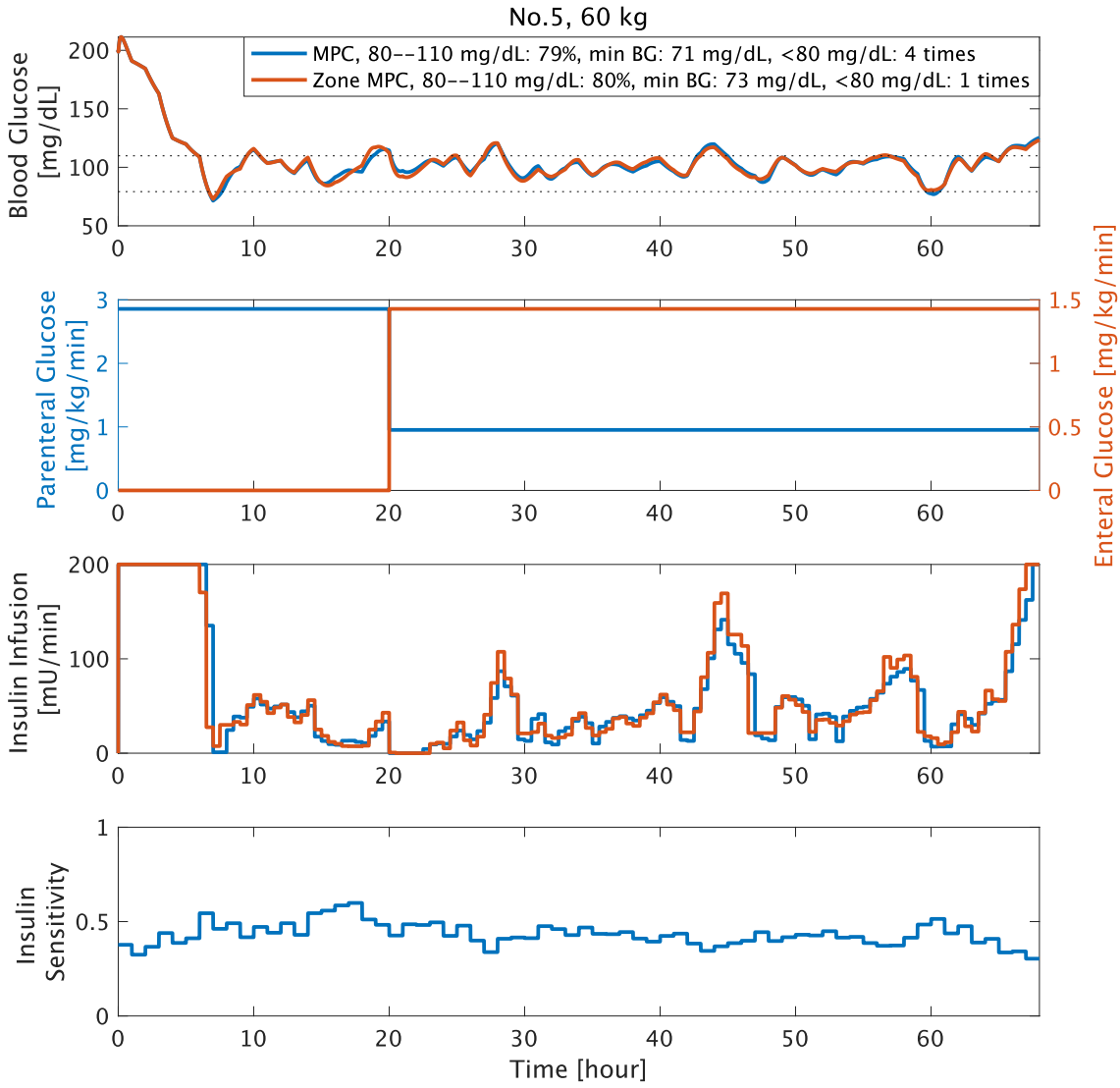


Figure 6.6: Simulation result for the virtual patient with 60 kg and insulin sensitivity profile No. 5 with the parenteral glucose infusion rate decrease from 2.86 to 0.94 mg/min/kg and enteral glucose infusion rate increase from 0 to 1.43 mg/min/kg at 20 hours. The top panel: BG levels of zone MPC system (blue line) and the desired BG range of 80–110 mg/dL (dotted line). The second panel: parenteral (blue line) and enteral (red line) glucose infusions. The third panel: insulin infusion rate.

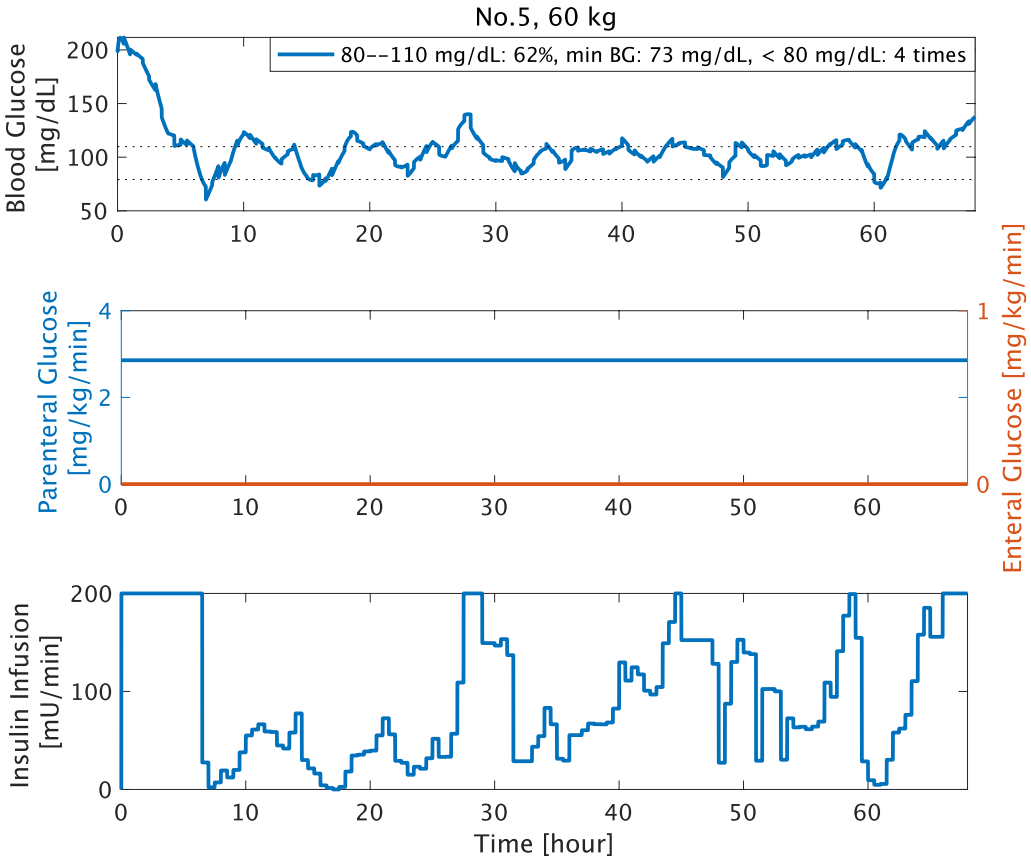


Figure 6.7: Simulation result for the virtual patient with 60 kg and insulin sensitivity profile No. 5 under BG measurement noise of Gaussian distribution with zero mean and standard deviation $\sigma = 7.5$ mg/dL. The top panel: BG levels of zone MPC system, the desired BG range of 80–110 mg/dL (dotted line). The second panel: parenteral (blue line) and enteral (red line) glucose infusions. The third panel: insulin infusion of the zone MPC system.

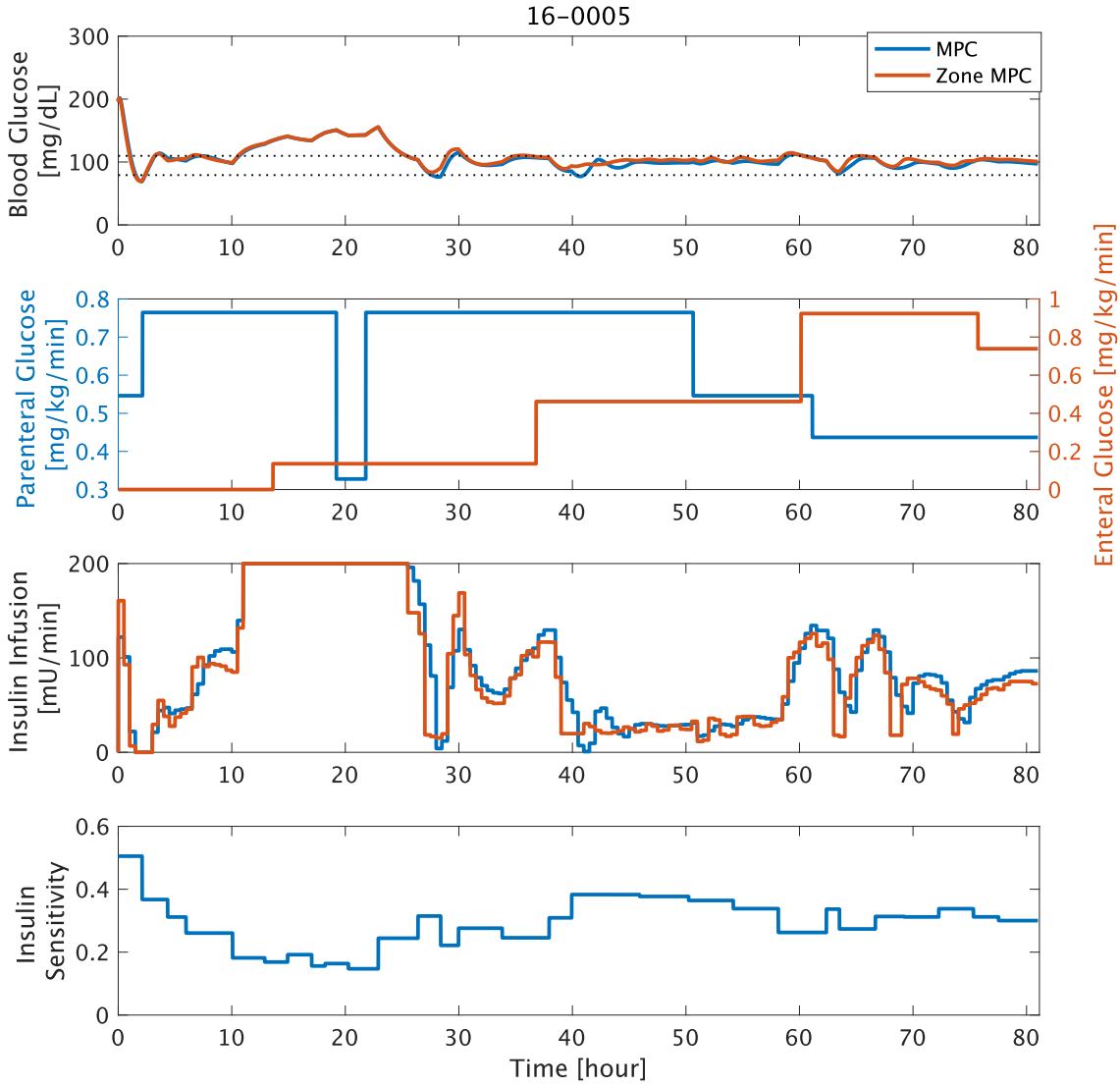


Figure 6.8: Simulation results of the zone MPC system and the MPC system for the ICU virtual patient No. 16-0005. The top panel: BG levels regulated by zone MPC (red line) and MPC (blue line), the desired BG range of 80–110 mg/dL (dotted line). The second panel: clinical parenteral (blue line) and enteral (red line) glucose infusions rates. The third panel: insulin infusions rates computed by zone MPC (red line) and MPC (blue line). The bottom panel: insulin sensitivity of the patient.

patients is 108 mg/dL, the mean percentages of duration time of BG within the range of 80–110 mg/dL is 68%, of BG below 80 mg/dL is 1.3% and the minimal BG level of all the patients is 48 mg/dL.

The mean BG levels, the minimal BG levels, mean percentages of duration time within the range of 80–110 mg/L (4.4–6.1 mmol/L), 80–125 mg/dL (4.4–7 mmol/L), 80–144 mg/dL (4.4–8 mmol/L) and below 80 mg/dL of the zone MPC system and the MPC system for the virtual patients of K of are given in Table 6.7. To compare the zone MPC system with the MPC system, the results are analyzed by two-tailed paired t-test. The two systems give comparable results on the percentage of duration time within the range of 80–110 mg/dL ($p > 0.05$), while the percentages of duration time within the range of 80–125 mg/dL ($p < 0.05$), 80–144 mg/dL ($p < 0.05$), and below 80 mg/dL (from 2.3% in the ordinary MPC system to 1.3% in the zone MPC system ($p < 0.05$)) are significantly improved when using zone MPC. No severe hypoglycemic event is observed in both systems, and the minimal BG levels for the zone MPC system and MPC system are 48 mg/dL and 49 mg/dL, respectively.

6.3 Discussion

In this chapter, we develop a glycemic control system with online identification of insulin sensitivity utilizing zone model predictive control because the desired BG level of ICU patients is given by the range of 80–110 mg/dL and zone MPC realizes a safe BG control for T1DM patients [50]. We set the target range of 90–100 mg/dL to regulate BG in ICU patients within the range of 80–110 mg/dL against measurement errors and sudden changes in patients. The developed system using zone MPC can maintain BG within the range of 80–110 mg/dL except when the insulin sensitivity is so low that insulin infusion at the maximum rate is not sufficient to lower BG below 110 mg/dL.

From the results of applying the system to the 30 virtual patients H, although it achieves a comparable result of 71% BG measurements within the range of 80–110 mg/dL to the system constructed in Chapter 5, the minimal BG of 67 mg/dL is improved from 60 mg/dL in MPC system and the percentage of BG measurements below 80 mg/dL tends to be reduced from 1.5% in MPC system to 1.3% in zone MPC listed in Table 5.1, which suggests that the utilization of zone MPC reduces hypoglycemic episodes efficiently.

As shown in Figures 6.4 and 6.5, the minimal BG measurements are improved from 60 mg/dL to 72 mg/dL and from 64 mg/dL to 68 mg/dL in the zone MPC system, respectively, compared with the MPC system. When controlled with a change of glucose infusion as shown in Figure 6.6, the minimal BG of 73 mg/dL in the zone MPC system

Table 6.6: Simulation results of the zone MPC system for the virtual patients K.

No.	Mean BG (mg/dL)	Min BG (mg/dL)	80–110 mg/dL (%)	80–125 mg/dL (%)	80–144 mg/dL (%)	< 80 mg/dL (%)
160003	110	71	50	79	92	4.2
160004	106	80	75	90	98	0.0
160005	108	69	75	84	95	0.6
160006	96	81	96	100	100	0.0
160007	120	75	26	65	85	2.4
160008	94	48	92	94	94	6.3
160009	108	71	62	79	98	1.8
160010	107	87	79	90	99	0.0
160011	97	64	96	96	96	3.9
160012	100	75	93	99	99	0.8
160013	112	86	65	85	96	0.0
160014	121	66	37	61	84	1.5
160015	97	89	100	100	100	0.0
160016	110	94	50	90	100	0.0
170001	112	66	52	84	93	2.1
170002	125	95	22	60	84	0.0
170003	99	51	98	99	99	0.6
170004	106	87	66	97	100	0.0
170006	122	75	39	56	67	3.7
170007	99	81	98	99	100	0.0
180002	100	85	98	100	100	0.0
180003	119	75	44	58	83	2.7
180004	103	82	90	93	97	0.0
180005	131	84	27	49	68	0.0
mean	108	48 †	68	84	93	1.3

† is the minimal BG level.

Table 6.7: Simulation results of the zone MPC system and the MPC system for the virtual patients K.

	Zone MPC	MPC	p-value
Mean BG (mg/dL)	108	106	–
Min BG (mg/dL)	48	49	–
80–110 mg/dL (%)	68	68	0.4883
80–125 mg/dL (%)	84	83	0.0093
80–144 mg/dL (%)	93	92	0.0007
< 80 mg/dL (%)	1.3	2.3	0.0013
< 80 mg/dL (patients)	12	16	–

compared with 71 mg/dL in the MPC system and one BG measurement below 80 mg/dL in the zone MPC system compared with four BG measurements in the MPC system also suggest the reduction of hypoglycemic events by utilization of zone MPC. Figure 6.7 represents that our system can regulate BG against the measurement noise of Gaussian distribution with zero mean and standard deviation of $\sigma = 7.5$ mg/dL. The simulation results demonstrate the safety and effectiveness of the system with online identification of insulin sensitivity using zone MPC.

In the previous chapter, we have already shown the effectiveness of the glycemic control system based on MPC with online identification of insulin sensitivity when applying to the virtual patients K compared with the other studies. In this chapter, we compare the results of the developed glycemic control system using zone MPC with those of the system using MPC. The simulation result in Figure 6.8 shows the rapid decrease of insulin infusion rate against the sudden decrease of BG in the developed system utilizing zone MPC. As listed in Table 6.7, although the mean BG level, the minimal BG level and percentage of duration time of BG within the range of 80–110 mg/dL of the new glycemic control system using zone MPC is comparable to the system using MPC, the percentages of duration time of BG within the range of 80–125 mg/dL and 80–144 mg/dL are significantly improved, the percentage of BG measurements under 80 mg/dL is significantly reduced from 2.3% to 1.3% and the number of patients whose BG becomes lower than 80 mg/dL is decreased. The results also suggest that the developed system utilizing zone MPC is effective for preventing hypoglycemia.

A similar evaluation has been made in the existing studies. The LOGIC-Insulin algorithm regulated BG within the range of 80–110 mg/dL of 69% [15] and 67% [16] in two trials. The eMPC system achieved 60% [20] and 46% [21] of BG measurements within the range of 80–110 mg/dL in two different trials respectively. The STAR achieved 83% of BG within the range of 80–125 mg/dL (4.4–7 mmol/L) in a virtual trial [17] and 83% of BG within the target range of 80–144 mg/dL (4.4–8 mmol/L) in a clinical trial [18]. The STOMP regulated 74% of BG within the range of 4.4–7 mmol/L and 86% of BG within the target range 4.4–8 mmol/L [19]. Moreover, 2.3% [15] and 1.5% [16] of BG below 70 mg/dL were observed by LOGIC-Insulin algorithm, 1.9% [20] of BG below 80 mg/dL was observed in eMPC system, 1.7% [17] and 1.4% [18] of BG below 80 mg/dL were observed by STAR system and 2.8% [19] hypoglycemia (BG $<$ 80 mg/dL) was achieved by STOMP. Furthermore, severe hypoglycemic episodes (BG $<$ 40 mg/dL) were 0.04% in [16], 3 patients in [17] and 0.06% in [19]. Our glycemic control system gives comparable results of the percentages of BG within the ranges to the existing systems, and comparable or slightly better results of the percentage of BG below 80 mg/dL with no

severe hypoglycemic events. However, it is difficult to compare with other studies due to different patients and conditions.

Although no severe hypoglycemic event is found in the present system, the minimal BG level in all the virtual patients K is 48 mg/dL, which is due to a sudden increase of insulin sensitivity at the time when the insulin infusion rate becomes large. To prevent hypoglycemia caused by such change in patient, we should avoid an excessive increase of insulin infusion rate or restrict the maximum insulin infusion rate especially when insulin sensitivity takes a lower value over a long time. Moreover, the overshoot of the initial BG response just after admission to ICU should also be prevented. Furthermore, we should confirm the performance of the BG control system by applying it to more patients.

6.4 Concluding Remarks

In this chapter, we develop a glycemic control system with online identification of insulin sensitivity utilizing zone MPC method to prevent hypoglycemic events. The difference of zone MPC and MPC is the setting of the target; the target is given as a range in zone MPC instead of a level. In the zone MPC system, the insulin infusion rate is determined from the error between the predicted BG and the near bound of the target zone only when BG is outside the zone excessive insulin infusion can be avoided. The utilization of zone MPC shows a reduction of hypoglycemic events successfully compared with the utilization of nonlinear MPC. Further improvement of the ability of hypoglycemia prevention is expected for safe BG control in critically ill patients because the developed system could not improve the minimal BG level due to a sudden change of insulin sensitivity in the patient. Furthermore, we should also confirm the performance of the BG control system by applying it to more patients.

Chapter 7

Conclusion

In this thesis, we studied a mathematical model of glucose-insulin metabolism in critically ill patients, and glycemic control method for critically ill patients to avoid stress-induced hyperglycemia and to maintain blood glucose levels within the desired range of 80–110 mg/dL (4.4–6.1 mmol/L). This chapter summarizes the results presented in this thesis.

In Chapter 2, we made a brief explanation of glucose-insulin metabolism and the mechanism of hyperglycemia in critically ill patients. In addition, we introduced the existing insulin infusion protocols and glycemic control methods for critically ill patients including tight glucose control, and pointed out the insufficient performance of the existing systems in maintaining blood glucose levels within the desired range and avoiding hypoglycemia.

In Chapter 3, as an early stage of developing a closed-loop glycemic control system, we developed a glycemic control system using nonlinear model predictive control method based on an existing glycometabolism model, the ICU minimal model [27], with no time-varying parameter. We also constructed a set of virtual patients based on clinical data given in the literature [42] with several typical time-varying insulin sensitivity to assess the effectiveness and safety of the control system. We made simulations of the glycemic control system when the patient-specific parameters of the model related to the insulin sensitivity were identified before control and treated as time-invariant parameters during the glycemic control and when the patient-specific parameters of the model were not identified. Although our system gives less than 1% of duration time of BG measurements below 80 mg/dL, it does not have a sufficient performance of maintaining BG within the desired range. The simulation results show that the system with insulin sensitivity known can provide a better glycemic control performance than the system with the patient-specific parameters unknown, which suggests that the feature of patients (especially insulin sensitivity) is the key to glycemic control.

From the results in Chapter 3, we discussed the model of glucose-insulin metabolism

in critically ill patients in Chapter 4. To easily deal with inter- and intra-individual differences of insulin sensitivity in critically ill patients, we modified the model used in Chapter 3 by introducing a parameter of insulin sensitivity. In addition, to more precisely represent glucose-insulin dynamics in ICU patients under parenteral and enteral glucose infusions, we introduced nonlinear effects of glucose utilization, a saturation of insulin effect, and a route of enteral glucose infusion into the model. The parameter values of the modified model were identified from clinical data of the ICU patients collected in the ICU of Kagawa University Hospital. Although we treated the parameters as a constant except the insulin sensitivity parameter, simulation results demonstrated that the model can represent BG in ICU patients well by only changing the insulin sensitivity parameter. The analysis of insulin sensitivity in critically ill patients suggests that there is no significant difference in insulin sensitivity between diseases and that insulin sensitivity value increases during 12–27 hours in most of the patients. To confirm the increase of insulin sensitivity in ICU patients we will collect and analyze more clinical data of ICU patients.

In Chapter 5, we developed an online identification algorithm of insulin sensitivity that updates insulin sensitivity parameter value in the model at the interval of 30 minutes based on the preceding 30 minutes data of BG measurements, glucose and insulin infusion rates. With the online identification algorithm of insulin sensitivity, a new glycemic control system using nonlinear model predictive control based on the modified model was developed. When applying the system to the virtual patients based on clinical data given in the literature [42] constructed in Chapter 3, simulation results showed the improvement in glycemic control compared with the system using the time-invariant model. However, the system did not have sufficient safety and needs to be improved. We also constructed another set of virtual patients created from clinical data of the patients in the ICU of Kagawa University Hospital to more appropriately evaluate the practical performance of the control system. By comparing with other studies, our glycemic control system gives comparable results of the percentages of duration time of BG within the range of 80–110 mg/dL (4.4–6.1 mmol/L), 80–125 mg/dL (4.4–7 mmol/L) and 80–144 mg/dL (4.4–8 mmol/L) and no severe hypoglycemic events observed. However, the ability to prevent hypoglycemia is insufficient and needs to be improved.

Based on the results in Chapter 5, to prevent hypoglycemic events we further improved the glycemic control system utilizing zone model predictive control, which is suitable for maintaining the controlled variable within a range, instead of the ordinary model predictive control method in Chapter 6. We set the target zone to 90–100 mg/dL to maintain BG within the range of 80–110 mg/dL against measurement errors and sudden change

of insulin sensitivity of patients and designed a zone model predictive glycemic control system. The glycemic control system using zone MPC was applied to the virtual patients constructed in Chapter 3 and the virtual patients created in Chapter 5. Simulation results showed that the control system using zone MPC made an improvement on the percentage of duration time of BG below 80 mg/dL and gave a comparable result on the percentage of duration time of BG within the desired range of 80–110 mg/dL to the system using nonlinear MPC developed in Chapter 5, which demonstrated successfulness of preventing hypoglycemia by utilizing zone model predictive control method. By combining the online identification algorithm of insulin sensitivity and zone model predictive control method, precise prediction of BG levels in ICU patients, and better and safer BG control can be obtained.

At the end of the thesis, we give future work. We constructed a closed-loop glycemic control system with the online identification algorithm of insulin sensitivity utilizing zone model predictive control under the situation that parenteral and enteral glucose infusion rates are known. Due to this condition, the system cannot lower the blood glucose level below 110 mg/dL by insulin infusion at the maximum rate in some cases. To improve the duration time of BG within the desired range we should consider two manipulated inputs of insulin and glucose, which may add the balance of BG level and nutrition to the objective of glycemic control. In the present study, we have demonstrated the safety of our glycemic control system using zone MPC for the virtual patients constructed from only 24 clinical data *in silico*. To confirm the performance of the system we must assess the system on more ICU patients. We expect that the results of this thesis can also be applied to other nutrition concentration control or drug treatment control, or a control system for maintaining a controlled variable within a desired range such as blood pressure control and so on.

Appendix A

Glycometabolism Models

A.1 The Hovorka Model

In the Hovorka model [42], there are five submodels of endogenous insulin secretion, insulin kinetics, enteral glucose absorption, insulin action and glucose kinetics, and a time-varying insulin sensitivity.

Endogenous insulin secretion submodel

$$U^u_{\mathrm{IE}}(t) = \frac{60}{1000} W \left(M_{\mathrm{I}}(G(t) - 5.5) + U_{\mathrm{IE,basal}} \left(F_{\mathrm{IE,basal}} + (1 - F_{\mathrm{IE,basal}} e^{-t \frac{\ln(2)}{t_{1/2,\mathrm{IE}}}}) \right) \right), \tag{A.1}$$

$$U_{\mathrm{IE}}(t) = \begin{cases} U^u_{\mathrm{IE}}(t), & \text{if } U^u_{\mathrm{IE}}(t) > 0 \\ 0, & \text{otherwise} \end{cases}, \tag{A.2}$$

where $U^u_{\mathrm{IE}}(t)$ is unconstrained endogenous insulin secretions while $U_{\mathrm{IE}}(t)$ is the actual endogenous insulin secretion. W denotes the body weight. M_{I} is the beta-cell responsiveness. $U_{\mathrm{IE,basal}}$ represents the basal insulin secretion level. $F_{\mathrm{IE,basal}}$ and $t_{1/2,\mathrm{IE}}$ represent a fraction and a half-time of the suppression of endogenous insulin secretion by exogenous insulin, respectively.

Insulin kinetics submodel

$$\frac{dI(t)}{dt} = \frac{1000}{60W} \frac{U_{\mathrm{IX}}(t) + U_{\mathrm{IE}}(t)}{V_{\mathrm{I}}} - k_e \frac{K_{\mathrm{M,I}}}{I(t) + K_{\mathrm{M,I}}} I(t), \tag{A.3}$$

where, $I(t)$ is the insulin concentration in plasma. $U_{\mathrm{IX}}(t)$ denotes the exogenous insulin infusion. V_{I} is the volume of insulin distribution. k_e is the rate of insulin clearance and $K_{\mathrm{M,I}}$ is the insulin concentration at which the fractional removal of insulin is halved.

Enteral glucose absorption submodel

$$\frac{dA_1(t)}{dt} = \frac{F_{\mathrm{GE}}U_{\mathrm{GE}}(t)}{60} - \frac{A_1(t)}{t_{\mathrm{max,G}}}, \tag{A.4}$$

$$\frac{dA_2(t)}{dt} = \frac{A_1(t)}{t_{\mathrm{max,G}}} - \frac{A_2(t)}{t_{\mathrm{max,G}}}, \tag{A.5}$$

where, $A_1(t)$ and $A_2(t)$ are the glucose content in stomach and small intestine, respectively. F_{GE} is bioavailability of the administrated enteral glucose $U_{\mathrm{GE}}(t)$. $t_{\mathrm{max,G}}$ is the maximum enteral glucose absorption time.

Insulin action submodel

$$\frac{dx_1(t)}{dt} = -k_{a1}(x_1(t) - I(t)), \tag{A.6}$$

$$\frac{dx_2(t)}{dt} = -k_{a2}(x_2(t) - I(t)), \tag{A.7}$$

$$\frac{dx_3(t)}{dt} = -k_{a3}(x_2(t) - I(t)), \tag{A.8}$$

where, x_1, x_2 and x_3 are the remote insulin that affect on glucose distribution and transport, glucose disposal and endogenous glucose production, respectively. k_{a1}, k_{a2} and k_{a3} are rate coefficients.

Glucose kinetics submodel

$$\frac{dQ_1(t)}{dt} = -F_{01}^c - k_{21}(t)Q_1(t) + k_{12}Q_2(t) - U_{\mathrm{R}}(t) + \frac{5.551}{W}\left(\frac{U_{\mathrm{GP}}(t)}{60} + \frac{A_2(t)}{t_{\mathrm{max,G}}}\right) + \mathrm{EGP}(t), \tag{A.9}$$

$$\frac{dQ_2(t)}{dt} = k_{21}(t)Q_1(t) - (k_{12} + S_{\mathrm{I,MOD}}(t)S_{\mathrm{ID}}x_2(t))Q_2(t), \tag{A.10}$$

$$G(t) = \frac{Q_1(t)}{V_{\mathrm{G}}}, \tag{A.11}$$

$$F_{01}^c = \frac{G(t)}{G(t) + K_{\mathrm{M,N}}}F_{01}, \tag{A.12}$$

$$U_{\mathrm{R}}(t) = \begin{cases} k_{\mathrm{R}}(G(t) - G_{\mathrm{R}})V_{\mathrm{G}}, & \text{if } G(t) \geq G_{\mathrm{R}} \\ 0, & \text{otherwise} \end{cases}, \tag{A.13}$$

$$\mathrm{EGP}(t) = \begin{cases} S_{\mathrm{I,MOD}}(t)\mathrm{EGP}_0(1 - S_{\mathrm{IE}}x_3(t)), & \text{if } (1 - S_{\mathrm{IE}}x_3(t)) > 0 \\ 0, & \text{otherwise} \end{cases}, \tag{A.14}$$

$$k_{21}(t) = S_{\mathrm{I,MOD}}(t)S_{\mathrm{IT}}\frac{x_1(t)}{K_{\mathrm{M,T}} + x_1(t)}, \tag{A.15}$$

where, Q_1 is accessible glucose that gives the blood glucose concentration G directly, while Q_2 is non-accessible glucose. F_{01}^c represents the non-insulin dependent glucose clearance. $k_{21}(t)$ is transfer rate from the accessible to the non-accessible glucose. k_12 denotes transfer rate from the non-accessible to the accessible glucose. U_{R} represents the renal glucose removal. $U_{\mathrm{GP}}(t)$ denotes the parenteral glucose infusion. $\mathrm{EGP}(t)$ represents the endogenous glucose production. S_{ID} is the insulin sensitivity of glucose clearance. V_{G} is the glucose distribution volume.

F_{01} represents the total non-insulin dependent glucose flux. $K_{\mathrm{M,N}}$ is the blood glucose concentration at which the fractional removal of non-insulin dependent glucose achieves half of its maximum value. k_{R} and G_{R} are the rate of renal glucose removal and a threshold value of glucose, respectively. EGP_0 and S_{IE} represent the endogenous glucose production when insulin concentration is zero and insulin sensitivity of endogenous glucose production, respectively. S_{IT} is a transfer rate (can be described as insulin sensitivity of distribution/transport), and $K_{\mathrm{M,T}}$ is the insulin concentration at which the fractional transfer rate is halved.

Time-variant insulin sensitivity

$$S_{\mathrm{I,MOD}}(t) = \frac{\mathrm{BIC_B}}{\mathrm{BIC}(t)}, \tag{A.16}$$

$$\mathrm{BIC}(t) = \begin{cases} \mathrm{BIC}_0 + \frac{\mathrm{BIC}_1 - \mathrm{BIC}_0}{60}(t - t_0), & \text{if } t_0 \le t < t_1 \\ \mathrm{BIC}_1 + \frac{\mathrm{BIC}_2 - \mathrm{BIC}_1}{60}(t - t_1), & \text{if } t_1 \le t < t_2 \\ \vdots & \vdots \\ \mathrm{BIC}_i + \frac{\mathrm{BIC}_{i+1} - \mathrm{BIC}_i}{60}(t - t_i), & \text{if } t_i \le t < t_{i+1} \\ \vdots & \vdots \\ \mathrm{BIC}_{N-1} + \frac{\mathrm{BIC}_N - \mathrm{BIC}_{N-1}}{60}(t - t_{N-1}), & \text{if } t_{N-1} \le t < t_N \end{cases}, \tag{A.17}$$

where, $S_{\mathrm{I,MOD}}$ is the time-varying insulin sensitivity computed by the centering basal plasma insulin concentration $\mathrm{BIC_B}$ and basal plasma insulin concentration $\mathrm{BIC}(t)$ which is defined in a piecewise-linear function with a 60 min step. BIC_i $(i = 0, \cdots N)$ represents the insulin concentration that can achieve blood glucose at normal level of 5.5 mmol/L without parenteral and enteral glucose infusion at time $t_i = 60i$ min.

A.2 The Glucosafe Model

This appendix lists main equations of the Glucosafe model [43], which contains four compartments of insulin kinetics compartment, insulin action on glucose uptake compartment, blood glucose concentration and glucose appearance compartment and endogenous glucose balance compartment and requires the informations of patients such as

- age [years]
- height [m]
- bodymass [kg]
- gender [female;male]
- diabetic status [not diabetic; type 1; type 2].

Insulin kinetics

$$\frac{dI(t)}{dt} = -(n_{\mathrm{K}} + n_{\mathrm{L}})I(t) - \frac{n_{\mathrm{I}}}{V_{\mathrm{P}}}(I(t) - Q(t)) + \frac{P(t) + U(t)}{V_{\mathrm{P}}}, \tag{A.18}$$

$$\frac{dQ(t)}{dt} = -n_{\mathrm{C}}Q(t) + \frac{n_{\mathrm{I}}}{V_{\mathrm{Q}}}(I(t) - Q(t)), \tag{A.19}$$

$$U(t) = \begin{cases} 0 \text{ mU/min}, & \text{if diabetic status} = \text{“type 1”} \\ 42 \text{ mU/min}, & \text{otherwise} \end{cases}, \tag{A.20}$$

where $I(t)$ and $Q(t)$ are plasma and peripheral insulin concentrations, respectively. $P(t)$ is exogenous insulin appearance rate (exogenous insulin infusion). $U(t)$ is post-hepatic endogenous insulin appearance rate. V_{P} and V_{Q} denote volumes of the plasma compartment and peripheral compartment, respectively. n_{L} and n_{K} represent insulin clearance rates of liver and kidneys, respectively. n_{I} is a diffusion constant for insulin between the plasma and peripheral compartments. n_{C} denotes insulin clearance rate of endocytosis.

Insulin action on glucose uptake

$$
\begin{aligned}
p(t) &= \frac{\gamma}{C} Q(t), && \text{(A.21)}\\
i^*(t) &= \frac{p(t) - p_0}{\sqrt[d]{(p(t) - p_0)^d + k^d}}, && \text{(A.22)}\\
i(t) &= \frac{i^*(t) - i^*(0)}{1 - i^*(0)}, && \text{(A.23)}\\
a(t) &= i(t) S_{\mathrm{I,GS}}, && \text{(A.24)}
\end{aligned}
$$

where $p(t)$ is steady-state insulin infusion rate per kg body mass. γ represents the peripheral and plasma steady-state insulin concentration ratio. C is a conversion factor between the steady-state plasma insulin concentration and the exogenous insulin infusion. $i^*(t)$ is insulin effect in response to $p(t)$. $i(t)$ normalizes $i^*(t)$ to be in the interval from zero to one. $a(t)$ represents a fraction of insulin effect with the insulin sensitivity $S_{\mathrm{I,GS}}$. p_0, d and k are parameters.

Blood glucose concentration and glucose appearance

$$
\begin{aligned}
\frac{dG(t)}{dt} &= \frac{(e(t) + z(t) + E(t))W}{V_{\mathrm{G}}}, && \text{(A.25)}\\
\frac{dN(t)}{dt} &= -e(t) + \mathrm{ECF}(t), && \text{(A.26)}\\
e(t) &= \begin{cases} 0.03245 \text{ mmol/kg/min} \times m_{\mathrm{gut}}, & \text{if } N(t) > 8.65 \text{ mmol/kg} \\ (-4.33 \times 10^{-4} \text{ kg/mmol/min } N(t)^2 & \\ +0.0075 \text{ min}^{-1} N(t)) \times m_{\mathrm{gut}}, & \text{otherwise} \end{cases} && \text{(A.27)}
\end{aligned}
$$

where $G(t)$ is blood glucose concentration. $N(t)$ is carbohydrate gut content. $e(t)$ represents glucose absorption rate from the enteral carbohydrate feed rate $\mathrm{ECF}(t)$. $z(t)$ is the parenteral glucose infusion rate. $E(t)$ represents endogenous glucose balance. W is the body mass. V_{G} is volume of glucose distribution. m_{gut} denotes a coefficient of impaired gut absorption.

Endogenous glucose balance

$$
\begin{aligned}
E(t) &= H(t) - R(t) - P_{\mathrm{GLUT4}}(t) - P_{\mathrm{GLUT1+3}}(t), && \text{(A.28)}\\
H(t) &= A_{\mathrm{H}} \min(G(t), G_{\mathrm{thresh}}) + B_{\mathrm{H}} a(t) + C_{\mathrm{H}}, && \text{(A.29)}\\
R(t) &= \frac{f(\max(0, F_{\mathrm{G}} G(t) - T_{\max}))}{W}, && \text{(A.30)}\\
P_{\mathrm{GLUT1+3}}(t) &= \frac{J_{1+3} G(t)}{G(t) + K_{\mathrm{M1+3}}}, && \text{(A.31)}\\
P_{\mathrm{GLUT4}}(t) &= \frac{J_4 G(t)}{G(t) + K_{\mathrm{M4}}} a(t), && \text{(A.32)}
\end{aligned}
$$

where $H(t)$ denotes hepatic glucose balance. $R(t)$ represent renal glucose excretion. $P_{\mathrm{GLUT1+3}}(t)$ is glucose uptake by GLUT 1 and GLUT 3. $P_{\mathrm{GLUT4}}(t)$ is GLUT 4 mediated glucose uptake. G_{thresh} is a threshold value of blood glucose concentration. A_{H}, B_{H} and C_{H} are coefficients. In equation (A.30), $f(\cdot)$ is a 7 mmol/L wide moving average function. F_{G} denotes a rate of glomerular filtration. $T_{\max}$ is the maximal rate of reabsorption. J_{1+3} and J_4 represent the maximal glucose uptake rates by the GLUT 1 and GLUT 3 and by the GLUT 4. respectively. $K_{\mathrm{M1+3}}$ and K_{M4} denote affinities of combined the GLUT 1 and GLUT 3 carrier and the GLUT 4 carrier.

The complete equations and parameters of the Glucosafe model can be find in [43] and [23].

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1. Sha Wu, Eiko Furutani: Blood glucose control of critically ill patients with time-varying insulin sensitivity using nonlinear model predictive control (in Japanese), *Systems, Control and Information*, vol. 29, pp. 258–265, 2016.

2. Sha Wu, Eiko Furutani, Tomonori Sugawara, Takehiro Asaga, Gotaro Shirakami: Glycemic control for critically ill patients with online identification of insulin sensitivity, *Advanced Biomedical Engineering*, vol. 9, pp. 43–52, 2020.

3. Sha Wu, Eiko Furutani, Tomonori Sugawara, Takehiro Asaga, Gotaro Shirakami: Glycemic control for critically ill patients using zone model predictive control, submitted to *IEEJ Transactions on Electrical and Electronic Engineering*.

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1. Sha Wu, Eiko Furutani: Nonlinear Model Predictive Glycemic Control of Critically Ill Patients Using Online Identification of Insulin Sensitivity, *38th Annual International Conference of the IEEE Engineering in Medicine and Biology Society*, Orlando, USA, 2016, pp. 2245–2248

2. Sha Wu, Eiko Furutani: Improvement of glycemic control in critically ill patients using online identification of insulin sensitivity, *1st IEEE Conference on Control Technology and Applications*, Hawaii, USA, 2017, pp. 548–553

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1. Sha Wu, Kenko Uchida: A New Glucose-Insulin Model Based on ICU Minimal Model and Normalization of Blood Glucose with Nonlinear Model Predictive Control (in Japanese), *1st Multi-symposium on Control Systems*, Tokyo, 2014

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