Modeling and Control of Blood Glucose in the Intensive Care Unit

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Abstract. *Patients in the intensive care unit suffer from hyperglycemia and high glycemic variability. Recent studies have shown that tight glucose control based on insulin therapy can stabilize blood glucose level. Thereby, patients with intensive insulin therapy showed lower mortality and shorter hospital stay than patients treated with conventional insulin therapy. These findings have driven the development of closed-loop systems for automatized insulin therapy in the intensive care unit. In this work, the major advances in modeling and control of blood glucose in the intensive care unit are presented. Models describing the underlying pathophysiology are compared regarding their quality and complexity. Furthermore, current protocols and advances in control strategy and design are presented.*

Keywords

Blood glucose control, intensive care unit, hyperglycemia, tight glucose therapy.

1. Introduction

High blood glucose (BG) level also described as hyperglycemia and high glycemic variability (GV) are common in patients within the intensive care unit (ICU). This type of hyperglycemia is also called stress-induced hyperglycemia. It is caused by numerous stress hormones the human body releases after trauma, infection, or inflammation. Also patients without a previous diagnosis of diabetes can suffer from glucose derailment in the ICU [1]. A central role in stress-induced hyperglycemia seems to be insulin sensitivity, which describes the effectiveness of insulin to regulate BG. However, the detailed pathophysiology is not yet well understood. Hyperglycemia is treated by an exogenous infusion of insulin. This so-called insulin therapy can lower BG significantly. The established conventional insulin therapy (CIT) suggests insulin infusion when BG exceeds $180\,\mathrm{mg/dL}$ [15].

In 2001, the study by Van den Berghe et al. revealed that tight glucose control (TGC) with a target level of 80 to $110\,\mathrm{mg/dL}$ can reduce mortality in the ICU. Furthermore, the study showed that the recovery of patients improved and the duration of stay was reduced significantly compared to patients who received CIT [2]. Despite the promising results, the findings are discussed controversially. In 2009, the NICE-Sugar study revealed that TGC might even increase mortality. Especially, the probability of severe and life threatening hypoglycemia increased, thus, favoring a BG target value of $180\,\mathrm{mg/dL}$ [3]. Further studies showed that apart from the target BG also the frequency of BG measurement is relevant for a successful insulin therapy (IT). Current CIT is limited by the low frequency of BG measurements (approximately every 4-6 h). Thereby, the quality of IT depends strongly on the [4]. Thus, very cautious glucose regulation with insulin is currently used to avoid hypoglycemia, based on experience and rough calculation rules. The use of continous glucose control (CGM) systems as already used in patients with diabetes mellitus (DM) shows great potential to improve IT in the ICU. Furthermore, the development of models describing the underlying pathophysiology is of great interest. Especially the development of closed-loop system for automatized BG control has get into focus.

This article gives a small outline of the history and recent developments in the field of modeling and control in the ICU. In section 2, the evolution of models describing the pathophysiology is presented. In section 3, the evolvement of current nutrition protocols and recent advances in the design of closed-loop systems is given. Section 4 provides a small discussion and an outline.

2. Models of Blood Glucose Metabolism

One of the first models describing the human BG metabolism were the models of Guyton et al. [5] and the so-called Minimal Model by Bergman et al. [6]. These models were developed describing the blood glucose metabolism during intravenous glucose tolerance test (IGTT) in DM patients. The complexity of these two models differs strongly. The Guyton model and the successive Sorensen Model describe the BG in great detail. The interaction of glucose, insulin and glucagon is modeled for different compartments (i.e. blood, liver, periphery) [5, 7]. In contrast, the Minimal Model describes the dynamics of glucose and insulin using only three compartments. However, mentioned models were

a milestone in the development of BG and built a foundation for many subsequent models.

Much effort has gone into developing models that describe the dynamics of BG in DM patients. Models such as the so-called UVA/PADOVA Type 1 Diabetes Simulator by Dalla Man et al. [8] were developed to describe the BG metabolism, especially studying the influence of external disturbances such as nutrition, insulin, changes in insulin sensitivity (IS) or the effect activity. The background to these efforts was the goal of developing a so-called artificial pancreas (AP) for an automatized IT in DM patients.

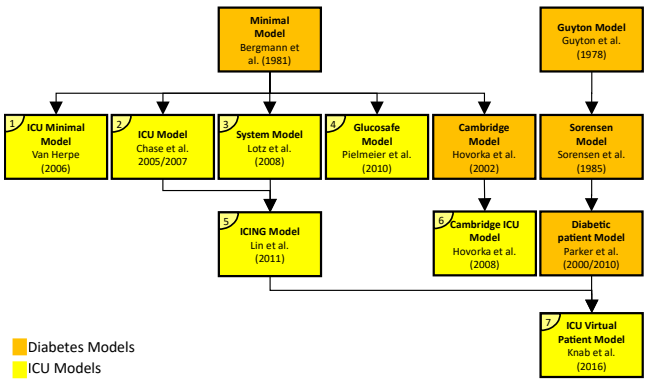

Fig. 1. Overview and historical development of models describing glucose metabolism in critically ill patients. Also DM models are shown that had a major impact on the development of models for the intensive care unit.

While much effort was spent on the development of models to describe the BG metabolism of DM patients, much fewer models exist to explain the pathophysiology of patients within in the ICU. The findings of Van den Berghe in 2001 [2] encouraged the development of BG models for the application in the ICU. Most recently developed models are based on the minimal Bergman model using compartments to describe the glucose and insulin interaction, thereby neglecting the influence of other dynamics (i.e. glucagon). An overview of the models and their historical development is given in figure 1.

Although the blood glucose dynamics in diabetic patients and ICU patients have many similarities, there are significant differences to consider. In the following, especially the ICU Minimal Model [9], the ICING Model [10], and the Cambridge Model [11] will be presented and compared.

The Minimal ICU Model was published in 2006 [9]. It is adapted from the original Minimal Model [6]. The Minimal ICU Model comprises a compartment for BG, a so-called remote compartment for the effect of insulin on BG, and a compartment describing the dynamics of insulin in the blood itself. In contrast to the original Minimal Model, a second insulin compartment describes the endogenous insulin section. The basal state of the model is given by the basal glucose and insulin concentration, which level during fasting. Thus, the influence hepatic glucose production (HPG) is only expressed by the basel BG level. The change of IS is not explicitly accounted for as system parameter underlying changes over time. The model accounts for externally supplied exogenous insulin and parenteral nutrition. The gastrointestinal tract is not considered.

The ICING Model [10] is based on the previously published ICU Model [12], the System Model [13], and Glucosafe Model [14], all of which date back to the Minimal Model [6]. The ICING Model has many similarities to the Minimal ICU Model and the original Minimal Model. It also comprises a compartment for BG, a remote compartment for the effect of insulin on BG and a compartment for the insulin. The HPG and the glucose consumption by the central nervous system (CNS) are described. In addition, the pancreatic insulin release (PIR) is modeled as a function of insulin concentration in blood. The balance between HPG, glucose consumption by the CNS and PIR determines the basal state of the model during fasting. The major difference from the Minimal ICU Model is the explicit use of IS as a time-dependent parameter. Furthermore, enteral nutrition is accounted for by a second order model of the gastrointestinal tract.

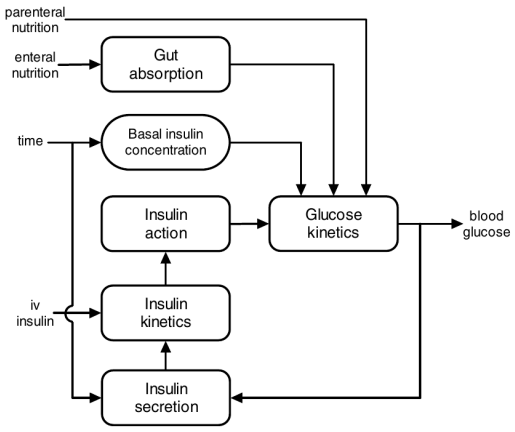

Fig. 2. Cambridge ICU Model (adapted from [11]).

Among the presented models, the Cambridge ICU Model has the highest complexity [11]. It is a further development of the Cambridge Model, which was originally developed for DM patients. The structure of the Cambridge ICU Model is shown in figure 2. The model comprises two compartments for the glucose kinetics. The effect of insulin on the glucose kinetics is modeled by three compartments rather than a single one as in the previously presented models. The insulin is again modeled as a single compartment. In contrast to the ICING Model, the HPG is not constant but can be suppressed by high insulin concentration in the remote compartments. Furthermore, the PIR is depending on the blood glucose concentration rather than the insulin concentration as in the ICING Model. Also, the renal glucose clearance above the glucose threshold is considered. Similar to the ICING Model, the gastrointestinal tract is described and a time-dependent IS is used.

The presented models vary in their complexity. A detailed comparison and the capability of the different models is given in table 1.

#	Order	Meal	IS	PIR	HGP	Valid
1	4	✗	✗	✓	✗	✗
2	3	✗	✓	✗	✗	✓
3	3	✗	✓	✗	✓	✓
4	3	✗	✓	✗	✓	✗
5	5	✓	✓	✗	✓	✓
6	8	✓	✓	✓	✓	✓
7	9	✓	✓	✓	✓	✓

Tab. 1. Comparison of models. Numbering according to figure 1. Order - order of differential equation system, Meal - submodel of gastrointestinal tract, IS - insulin sensitivity, PIR - pancreatic insulin release, HGP - hepatic glucose production, Valid - validated with clinical data.

3. Protocols and Control Algorithms

Essential for successful insulin therapy is an appropriate protocol, reducing the risk of hyper- and hypoglycemia. The following section gives an overview of current clinical protocols, assistant systems currently used in clinical practice and current research state of art.

The ESPEN guidelines [15] and the Yale insulin infusion protocol [16] are one of the gold standards for the treatment of hyperglycemia in the ICU. Currently, the ESPEN guideline recommends administration of insulin when BG exceeds $180\,\mathrm{mg/dL}$. In addition to these existing protocols to treat hyperglycemia in the ICU, clinical protocols were developed based on existing mathematical models. In 2006, the SPRINT (Specialized Relative Insulin Nutrition Tables) protocol was developed based on the ICING model [12]. This protocol provides tables for an improved nutrition and TGC [17]. The SPRINT protocol was successfully evaluated in clinical trials; treated patients were longer in the normoglycemic range compared to patients receiving CIT.

Although improved protocols can enhance the quality of IT, there is no significant reduction of workload for the clinical staff. One of the first assistance systems to support clinical staff was the Glucommander, developed in 1984 [18]. It provided recommendations of insulin infusion based on a simple algorithm. In clinical usage, it proved to be simple and robust [18]. In 2005, GRIP, a computer-driven protocol for the ICU was developed [19]. It has a graphical user interface and should support clinical stuff during IT. The GRIP algorithm gives a recommendation of insulin infusion rate based on the previous BG measurements and previous insulin infusion rate. Furthermore, GRIP provides the time when the next BG measurement should be done. In 2013, the GlucoCare System was developed as an insulin-dosing calculator [20]. The underlying algorithm is based on the Yale insulin infusion protocol [16]. The LOGIC-Insulin Software was developed especially for TGC to maintain BG at 80 to $110\,\mathrm{mg/dL}$, thereby assisting clinical staff and reducing workload [21]. In clinical studies, such systems were able to stabilize the blood glucose level and reduce the risk of hypoglycemia [18, 21, 22].

In the last years model-based closed-loop algorithms for an automatized IT were developed. However, most of the algorithms were only tested in an in-silico environment. The algorithms range from simple proportional–integral–derivative (PID) controller to model predictive control (MPC) algorithms. In 2007, Wintergeist et al. developed a PID controller for IT in the pediatric ICU. The algorithm was tested in a clinical trial and was able to safely and effectively control BG [23]. In 2012, the stochastic targeted (STAR) glycemic control forecast was developed [24, 25]. This protocol recommends insulin infusion and nutrition based on previous BG measurements. Thereby, a stochastic model based on the ICING model is used to give a prediction of patient's IS. This prediction is used to improve nutrition and insulin infusion to achieve BG of 80 to $120\,\mathrm{mg/dL}$. In 2015, the stochastic model predictive (STOMP) glycaemic control algorithm was published, which is a further development of the STAR protocol [26]. Similar to the STAR protocol, the STOMP algorithms uses a stochastic model of the future IS. An MPC algorithm is then used to calculate the optimal nutrition and insulin infusion. A similar MPC algorithm was developed based on the ICING model by Knab et al. [28]. In 2019, Reenberg et al. developed a similar MPC algorithm based on the Cambridge ICU Model [27]. This control algorithm showed good results in in-silico trials.

4. Discussion

Models of blood glucose metabolism have improved over the years and provided essential knowledge enhancing insulin therapy. Although the models have similar structures modeling glucose and insulin interaction, they differ in their complexity. While a highly complex model enhances a detailed understanding of the pathophysiology, it has the disadvantage, that a variety of model parameters need to be identified. Considering the application in the ICU, models comprising the gastrointestinal tract are advantageous. Also the use of IS as a time-variant parameter seems to be essential to describe the pathophysiology of hyperglycemia. However, none of the models considers the influence of glucagon on the BG metabolism.

Nutrition protocols and computerized assistance systems provide important information on nutrition and insulin dosing during IT, reducing workload and increasing success of IT. Especially the frequency of BG seems to have a significant impact on the quality of TGC. In-silico studies show promising results of closed-loop systems for fully automatized insulin therapy. However, currently, there is no closed-loop system approved for patients for a fully automatized glucose therapy without intervention.

Abbreviations

AP	artificial pancreas
BG	blood glucose
CGM	continous glucose control
CIT	conventional insulin therapy
CNS	central nervous system
DM	diabetes mellitus
GV	glycemic variability
HPG	hepatic glucose production
ICU	intensive care unit
IGTT	intravenous glucose tolerance test
IS	insulin sensitivity
IT	insulin therapy
MPC	model predictive control
PIR	pancreatic insulin release
TGC	tight glucose control

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