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Development and Optimization of Glucose-Insulin System Models and Methods for Intensive Care Patients under Model-based Glycemic Control

Ph.D. Dissertation

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I, Yahia Anane, hereby declare that this dissertation, and all results claimed therein are my own work, and rely solely on the references given. All segments taken word-by-word, or in the same meaning from others have been clearly marked as citations and included in the references.

Nyilatkozat önálló munkáról, hivatkozások átvételéről

Alulírott Yahia Anane kijelentem, hogy ezt a doktori értekezést magam készítettem és abban csak a megadott forrásokat használtam fel. Minden olyan részt, amelyet szó szerint, vagy azonos tartalomban, de átfogalmazva más forrásból átvettem, egyértelműen, a forrás megadásával megjelöltem.

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Summary

Hyperglycemia (increased blood glucose level) is a common complication in intensive care units (ICU), and it has been associated with higher patient mortality and morbidity. Tight control of blood glucose (BG) concentrations to more normal levels can considerably lessen the deleterious outcomes of hyperglycemia. Hypoglycemia and glycemic variability, on the other hand, have both been linked to an increased risk of death in critically ill patients.

Glycemic control (GC) protocols directly capturing and controlling for patient-specific intra and inter-patient variability can reduce negative outcomes related to poor control, as well as provide relatively high nutrition delivery and economic cost savings. However, they have been offset by a range of clinical trials using ad-hoc clinical protocols, which could not repeat early successful results.

This research aims to enable enhanced model-based glycemic control through better modeling and implementation of new parameter estimation methods and by analyzing and addressing several key model parameters in different treatment phases.

The Stochastic TARgeted glucose control (STAR) protocol used in this research is an example of a model-based approach built on the same models used to develop and implement the SPRINT protocol, the only protocol to reduce organ failure, mortality, and hypoglycemia. Built on the Intensive Control Insulin-Nutrition-Glucose (ICING) model of fundamental Glucose-Insulin system dynamics, it directly captures inter- and intra- patient variability and drives clinically validated virtual patients. It is driven by a model-based patient-specific insulin sensitivity (SI), uniquely identified from clinical data, whose utility has also been clinically validated.

One of the key elements and potential limitations of model-based glycemic control in general, and the ICING model in particular, is its assumed value for Endogenous glucose production (EGP). The assumed EGP value directly impacts the identified value of SI by directly contributing to the net glucose flux balanced by insulin-mediated glucose uptake. However, EGP cannot be measured directly in clinical care and relies on tracer studies with significant errors in research.

Understanding the relationship between hyperglycemia, insulin resistance, and high endogenous glucose production has a huge impact on model-based control and treatment in intensive care units. The study conducted in this thesis confirmed the wide variability of EGP across ICU patient cohorts. Estimating a low EGP value can cause bias in the identified SI value, which can limit the accuracy of the ICING model and potentially reduce the quality of GC treatment recommendations. In these cases, numbering 1-10% of possible treatment hours in the three cohorts, the model could not follow the blood glucose dynamics. Estimating and adjusting EGP to a higher value using the novel method developed and presented in this thesis shifted the identified SI to a physiologically realistic range and significantly improved blood glucose fit to measured data lowering modeling error by up to 90%. The next step was to think about how to implement the new EGP estimation method on the STAR

clinical application.

Based on data, 80+% of these constrained SI episodes happen within the first 96H and 90+% of them last for 3h. For this, we concluded that the most practical scenario to handle these situations is to keep the increased EGP until 4 days of treatment have passed. After that, if it happens again, we may set back EGP to the initial value after 3h each time we increase it. The clinical implementation of the EGP estimation method presented can effectively capture and handle patients' EGP variability.

On top of the suggested EGP estimation method, this analysis further initiates the idea of implementing a customized model-based control designed explicitly for the early phase of patient treatment, exactly the first 24h, where patients have a highly variable health state, low insulin sensitivity, and high blood glucose levels, as expected, given the stress response physiology. Results aligned with the clinical expectations, insulin sensitivity was smaller in the early ICU stages, and SI variability and measured blood glucose levels were the highest across the 3 cohorts.

This customized model is intended to effectively handle patients' variability, hyperglycemia, and insulin resistance by implementing various adjustments such as a higher glycemic target band, performing more frequent BG measurements, and more modulated insulin/nutrition intakes. These beneficial impacts may arise for STAR or any other model-based protocol from improved predictions and, thus, more accurate GC during treatment for early-stage treatments.

Most of the published models of human glucose-insulin systems, like the ICING model, are deterministic ones, i.e., ordinary differential equations models which are used to describe the physiological processes. These kinds of models are known as imperfect in the sense that modeling the uncertainty, system noise, and the stochastic nature of the physiological system are not taken into consideration.

Palancz et al. suggested the stochastic Ito version of the ICING model (ICING SDE) equations with parametric stochastic noise term. The computation of the system trajectories and their statistical futures were carried out using Runge-Kutta method with Wiener-type diffusion process term. Parameter estimation is achieved via the maximum likelihood technique. This type of stochastic model allows not only the characterization of the noise integrated into the stochastic term but also enables the reduction of the modeling error.

In my dissertation, a comparison is presented between the original ICING and its stochastic extension. The results show that ICING SDE was slightly more accurate in terms of modeling error, however, considering the significant computational overhead of the stochastic model simulation and the difference between the accuracy of the two models, led us to the conclusion that the increase in accuracy due to the application of the stochastic ICING model the increase in efficiency is not expected to be proportional to the inconvenience caused by the increased running time. Based on these - considering the currently used tablet computing platform - it is not advisable to use the stochastic ICING model in clinical practice.

Összefoglaló

A hiperglikémia, vagyis a hosszabb ideig fennálló kórosan magas vércukorszint gyakori szövődmény az intenzív osztályokon, amely összefüggésbe hozható a betegek magasabb mortalitásával és morbiditásával. Klinikai adatok alapján a vércukorszint egészséges emberekre jellemző, ún. normoglikémiás tartományban tartása jelentősen csökkentheti a hiperglikémia káros következményeit. A betegek normoglikémiás tartományban tartását célzó vércukor szabályozási protokollok nem csak csökkenthetik a hiperglikémia negatív következményeit, de hozzájárulhatnak a megfelelő szintű energiabevitel biztosításához is a kezelés során.

Az első, pozitív kimenetelű, a hiperglikémia negatív következményeinek elhárítását célzó protokollok hatását vizsgáló klinikai kísérletek eredményeit sajnos a későbbi klinikai vizsgálatok nem tudták megismételni. Emiatt az intenzív osztályon végzett inzulin terápiát támogató kezelési protokollok aktívan kutatott terület volt az elmúlt évtizedekben és az a mai napig. Az áttörést az ún. modell-alapú szoros vércukor szabályozási protokollok kidolgozása jelentette, amely protokollok élettani modellek felhasználásával képesek figyelembe venni a betegek változékonyságát, mind egy adott beteg ápolása során, mind különböző betegek esetén.

A disszertációban ismertetett kutatás célja, hogy lehetővé tegye a modell-alapú szoros vércukor szabályozás hatékonyabb megvalósítását az intenzív osztályon történő kezelés különböző fázisaiban új paraméterbecslési módszerek segítségével, valamint a protokoll megvalósítása során alkalmazott modellek pontosságának növelésével.

A jelen kutatásban használt Stochastic TARgeted (STAR) vércukor szabályozási protokoll jelenleg az orvosi ellátásban az egyik legszélesebb körben alkalmazott modell-alapú szoros vércukor szabályozási módszer, az egyetlen, amely a hiperglikémia jelentős csökkentése mellett bizonyítottan csökkentette a szervi elégtelenségek számát és a mortalitást.

A STAR protokoll a betegek vércukorháztartásának dinamikáját az Intensive Control Insulin-Nutrition-Glucose (ICING) modelljének segítségével írja le. A modell helyességét több tanulmányban igazolták. A STAR használata során az ICING modell úgy alkalmazták, hogy a betegek állapotát egyetlen betegparaméterrel, a beteg inzulin érzékenységgel - insulin sensitivity (SI) - lehessen jellemezni.

Az ICING modell STAR protokoll megvalósítása során történő alkalmazásának egyik kulcseleme és egyben egyik lehetséges korlátja a szervezet belső glükóz termelésének mértékét jellemző, ún. endogén glükóz kibocsátás (EGP) paraméter állandó voltának feltételezése, ill. egy adott fix paraméter értékének használata. A feltételezett és adott esetben a valóságostól eltérő EGP érték közvetlenül befolyásolja az ICING modell alapján identifikálható, a beteg állapotát jellemző SI értéket, mivel a szervezet belső glükóz termelése közvetlenül hozzájárul az inzulin által moderált szervezetre jellemző glükózfelvétel segítségével kiegyensúlyozott nettó vércukorszint kialakításához. Sajnos a szervezet belső glükóz termelésének mértéke nem mérhető közvetlenül, az intenzív osztályon történő kezelés során a mérésére szolgáló radioaktív nyomkövetőre alapuló módszerek invazivitása, valamint lehetséges mellékhatásai

miatt. Emiatt van szükség olyan módszerekre, melyek segítenek az endogén glükóz kibocsátás aktuális mértékének meghatározásában.

A hiperglikémia, és az ezzel párhuzamosan gyakran jelentkező kórosan alacsony inzulin érzékenység, másnéven inzulinrezisztencia, valamint a magas endogén glükóz termelés közötti kapcsolat megértése óriási hatással lehet az intenzív osztályokon végzett modellalapú vércukor szabályozásra. Jelen disszertációban ismertetett kutatások megerősítették az EGP széles tartományok közötti változékonyságát az intenzív osztályon történt kezelések során.

Mint említettük, a tévesen megválasztott, túlzottan alacsony EGP érték torzíthatja az ICING modell alapján számított SI értéket. Ez korlátozhatja az ICING modell pontosságát, és potenciálisan ronthatja a vércukor szabályozás során adott kezelési ajánlás megbízhatóságát. A disszertációban bemutatott tanulmány megmutatta, hogy a megvizsgált három betegcsoportban a betegek kezelési óráinak 1-10%-ában a modell nem tudta pontosan követni a vércukor változás dinamikáját, feltételezhetően amiatt, hogy az SI értéket az EGP valóságostól eltérő értéke miatt nem lehetett megfelelő pontossággal meghatározni. Ezt a feltételezést az támasztja alá, hogy amennyiben fent említett kezelési időszakokban a dolgozatban bemutatott új módszerrel az EGP paramétert magasabb értékre állítjuk, akkor az újból identifikált SI élettani szempontból reális tartományba kerül. A módszer alkalmazásával jelentősen redukálható az ICING modell alapján végzett szimuláció segítségével számolt vércukorszint adatok közötti különbség, lényegesen csökkentve a modellezés hibáját.

A kutatás következő lépése az új EGP becslési módszer gyakorlati megvalósításának megtervezése volt a STAR protokoll megvalósítását támogató klinikai alkalmazásban. Az adatok kiértékelése alapján a kórosan alacsony SI értéket eredményező kezelési epizódok több, mint 90%-a az első 96 órán belül következett be, és ezek több, mint 90%-a 3 óráig tartott. Ez alapján a gyakorlati szempontból hatékony és legkönnyebben megvalósítható kezelési forgatókönyv, ha a megemelt EGP paraméter a kezelés első három napján alkalmazzuk, majd visszatérünk az eddig alkalmazott EGP paraméter alkalmazásához. Amennyiben a harmadik nap után kórosan alacsony SI értéket kapunk az SI identifikáció eredményeként, akkor újból megemeljük az EGP értékét és megismételjük az SI meghatározását, azonban a megemelt EGP értéket 3 óra múlva visszaállíthatjuk az eredeti EGP értékre. A javasolt EGP becslési módszer vércukor szabályozás során történő klinikai alkalmazása hatékonyan képes kezelni a betegek EGP paraméterének változékonyságát.

A javasolt EGP becslési módszer mellett a disszertációban ismertetett eredmények tovább finomíthatják a személyre szabott modell alapú vércukor szabályozás bevezetésére vonatkozó elképzeléseket, különösen a betegek kezelésének korai szakaszára, egész pontosan az első 24 órára vonatkozóan. A kezelés ezen szakaszában a betegek egészségi állapota változó, inzulinérzékenységük általában alacsony szinten van, vércukorszintjük pedig ennek megfelelően magas a szervezetet ért trauma által kiváltott stresszreakció eredményeként. A betegek állapota és kezelési története alapján megválasztott modell paraméterek alkalmazása tovább erősítheti a betegek személyre szabott kezelését kompenzálva a betegek változékonyságát, és kezelve a hiperglikémia és inzulinrezisztencia kártékony következményeit. Ezek a jóté-

kony hatások a STAR mellett bármely más modellalapú protokoll esetében jelentkezhetnek amennyiben az adott protokoll esetén lehetséges a betegek kezelésének első szakaszában figyelembe venni a feltételezhetően magasabb endogén glükóz termelést.

A legtöbb irodalomban közölt modellje az emberi vércukor szabályozásnak, hasonlóan az fent említett ICING modellhez, determinisztikus modell, azaz közönséges differenciálegyenlet rendszer alkalmaz, a fiziológiai folyamatok leírására. Az ilyen típusú modellek abban az értelemben nem tökéletesek, hogy a változók mérésének bizonytalansága, a modellezés során meghatározott paraméterek hibája, valamint a fiziológiai rendszer sztochasztikus jellege nem vehető figyelembe, ill. nem írható le velük.

Palancz és munkatársai az ICING modell sztochasztikus kiterjesztését javasolták, mely esetén a modell egyenletek egy időfüggő paraméterezhető sztochasztikus zajtaggal egészülnek ki. A modell szimulációja Runge-Kutta módszerrel alapján a Wiener-típusú diffúziós folyamattal leírt tag figyelembevételével történik. A javasolt sztochasztikus modell esetén a paraméterbecslés, mivel az SI mellett a sztochasztikus taghoz tartozó, annak hozzájárulását befolyásoló időfüggő paramétert is becsülni kell, maximum likelihood módszerrel történik. A sztochasztikus modell nemcsak a sztochasztikus tag által reprezentált zaj jellemzését teszi lehetővé, hanem segítségével a modellezési hiba is csökkenthető.

Disszertációmban bemutatom az eredeti ICING modell és annak sztochasztikus kiterjesztésének összehasonlítását. Az eredmények azt mutatják, hogy az ICING SDE valamivel pontosabb volt a modellezési hiba tekintetében, azonban a sztochasztikus modell szimulációjának jelentős számítási többletigényét figyelembe véve, valamint a két modell pontossága közötti különbséget, arra a következtetésre jutottam, hogy a sztochasztikus ICING modell alkalmazása miatti pontosságnövekedés miatti hatékonyság növekedés várhatóan nem lesz arányban a megnövekedett futási idő okozta kényelmetlenséggel. Ezek alapján – a jelenleg alkalmazott táblagép számítási platformot figyelembe véve – nem célszerű a sztochasztikus ICING modell alkalmazása a klinikai gyakorlatban.

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Introduction

Stress-induced hyperglycemia is common in critical care, and it can happen to people who have never had diabetes [Kri04a; Van+01a]. In the critically ill, hyperglycemia was once thought to be a beneficial adaptive response [VMV09]. However, [Van+01b] and [Kri04b] have shown that actively regulating blood glucose (BG) concentrations to more normal levels with insulin dramatically reduced mortality in critical care patients. These publications heralded the start of a new era in ICU hyperglycemia research and prevention.

Hyperglycemia has been linked to an increase in not just mortality but also other unfavorable clinical outcomes [Bla+08; Kri03; Kri04a; Van+01b]. Severe infection [Bis01], sepsis and septic shock [Bra+05; Das03; MR04b; Van+01b], myocardial infarction [Cap+00], polyneuropathy and multiple-organ failure [Lan+05; Van+01b]. Lower blood glucose levels were linked to lower mortality and/or complications in each of these cases or patient subgroups.

With aggressive blood glucose control with intensive insulin therapy, there was also evidence of considerable reductions in the requirement for dialysis, bacteraemia tests, and the number of blood transfusions [Kri04a; Van+01b; Van+03]. All of these findings led to the conclusion that maintaining normal blood glucose levels in critical care had a major therapeutic impact. They also provide a compelling case for the association between high blood sugar and glycemic variability and bad outcomes. Lower glycaemic levels, on the other hand, produce superior results regardless of how they are acquired.

Low insulin sensitivity, known as insulin resistance, and stress-induced surges in endogenous glucose production (EGP) manifest as stress-induced hyperglycemia in critically ill patients. It occurs primarily early in ICU stay, and is linked to increased morbidity and mortality [Kri03; MMB01; Cha+18a; Cha+18b; Plu+16; And+04; Fal+09; Jer+05; Ola+18; Sig+12; Ump+02; Wu+13]. Glycemic control has proven difficult [Cha+18b; Cha+11b; CD17; Gri+09] due to the risk of hypoglycemia [Dos+08; Dun+10; EB09; Fin+12; Kal+15] and high levels of intra- and inter- patient variability. Thus, safe, effective control has proven elusive, with clinical protocols often lacking patient-specificity and failing to consider inter/intra-patient variability [Le +10; Lin+08; Uyt+18]. There is thus a need for model-based patient-specific

glycemic control solutions [Cha+18a; Cha+18b; Cha+11b; Cha+11a; CDP16; Pre+16].

Glycemic control (GC) protocols directly capturing and controlling for patient-specific inter and intra-patient variability can reduce negative outcomes related to poor control [Cha+08a; Eva+11; Fis+12; Ste+16; Ste+18b], as well as provide leading nutrition delivery [Ste+18a] and economic cost savings [KJ06; Van+06b]. However, they have been offset by a range of clinical trials using ad-hoc clinical protocols [Gri+09; Bru+08; Fin+09; Kal+14; Pre+09], which could not repeat early successful results [Cha+08a; Kri04a; Van+01a; Van+06a]. These tradeoffs and issues are reviewed in [CBD19] from a control systems perspective.

1.1 Problems and challenges

The management of glycemic control in intensive care units (ICUs) is an important factor in the treatment of critically ill patients. Efficient control of blood glucose levels can help prevent complications such as sepsis, stress hyperglycemia, and increased morbidity and mortality. However, the physiological changes that occur in critically ill patients, as well as the frequent interventions required in the ICU setting, can make it challenging to maintain optimal glycemic control.

To address these challenges, there is a need for a model for glycemic control in the ICU that can be used in real-time clinical settings and effectively addresses the specific needs and limitations of most ICUs. While complex physiological models may be accurate when tested with rigorous laboratory data, they may not be practical for real-time glycemic control using less frequent and noisier blood glucose measurements, which are often the norm in the ICU setting.

Therefore, an effective model for glycemic control in the ICU must meet the following requirements:

1. It must accurately reflect the insulin and glucose metabolic system of critically ill patients;
2. It must account for and track inter and intra-patient variability over time;
3. It must have patient-specific model parameters that can be identified quickly.

This will allow the model to be used to guide the administration of insulin and other glucose-lowering therapies in real-time, enabling clinicians to optimize glycemic control and improve patient outcomes.

1.2 Research goals

The main research goals of this study are as follows:

- To improve the accuracy of the insulin-glucose system modeling by identifying and addressing any limitations or weaknesses in the STAR protocol and ICING model.
- To develop more accurate methods for estimating ICING model parameters, EGP and SI in particular, taking into account the inherent variability and complexity of the insulin-glucose system.
- To analyze and investigate the inter and intra-patient/cohort differences (Hungarian, Malaysian and New Zealand cohorts) in terms of glycemic control outcomes such as insulin sensitivity and blood glucose levels and try to identify the physiological contributors to patients' critical conditions such as insulin resistance and hyperglycemia.

Overall, the aim of this research is to gain a deeper understanding of the insulin-glucose system and to develop more accurate and reliable modeling approaches that can be used to improve the management and treatment of critically ill patients in the ICU.

1.3 Research overview

This thesis presents the analysis and investigation of several methods to improve the model-based glycemic controlling, insulin-glucose system modeling and parameter estimation focusing on insulin sensitivity and endogenous glucose production.

Chapter 1 contains background and methods used in this study: Model-based control, STAR protocol, INCING model, insulin sensitivity, EGP and clinical data. **Chapter 2** presents a new endogenous glucose production parameter estimation method for ICU patients with high insulin resistance that can represent the physiological EGP value of critically ill patients and suppress modeling limitations. **Chapter 3** offers suggestions of clinical applications scenarios that can be applied for the new EGP estimation method by analysis of time occurrence and duration of insulin resistance episodes. **Chapter 4** provides analysis of insulin sensitivity and its variability, blood glucose level and modeling accuracy in the first 24h compared to the rest of the treatment time and the change in these physiological aspects in the first 5 days of treatment. **Chapter 5** contains an assessment analysis of a new stochastic differential equation version of the ICING model and an analysis of the difference between the accuracy of the original deterministic version and the new stochastic approach

Background and methods

2.1 Model-based glycemic control in critical care

Clinical interventions controlling blood glucose levels of hyper-or-hypo-glycemic typically focus on modulating two common exogenous inputs of the human metabolic system: glucose and insulin. The hardware executing glucose control by modifying insulin and dietary inputs has been successfully developed and is now included in standard critical care equipment. Blood glucose sensors come in a variety of configurations, including discrete and continuous point-of-care devices as well as laboratory-grade measurement systems. [Cha+06] As a result, the success of a glucose control system is contingent on effectively converting available clinical data into appropriate recommendations for glucose and insulin infusions.

The combined limitations of maintaining blood glucose concentrations within a relatively tight band for each individual patient while preventing excess variability define the glycaemic control dilemma. Insulin and glucose inputs are the 'actuators' available in exercising control. The only variable state that can be observed in clinical real-time is blood glucose levels. Due to these circumstances, only model-based techniques are now capable of providing the robust, adaptable, and patient-specific solutions required to manage highly dynamic ICU patient metabolism. Model-based glycemic control methods have shown promising ability to provide safe glycemic control with little or no hypoglycemia in the ICU [Cha+08b; Cha+09; Cha+07; Eva+11].

Model-based control relies on a physiological model that captures the glucose-insulin system dynamics and can accurately predict blood glucose levels, taking the insulin and glucose as inputs. The controller algorithm uses these blood glucose predictions to select the optimal treatment which consists of insulin and carbohydrate-nutrition interventions for forthcoming periods.

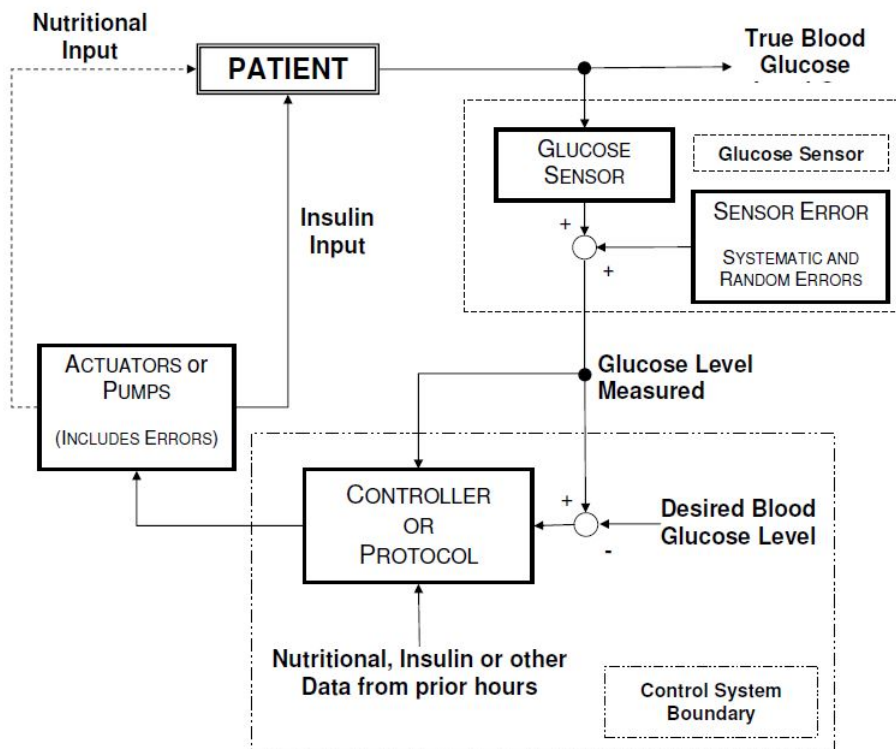


Figure 2.1: Basic model-based glycemic control system schematic showing the primary blocks encompassing sensing, actuation and control implementation. The control system boundary is shown by dash-dot lines, and the nutritional input line is dashed to indicate that this quantity may be controlled as part of glycemic control or set based on other clinical requirements. Sensor errors are shown as a separate block due to their potential size and impact on control. There may be some error in the actuators or pumps depending on their design specifications such as dosing limits and precision. This schematic diagram shows all possible set up of glycemic control systems. Arrows are suggestive and may not all exist in one setting [Lin07b].

2.2 STAR protocol

STAR (Stochastic TARgeted) [Eva+12] is a flexible, model-based glycemic control (GC) solution that directly accounts for inter and intra-patient variability with a stochastically estimated maximum 5% risk of BG below 4.4 mmol/L. In real time, it gives patient-specific therapy. Stochastic forecasting provides a framework for controlling future outcomes, including mild, moderate, and severe hypoglycemia mitigation. STAR was likewise created with the goal of using the most basic and transparent control logic possible. This feature aimed to make its choices as clear as possible, so that they could be directly translated into safe, effective, and clinically acceptable therapy recommendations [Ste+16]. STAR is the only protocol to reduce organ failure, mortality and hypoglycemia [Cha+10a].

The model is used to evaluate present patient insulin sensitivity and its probable variation over the next 1 to 3 hours after a BG measurement is taken. Insulin is given in bolus doses to avoid unintentional delays. Infusions, on the other hand, may be used. Increases in insulin rate to +2U/hour are limited by robustness to glucometer measurement error, with upper limitations on the total bolus dose (6U/h) and any additional infusion rate for extremely resistant patients (3U/h). As a result, total insulin is limited to 9 units per hour. If necessary, insulin can be lowered to 0U/h from any rate. Enteral nutrition is maintained at 30–100% of the American College of Chest Physicians (ACCP) target, with variations limited to 30% per intervention cycle. Nutrition administration can be adjusted to a fixed constant rate or zero if clinically indicated.

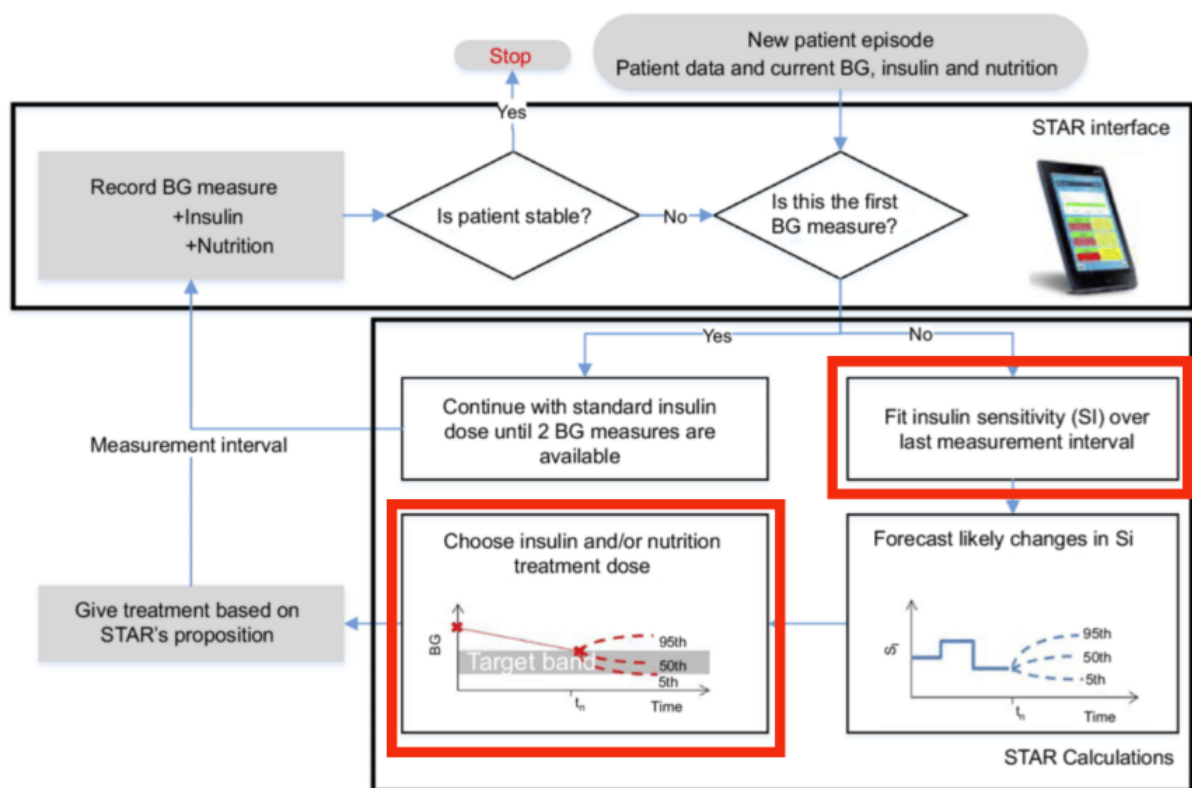


Figure 2.2: Illustration of the STAR protocol. Grey blocks refer to actions taken by nurses. Red boxes refer to the area of focus for our research and thesis

Based on the limits indicated, stochastic forecasts for the projected 5th percentile / 95th percentile of BG outcomes are created for each permissible insulin/nutrition combination and treatment interval (Figure 2.2, bottom right). The 5th percentile of BG outcomes is targeted to the lower limit of the desired range (4.44 - 4.72 mmol/L) for all treatment intervals to keep BG levels under control. Hypoglycemia is thus controlled directly, as insulin rates cannot be suggested if the expected 5th percentile is less than this threshold. The lower limit tolerance ensures that interventions are constant between measurement periods (1, 2 and 3-hourly). Because of the skewed form of the BG result distribution, which ensures that BG

outcomes best overlap the lower (4.44 – 7.0 mmol/L) section of the targeted BG range (4.44 – 8.0 mmol/L), the 5th percentile target is prioritized for control. This range of 4.44 – 8.0 mmol/L is linked to improved clinical treatment results.

The treatment of the 95th percentile of patient outcomes determines the tightness of the automated glycemic control provided by STAR. Only if a desired 2- or 3-hourly treatment will allow BG to climb over the target range is this upper limit used to limit treatment intervals. As illustrated in Figure 2.2, monitoring the likelihood of a predicted BG outcome allows for more explicit direct control over intra-patient variability, limiting the danger and occurrence of mild hyperglycemia. Regardless of the 95th percentile forecast, hourly measurements are always available.

STAR optimizes performance (time in target BG band) while minimizing the risk of moderate hypoglycemia (5% for BG below 4.44 mmol/L and 1% for BG below 4.0 mmol/L). The control sets the permissible insulin/nutrition combinations within this target. Maximizing nutrition rate is prioritized, especially for patients with extended stays, but not at the expense of aggravating hyperglycemia. As a result, STAR ranks permissible treatments according to their nutrition rate, guaranteeing that the treatment with the highest enteral nutrition rate is chosen [Ste+16].

STAR is built on the Intensive Control Insulin-Nutrition-Glucose (ICING) model of fundamental Glucose-Insulin system dynamics [Lin+11b], it directly captures inter and intra-patient variability [Lin+11b], and drives clinically validated virtual patients [Cha+18b; Dic+18; Cha+10b]. It is driven by a model-based patient-specific insulin sensitivity (SI), uniquely identified from clinical data [Doc+11; DCD12], whose utility has also been clinically validated [McA+11; Lot+08].

In Figure 2.2, the red boxes highlights the central area of focus for this extensive research endeavor. The research aims to undertake two pivotal phases: the identification and fitting of insulin sensitivity, and the subsequent simulation of blood glucose levels, which both rely on the ICING model. Enhancing the outcomes of these two crucial stages holds the key to advancing the STAR treatment selection, thereby leading to improved clinical outcomes and enhanced safety measures.

2.3 ICING model

Model-based glycemic control as shown in Figure 2.1 is based on a physiological model that captures the dynamics of the glucose-insulin system and allows for precise blood glucose prediction. The published literature has a rich history of metabolic modeling of the glucose-insulin system. The vast majority of these models are based on differential equations and compartment modeling. Razak [2011], Le Compte [2009] and Lin et al. [2011] [Lin+11a; Lin+11b]. has thoroughly examined these models.

The ICING model described by Lin et al [Lin+11b] is used throughout this thesis. This

model was created to be more physiologically comprehensive than its predecessors, primarily through the inclusion of more precise insulin kinetics. Equations (2.1)-(2.7) present the current ICING model definition.

Table 2.1 shows the current values and descriptions of the corresponding parameters. The exogenous input variables to the model are listed in Table 2.2.

$$\frac{dG(t)}{dt} = -p_G G(t) - S_I(t) G(t) \frac{Q(t)}{1 + \alpha_G Q(t)} + \frac{P(t) + EGP - CNS}{V_G}, \quad (2.1)$$

$$\frac{dQ(t)}{dt} = n_I (I(t) - Q(t)) - n_C \frac{Q(t)}{1 + \alpha_G Q(t)}, \quad (2.2)$$

$$\frac{dI(t)}{dt} = -n_K I(t) - n_L \frac{I(t)}{1 + \alpha_I I(t)} - n_I (I(t) - Q(t)) + \frac{u_{ex}(t)}{V_I} + (1 - x_L) \frac{u_{en}(t)}{V_I}, \quad (2.3)$$

$$\frac{dP_1(t)}{dt} = -d_1 P_1(t) + D(t), \quad (2.4)$$

$$\frac{dP_2(t)}{dt} = -\min(d_2 P_2(t), P_{\max}) + d_1 P_1(t), \quad (2.5)$$

$$P(t) = \min(d_2 P_2(t), P_{\max}) + P_N(t), \quad (2.6)$$

$$u_{en}(t) = \min(\max(u_{\min}, k_1 G(t) + k_2), u_{\max}). \quad (2.7)$$

The ICING model is illustrated schematically in Figure 2.3. The glucose-insulin system is shown, as well as the gastric component, which models the transit of glucose from nutrition to the gut and subsequent absorption into the glucose compartment. $G(t)$, $I(t)$, and $Q(t)$ represent the glucose, plasma insulin, and interstitial insulin compartments of the glucose-insulin system, respectively. Solid arrows indicate the kinetics, appearance, and clearance of insulin and glucose. A dashed arrow indicates the dynamic interplay between interstitial insulin and insulin-mediated glucose absorption, which is determined by the SI model parameter.

In the ICING model, insulin sensitivity (SI) is the critical patient-specific parameter that is fitted hourly to clinical blood glucose measurements using an integral-based fitting method [Han+05]. The identification of SI relies not only on measured BG concentrations, but also the interstitial insulin concentration and total glucose flux through the compartment, both of

2. BACKGROUND AND METHODS

Table 2.1: Parameter values and descriptions for the ICING model

Parameter	Value	Unit	Description
P_G	0.006	min^{-1}	Non-insulin mediated glucose removal
EGP	1.16	$mmol/min$	Endogenous glucose production rate
CNS	0.3	$mmol/min$	Central nervous system glucose uptake
V_G	13.3	L	Plasma glucose distribution volume
V_I	3.15	L	Plasma and interstitial insulin distribution volume
α_G	0.0154	L/mU	Insulin binding saturation parameter
α_I	0.0017	L/mU	Hepatic insulin clearance saturation parameter
n_I	0.003	min^{-1}	Trans-endothelial diffusion rate
n_C	0.003	min^{-1}	Interstitial insulin degradation rate
n_K	0.0542	min^{-1}	Renal insulin clearance rate
n_L	0.1578	min^{-1}	Hepatic insulin clearance rate
x_L	0.67		Fractional first-pass hepatic insulin extraction
d_1	0.0347	min^{-1}	Glucose transport rate from stomach to gut
V_2	0.0069	min^{-1}	Glucose transport rate from gut to plasma
P_{max}	6.11	$mmol/min$	Maximum glucose flux from gut to plasma
k_1	45.7	mU/min	Maximum endogenous insulin secretion rate
k_2	1.5		Insulin secretion suppression factor 1
k_3	1000		Insulin secretion suppression factor 2

Table 2.2: Exogenous input variables to the ICING model

Variable	Unit	Description
$G(t)$	$mmol/L$	Blood glucose
$Q(t)$	mU/L	Interstitial insulin concentration
$I(t)$	mU/L	Plasma insulin concentration
$P_N(t)$	$mmol/min$	Intravenous glucose input rate (parenteral nutrition)
$D(t)$	$mmol/min$	Oral glucose input rate (enteral nutrition)
$U_{EX}(t)$	mU/min	intravenous insulin input rate

which cannot be measured directly in clinical real-time. These other factors are primarily influenced by insulin kinetics, defined by n_I and n_C , and the modeled endogenous insulin (U_{en}) and endogenous glucose production (EGP) appearance rates. However, with limited clinical data available, only one model parameter, SI can be uniquely identified [Doc+11]. Hence, these other parameters must be treated as population constants or modeled independently.

Insulin sensitivity is identified using an integral-based fitting method. SI is determined not just by BG concentrations, but also by interstitial insulin concentration and total glucose flux through the compartment, both of which are can not be measured in clinical real-time. With the limited clinical data available, only one model parameter, SI can be uniquely identified [Doc+11]. Hence, other ICING model parameters must be treated as population constants or modelled independently.

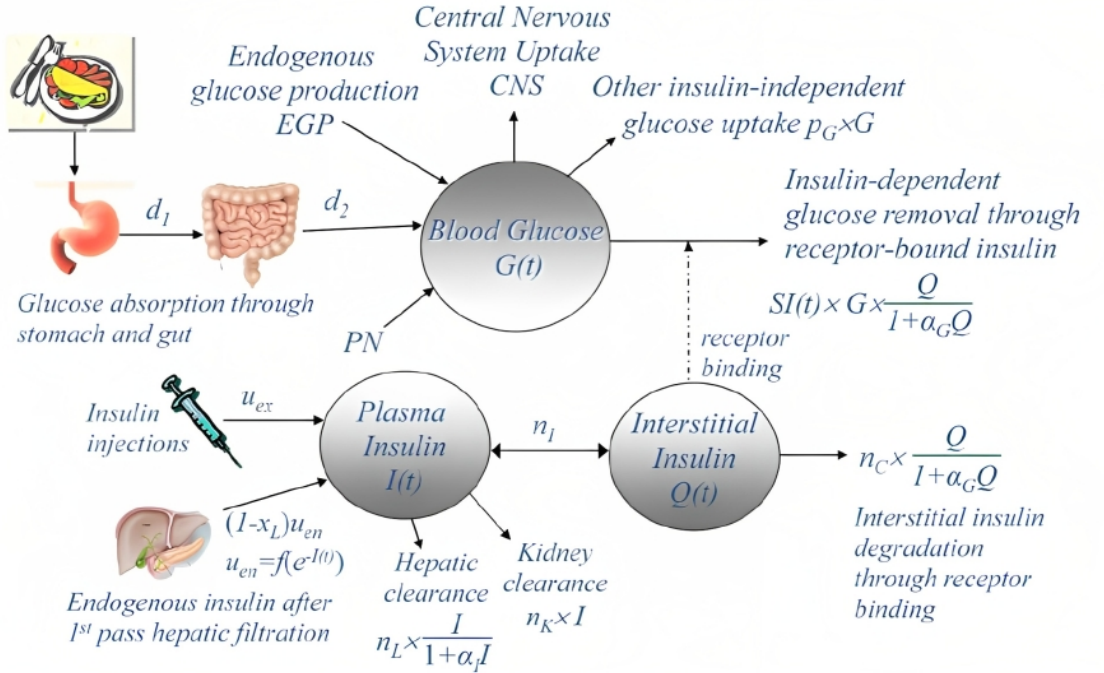


Figure 2.3: Schematic diagram of the ICING compartment model

2.4 Insulin sensitivity SI

The SI value identified using the ICING model is a whole-body insulin sensitivity incorporating any trade-offs due to the assumed EGP value. It reflects the tradeoff between insulin and glucose inputs and the observed net output flux in BG [DCD12]. Low values indicate greater insulin resistance and the need to either add insulin or reduce nutrition to achieve lower glycemic levels, where insulin saturation can occur at high doses [Nat+00; Doc+10; Pri+96; RMG81; Jam+12], necessitating a reduction in nutrition to achieve euglycemia [Ste+18a]. Given its whole body sensitivity definition, SI also captures changes in the patient state [Jam+12; Bla+08; Lin+11a; Muh+18], response to drug therapy [Pre+11a; Pre+11b; Jam+15], and other treatments [Jam+15; Sah+14].

SI is identified hourly, and variability is assessed by the hour-to-hour change in SI levels [Pre+12; Uyt+21] (Figure 2.4). An SI profile over time can be used to create a virtual patient [Cha+18b; Cha+10b; Cha+07], which has been successfully used to design GC protocols [Fis+12; Lon+06b; Lon+06a]. Virtual trials on cohorts of virtual patients can evaluate GC changes and/or new technologies before clinical use [Cha+18b; CBD19; Zho+18].

The insulin sensitivity SI is a critical time-varying, patient-specific parameter that can be identified using either retrospective data from simulation-based virtual patient studies or clinical real-time data. The procedure for fitting must be able to account for significant patient variation over time. It must also be computationally simple enough to be performed in clinical

real-time, ideally in 1-5 minutes. Finally, fitting the patient-specific parameters in any of the presented models is typically a non-convex optimization problem due to the series of non-linear differential equations involved [CC01].

To identify SI with the ICING model, the integral-based method is used. The insulin sensitivity function is designed to be piecewise constant, with a new value determined every hour, as this has been shown to adequately capture SI variation [Lin+06; Lin+08].

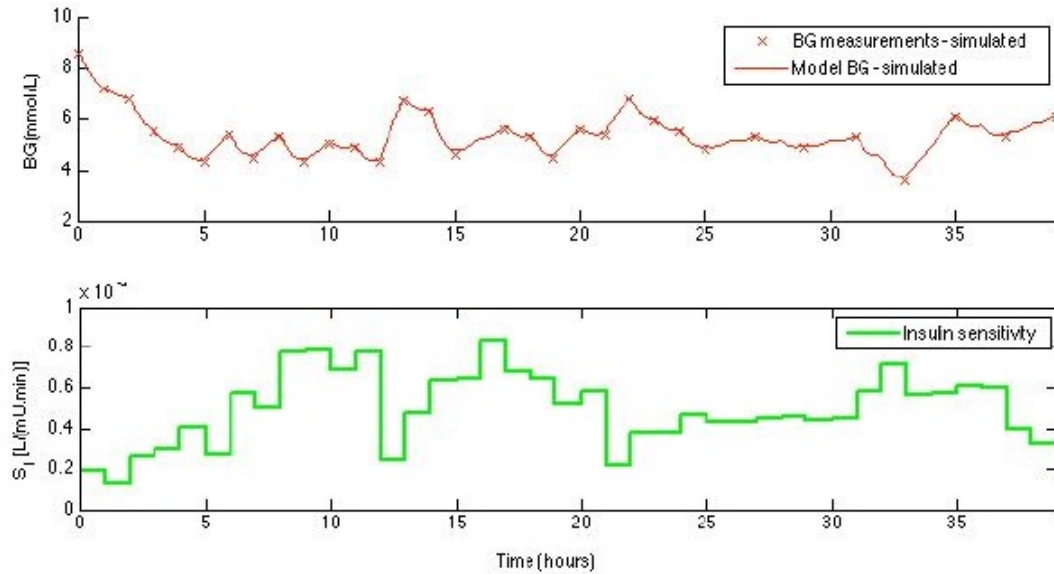


Figure 2.4: Example of SI fitting of a randomly selected patient, measured and simulated BG time-series (top) and SI stepwise function (bottom)

Clinical patient data, including current and prior last BG measurement and insulin/nutrition inputs are utilized with ICING model to identify hourly SI values using the integral-based method [Lin+11b; Doc+11; DCD12]. In the real-time clinical application, the identified SI value is used to predict future SI using stochastic models, which will also be used for the prediction of future patient blood glucose based on given treatment suggestions. Negative SI values are prevented by constraining the identified value to a minimum value of $1E-7$, where the physiological minimum is $1E-5$.

2.5 Endogenous glucose production (EGP)

Endogenous glucose production can account for a large portion, if not all, of the glucose appearance, especially early in a patient's ICU stay. EGP includes glucose released into the bloodstream from either stored glycogen (glycogenolysis) or from non-carbohydrate substrates (de novo glucose production) (gluconeogenesis). EGP is primarily found in the liver and, to a lesser extent, the kidneys in humans [Han+05]. The rate of production is determined by both the stimulus and the availability of substrates.

Insulin and hyperglycemia both inhibit EGP. EGP is stimulated by hypoglycemia and the counter-regulatory hormones (glucagon, cortisol, catecholamines, and growth hormone) [Han+05]. In healthy people, the delicate balance of these mediators keeps plasma glucose levels relatively constant throughout life. In critical illness, however, counter-regulatory hormones are significantly elevated almost immediately after critical-insult, but rapidly decline over the first 12-48 hours [Che+87; Fra86; Jää+75; Wei90]. These hormones can increase hepatic glucose production, causing or exacerbating stress-induced hyperglycemia [Che+87; Fra86; Jää+75; Wei90].

Modeling EGP as a function of insulin and glucagon concentrations may be overly complicated for clinical use in the critical care setting. Without explicitly measuring these hormone concentrations, modeling errors may be introduced into an already complex system with significant inter and intra-patient variability. Similarly, there are currently no methods for measuring these hormones in real time at the bedside. As a result, a clinical model cannot rely on these physiologically important hormones to provide patient specificity or real-time insight in order to reduce variability in this model element.

Several published glucose dynamics models for healthy and diabetic subjects include explicit glucose appearance from EGP. EGP rates have been determined as a function of plasma insulin concentration [Hov+02], blood glucose and insulin concentrations [And+94; Arl+00; Lot+06], and glucose, insulin, and glucagon concentrations [CC01; Par+00].

The four published critical care specific models include EGP as a function of insulin [Hov+08], BG and insulin [Pie+10], a constant [Lin+11a], or not specified [Van+06c]. In reality, EGP is influenced by the interaction of several hormones that are elevated during critical illness [Gel+84]. These interactions are far too complex to be accurately captured by clinically relevant models that are relatively simple.

Table 2.3 presents results from a number of published studies on critically ill patients and healthy controls to provide context for the EGP models proposed in this study. The nutritional status of the subjects ranged from fasted to receiving approximately ACCP goal feed (25 kcal/kg/day) with 50% glucose via parenteral route [Cer+97]. The majority of studies assessed EGP at a single point in time, ranging from during surgery to 96 hours after ICU admission. The reported mean EGP values for critically ill patients ranged from 0.10 to 2.36 mmol/min.

In the context of the physiological system model of Equations 2.1-2.7, EGP represents net endogenous glucose produced, primarily by the liver, to assist in BG regulation. EGP can represent a significant proportion of the glucose appearance in the plasma, particularly in the early stages immediately post insult, and when patients are receiving little exogenous nutrition [MMB01; Tho+04; Bla+82; DBP09]. Only a few studies have been carried out on critically ill populations to determine EGP, as shown in Table 2.3, where fasted estimation may be quite high compared to not fasted patients. The overall range in Table 2.3 is still relatively large, representing the diversity of physiological response. STAR currently sets

Table 2.3: EGP reported values in critically ill patients and healthy controls from several studies

Study	Subject type	Nutritional information	EGP (mmol/min)
[WNK97]	Healthy controls: Young (< or = 30 yr)	Fasted	1.73
	Healthy controls: Old (> or = 60 yr)	Fasted	1.82
	Trauma patients: Young (< or = 30 yr)	Fasted	2
	Trauma patients: Old (> or = 60 yr)	Fasted	2.27
[Tap+99]	Surgical ICU patients	Not fasted	1.2
	Surgical ICU patients	Not fasted	1.04
[Chi+00]	Cardiac surgery patients with cardiogenic shock	Fasted	2.36
	Healthy controls	Fasted	0.86
[Cha+00]	Septic patients	Not fasted	1.42
	Healthy controls	Not fasted	0.91
[Rev+05]	ICU patients with severe sepsis/septic shock	Fasted	1.18
	ICU patients with cardiogenic shock	Fasted	1.2
	Healthy controls	Fasted	0.58

EGP as a cohort-based constant of 1.16 mmol/min based on Chambrier et al [Cha+00] and optimized over a large cohort [Lin+11b].

2.6 Clinical data and patient cohorts

2.6.1 Patient cohorts

Clinical data in this study were collected from 4 independent cohorts of 737 hyperglycemic critically ill patients from 4 different ICUs. Specifically, 93 patients from Kalman Pandy Hospital, Gyula, Hungary, 216 from the International Islamic University Malaysia Medical Centre, Malaysia, 408 from Christchurch Hospital, Christchurch, New Zealand and 20 From the Centre Hospitalier Universitaire of Liège (CHU) ICU, Belgium.

The selection criteria for patients were: (i) glycemic control of more than 60 hours; (ii) insulin administration at the beginning of the glycemic control; (iii) at least 10 BG measurements during the treatment. Diagnosed diabetic patients were excluded.

New Zealand (NZ) cohort

New Zealand patients were treated using the STAR glycemic control protocol as a standard of care with BG target range 4.4-8.0 mmol/L and insulin delivered via bolus [Ste+16]. The main goal is to control BG with a 5% risk of BG < 4.4 mmol/L (80 mg/dL) in the same time maximize nutrition given towards a target of 25 kcal/kg/day.

Hungarian (HU) cohort

Hungarian patients were treated using STAR with the same target range but with continuous insulin infusion [Ste+16]. with a higher carbohydrate nutrition formula than the New

Zealand ICU. It has a similar 5% risk of $BG < 4.4$ mmol/L, with different delivery of insulin and nutrition [CD17].

Malaysian (MLS) cohort

Malaysian patients were treated using STAR, but using a higher target range of 6.0 – 10.0 mmol/L with continuous insulin infusions [Nat+00].

Belgium (BE) cohort

The protocol applied at CHU of Liège targets the 5.6- 8.3 mmol/L (100-150 mg/dL) band, and is characterized by an insulin infusion-only approach with a 1- or 4- hour time interval between BG measurements. Enteral and parenteral nutrition is decided by clinicians and ICU practice [Ump+02].

2.6.2 Patient data

Clinical data contains clinical diagnosis, BG measurements, insulin/nutrition treatments and time. Ethics approval was obtained from each local ethics committee for the analysis of this de-identifiable and anonymized data.

The patient data files (.mat) used in our studies contains a variable structure 'PatientStruct'. This structure contains several data fields representing raw data for a given patient which are required to run the simulation. Table 2.4 describes the variable fields contained in this structure.

Table 2.4: Fields contained in a 'PatientStruct' patient clinical data

Data field	Description	Units
Treal	Time at which BG measurement was taken	minutes
Greal	BG concentration	mmol/L
u	Cell structure containing time and rate information for insulin infusions	
u(1,1)	Time at which a change in insulin infusion occurred	minutes
u(1,2)	Rate of insulin infusion	mU/min
Uo	Rate of insulin infusion at time t=0	mU/min
P	Cell structure containing time and rate information for enteral dextrose	
P(1,1)	Time at which a change in nutrition occurred	minutes
P(1,2)	Rate of enteral dextrose infusions	mmol/min
Po	Rate of dextrose infusion at time t=0	mmol/min
PN	Cell structure containing time and rate information for parenteral dextrose	
PN(1,1)	Time at which a change in parenteral dextrose occurred	minutes
PN(1,2)	Rate of parenteral dextrose	mmol/min
rawSI	Cell structure containing model-based SI stepwise function	
rawSI(1,1)	Time at which a change in hourly basis	minutes
rawSI(1,2)	Identified model-based insulin sensitivity	liter/mU/min
ID	An identifier string for this patient (optional)	text

Estimating enhanced EGP

3.1 Introduction

One of the key elements and potential limitations of model-based glycemic control in general, and the ICING model in particular, is its assumed value for EGP. The assumed EGP value [Lin+11b; Cha+00] directly impacts the identified value of SI by directly contributing to the net glucose flux balanced by insulin-mediated glucose uptake. However, EGP cannot be measured directly in clinical care and relies on tracer studies [Vic+97; Vic+99] with significant errors in research. Hence, this value could be in error and, critically, is not identifiable using clinically available data. Thus, significant error in the assumed value due to patient variability would bias identified SI and potentially limit control safety and efficacy.

In the current version of STAR, EGP is an a priori assumed, cohort-based constant, optimizing model performance across the entire cohort in all hours [Lin+11b; Pre12]. However, in the identified SI profile for some patients, there are instances where SI is constrained to a non-negative non-physiological lower limit, which can result in a poor fit to BG measurements, signaling the assumed value of EGP, at least in this case, is insufficient [Pre12]. This SI lower limit is two orders of magnitude lower than the clinical range, and when constraint to this level is an indication the assumed EGP is too low for these patient hours due to surging EGP. This issue typically occurs early in ICU stay and stress-induced hyperglycemia, where such bursts of EGP are common for some patient demographics [MMB01; Tho+04; Bla+82; DBP09]. Notably, such problems are not unique to model-based control of adult ICU patients [Dic+13].

This study uses clinical data from 717 patients using STAR from 3 independent clinical cohorts to formally analyze the impact of the choice of EGP value on identified insulin sensitivity values based on the accuracy of the fit to measured BG data. In particular, when SI is constrained to its lower limit, it is possible to find a higher EGP value leading to a better fit to BG data at a physiological SI value. The time and frequency of these events are important for understanding these cohorts and the physiological stress response, as well as reducing

limitations to model-based GC.

3.2 Methods

3.2.1 Insulin resistance and constrained SI

In this study, constrained SI = 1E-7 L/mU/min in STAR is used as an indication of insulin resistance. All ICING model parameters except SI are fixed, including EGP, to cohort-based constant values to ensure the model is identifiable. Negative SI values are non-physiological and prevented by a non-negative constraint to SI=1E-7 L/mU/min, which is 100x below its physiological lower limit of SI=1E-5. Constrained SI = 1E-7 L/mU/min values are thus an indication of insufficient incoming glucose flux to fit the data.

Figure 3.1 shows an example of such a case, where extreme stress response due to the initial insult results in an assumed EGP value potentially low, based on an SI value identified at the lower limit and poor fit to measured blood glucose data. The early discrepancies between the simulated BG and measured BG is due to the sudden rise in BG level resulting from the stress response likely causing a surge in EGP, which in the model-based estimation results in extremely low identified values of insulin sensitivity. As noted, these surges are common early in the stay for severe sepsis and other severe critical illness. In the case of this particular patient, the constant EGP (1.16 mmol/min) limits the ability of the STAR model to closely follow the BG dynamics without identifying a negative SI value, where a negative value is a clear indication of an assumed EGP value being too low.

3.2.2 EGP estimation during severely low SI

Parameter estimation is the critical phase of the physiological system modeling since this will determine the model fit to the measurement data. The model-based EGP estimation method is developed to adjust the EGP according to the BG concentration and initially identifies SI value when it hits the lower constraint limit (see Figure 3.2). It elevates EGP from this initial value until the model can match the measured blood glucose levels. In particular, the elevated EGP value is identified using a simple least squares method minimizing the squared error between the linear interpolated blood glucose measurements (G_m) and the BG simulated by the ICING model (G_s).

The EGP value was estimated using a linear approximation method on blood glucose measurements, which were not necessarily taken at equal time intervals. This estimated EGP is obtained:

$$EGP_{LS} = \arg \min_{EGP} \sum_{k=1}^K (G_m(t_k) - G_s(t_k, EGP))^2 \quad (3.1)$$

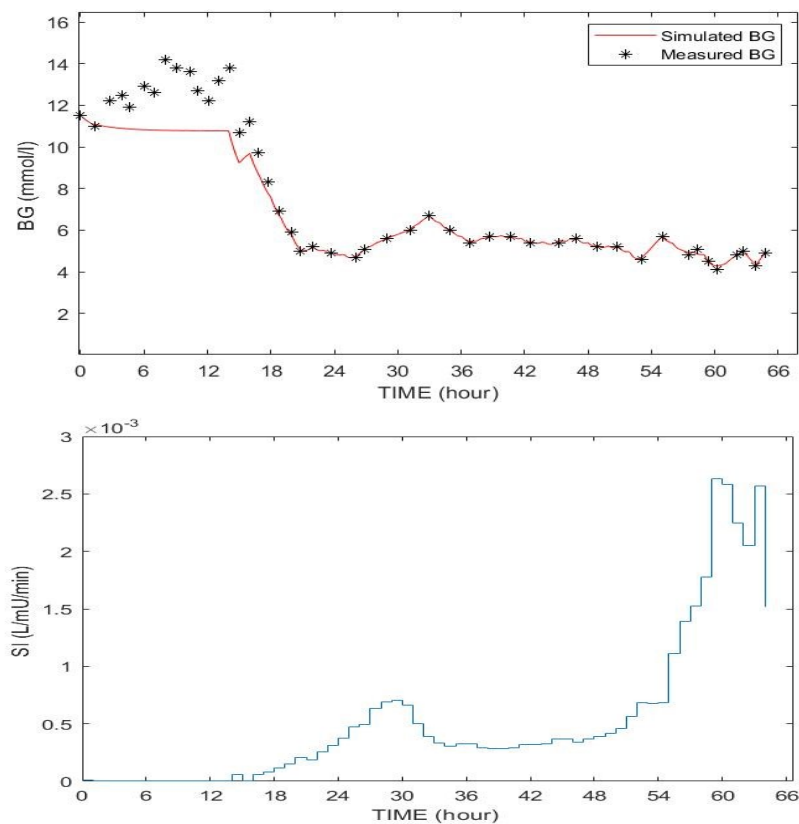


Figure 3.1: Example of poor BG fitting (top figure) with SI time function (bottom figure). The red curve is the simulated BG using the fixed EGP; the BG measurements are shown by stars (*).

such that $EGP \in [1.25, 3.5]$

where t_k is the k -th time instant of the measurement with $k=1, 2, \dots, K$ and K is the number of measurements. G_s is the simulated blood glucose level, while G_m is the measured blood glucose level.

The EGP parameter values range is defined as $1.25 < EGP < 3.5$ mmol/min with a step value of 0.25 mmol/min, which gives a vector of $N=10$ after the initial fixed value of $EGP = 1.16$ mmol/min. The optimal step size was experimentally determined via convergence analysis until decreasing the step size did not affect the EGP value found, but only increased the calculation time. Since the problem space is small the minimum value can be found by a simple linear search.

This estimation method selects the EGP value minimizing the fitting error in the hour prior to the measurement. Once a new EGP value is identified by the above method, it is used in the model for the remaining patient hours. The EGP estimation method is embedded into the

SI identification process of the STAR protocol, as can be seen in Figure 3.2. The main steps of the method are as follows:

- Step1: Test if the identified SI value in the current hour is constrained to the lower minimum ($SI = 1E-7$ L/mU/min). If yes, then the EGP method is executed; if not, then the SI identification and the treatment calculation in STAR is executed without any modifications.
- Step2: If the SI value in the current hour is constrained to the lower minimum ($SI = 1E-7$ L/mU/min) then a new EGP value is estimated. A total of 10 different BG trajectories corresponding to 10 different EGP values [1.25; 1.50; 1.75; 2.00; 2.25; 2.50; 2.75; 3.00; 3.25; 3.50] are simulated by ICING. Fitting error to the interpolated measured BG for each BG trajectory is used to select the EGP value minimizing the error according to equation 4.1.
- Step3: Re-identify SI with the new estimated EGP and use this new SI value to proceed with the treatment calculation, which is the selection of the optimized insulin and nutrition intake to be given to the patient according to the original STAR protocol [Eva+11; Fis+12; Ste+16; Eva+12]. Note that in this particular study, this new EGP value is used for the rest of the patient's treatment. This EGP may change if a new constrained SI occurs, then the method is executed again and the estimated EGP may change.

3.2.3 Analyses

In the first phase, the analysis is done for all patients in all treatment hours. In the second phase, the rest of the analysis is done on the subset of the patients with at least one low minimum SI (constrained $SI = 1E-7$ L/mU/min). In the first phase, the insulin sensitivity and the proportion of patients and the time of occurrence where EGP is modified based on constrained $SI = 1E-7$ L/mU/min are reported. In the second phase, distributions of EGP values are reported and compared across cohorts.

More importantly, the identified values of SI are compared for each cohort using SI with the fixed EGP value currently used, and the SI when EGP is estimated with our method, where relatively modest changes would indicate no significant impact on the performance of STAR, but would also alleviate any biases induced in the proportion of hours where EGP was changed. Modeling error between simulated BG and measured BG is analyzed. The median and interquartile range (IQR) of absolute error per cohort and maximum per-patient error (in percentage) are compared in those affected hours only for fixed EGP and estimated EGP.

3.3 Results

3.3.1 Distribution of SI values

Figure 3.3 shows the distribution of all SI values identified for the 3 cohorts. In particular, a higher proportion ($\approx 9\%$) of these values are close to the minimum SI value (insulin resistance) in the Malaysian and ($\approx 4\%$) New Zealand cohorts compared to the Hungarian cohort

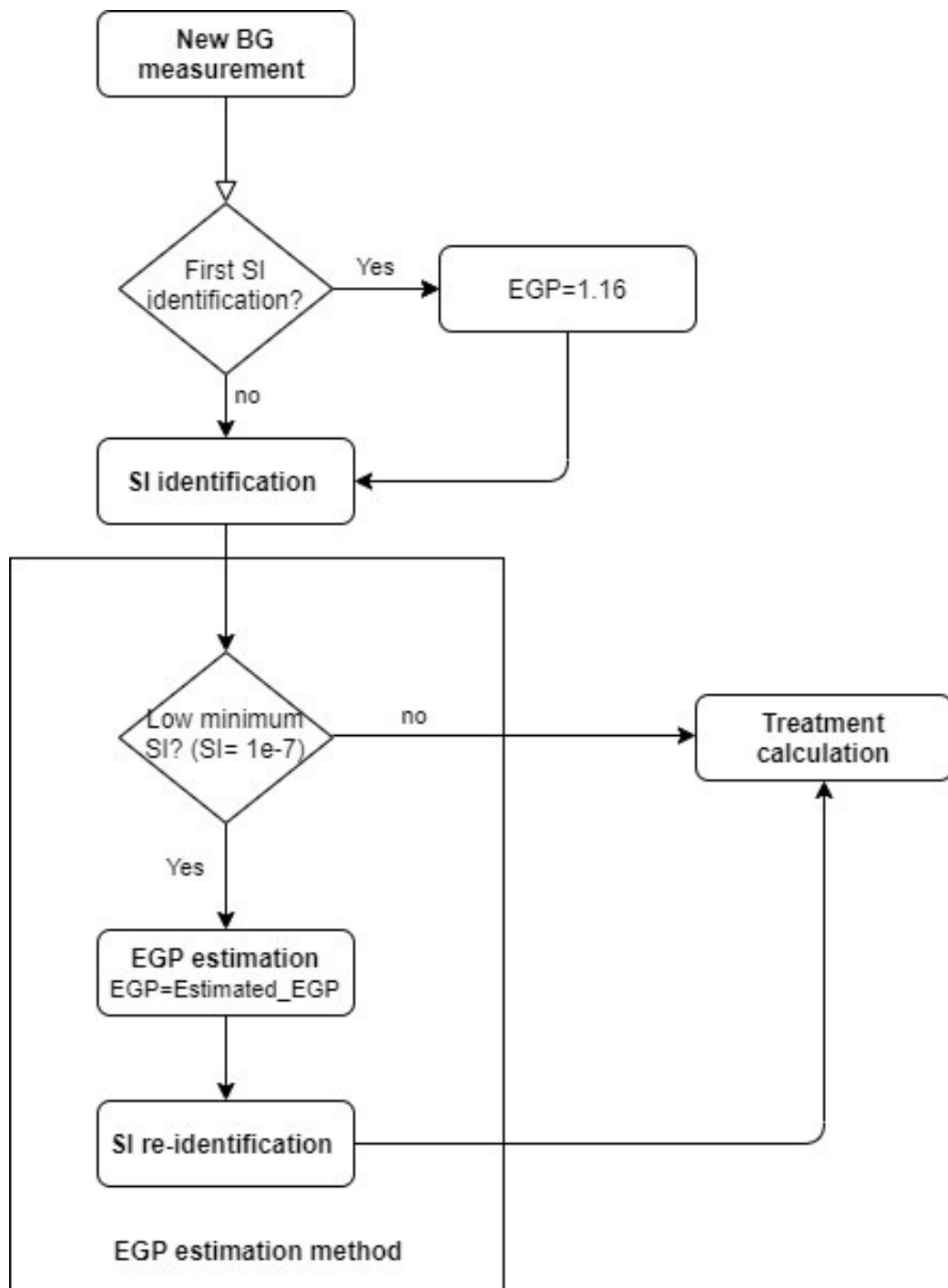


Figure 3.2: Flowchart of the implementation of the new EGP estimation method embedded into the SI identification process. Treatment calculation includes the selection of the optimal insulin and nutrition intake to be given to the patient according to the original STAR protocol.

with less than 1%. Table 3.1 shows a high proportion of patients are affected in all cohorts,

3. ESTIMATING ENHANCED EGP

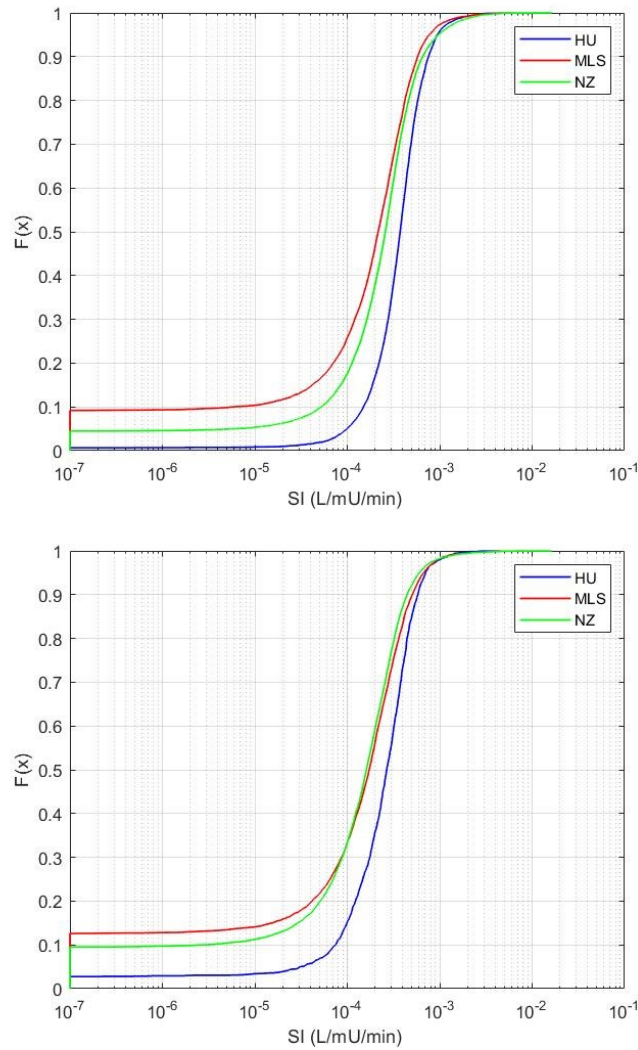


Figure 3.3: Distribution of identified SI for each cohort (New Zealand (NZ), Hungarian (HU) and Malaysian (MLS)) using the standard, fixed value for EPG of 1.16 mmol/min. The upper figure is, all patients ($N = 717$), and the lower figure, is only patients with SI constrained to the minimum value for at least 1 hour ($N = 330$). The proportion of values at the lower limit of $SI = 1e-7$ L/mU/min in Table 3.1 match the starting points in this figure (left). Note that the x-axis is a log scale.

but relatively low hours in proportion. Thus, $\approx 22-62\%$ of all patients are affected, but the number of hours this excessive stress response impacts EGP is $<10\%$. Again, the Hungarian cohort, which had the highest SI values in Figure 3.3, is the least affected, and the Malaysian cohort is the most affected.

Further analysis considers only patients with constrained $SI = 1E-7$ L/mU/min values (patients with at least one SI value constrained to the lower minimum limit), which represents

Table 3.1: Statistics of patients where si was constrained to $SI=1e-7$ l/mu/min using the standard, fixed value for EGP of 1.16 mmol/min

	NZ	MLS	HU
Total number of patients	408	216	93
Proportion of patients with constrained SI	42.89% (N = 175)	62.03% (N = 134)	22.58% (N = 21)
Total number of treatment hours	24119	10693	9524
Proportion of hours with constrained SI out of total hour	4.48% (1080 hours)	9.18% (982 hours)	0.87% (81 hours)

62.03% of Malaysian patients, 42.89% of New Zealand patients and 22.58% of Hungarian patients. Their details are also in Table 3.1

3.3.2 SI distribution with fixed EGP vs. estimated EGP

Using the EGP estimation method presented results in new SI values in the current and remaining treatment hours for those patients in Table 3.1 who had SI constrained to the minimum value at least once. The resulting SI distribution in Figure 3.4 is shifted to higher SI values with far fewer low minimum SI values than in Figure 3.3. Trends across cohorts match those in Figure 3.3.

3.3.3 Estimated EGP distribution

Figure 3.5 shows the new estimated EGP distribution for all hours in Table 3.1 where SI was constrained using a fixed EGP value, and EGP was thus increased. In $\approx 80\%$ of these cases, the estimated EGP was between 1.25-2 mmol/min. However, fewer differences were seen for almost 20% of cases with EGP values between 2.0 and 3.5 mmol/min, which is the upper value in the estimation method used here, although this choice was arbitrary at 3 times the assumed value. Trends by cohort followed those seen in Figures 3.3-4 and Table 3.1.

3.3.4 Constrained SI occurrence

Figure 3.6 shows the distribution in time of low minimum SI occurrence for the three cohorts. Approximately 24-50% of cases occur in hours 1-24, with 35-65% in hours 1-48 and 60-75% within 72 hours. These results include all events, even those lasting only 1 hour, which may also be due to a data entry error, significant measurement errors, nutrition stoppage for clinical reasons and/or clinical errors [Lin+08; Lin+11b; Lin+06; Lin07a]. The overall trends for the NZ and Malaysian cohorts are exponential, with most episodes arising in the first hours, as expected, given stress response physiology. The Hungarian cohort has relatively very fewer episodes and, thus, no specific pattern.

3.3.5 BG fitting

Figure 3.7 shows an example of the patient shown in Figure 3.1, where the estimation method was applied. The simulated BG trajectory with the estimated and increased EGP is more flexible in approaching the blood glucose measurement points and was able to follow the BG

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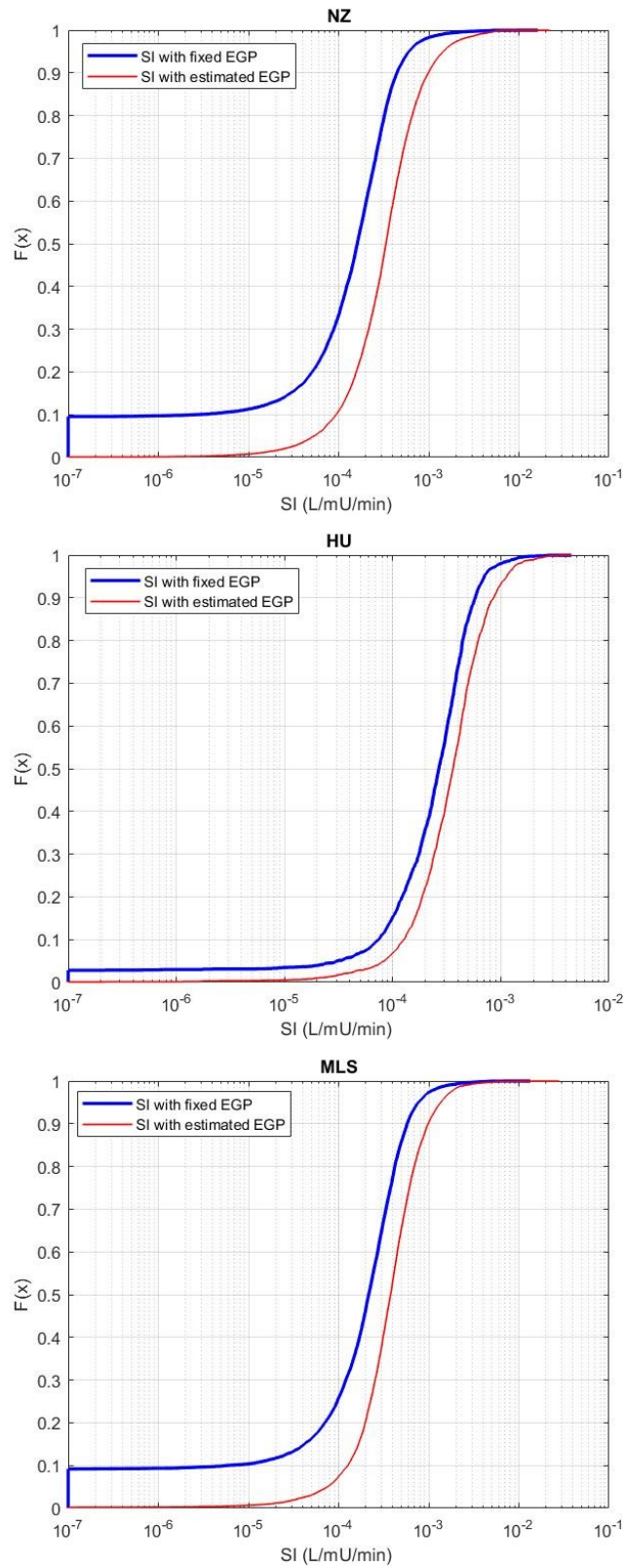


Figure 3.4: Distribution function of SI values with Fixed EGP vs. The new estimated EGP for the: New Zealand (NZ), Hungarian (HU) and Malaysian (MLS) cohorts. Note that the x-axis is a log scale.

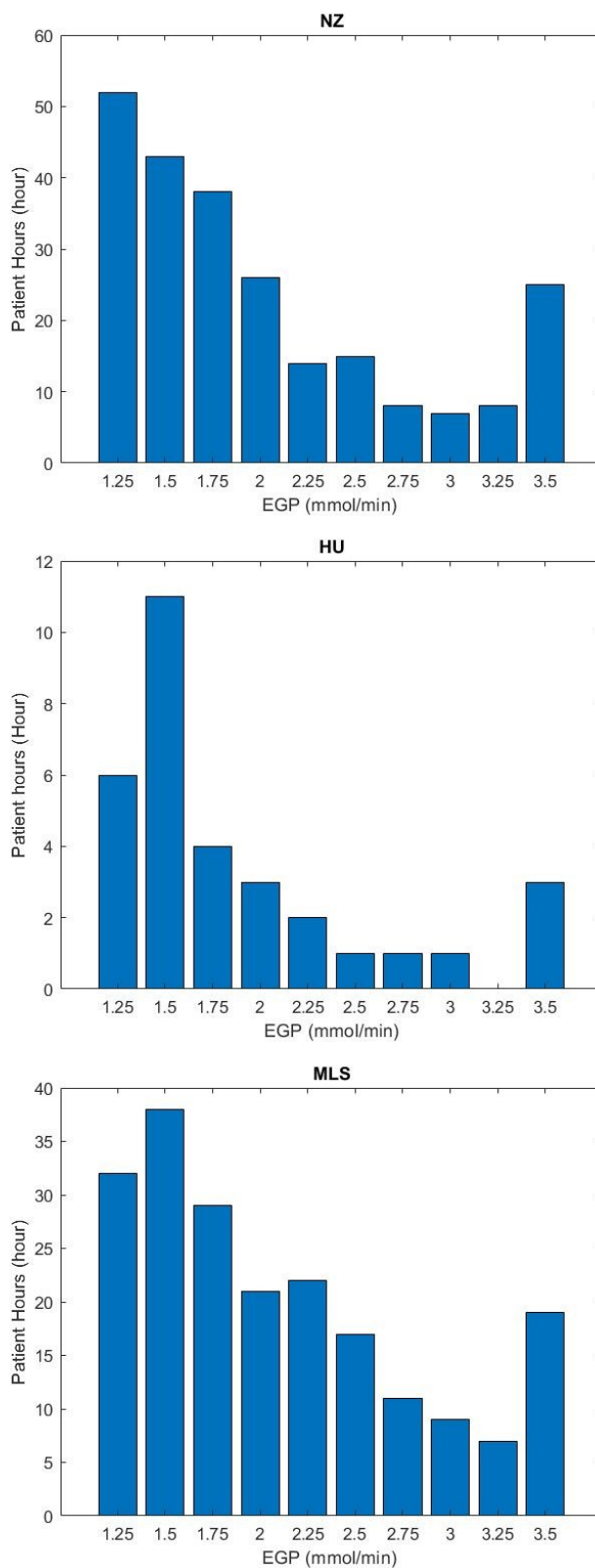


Figure 3.5: Distribution of the estimated EGP for the three cohorts for the hours where it was constrained and the proposed method applied in Table 3.1; New Zealand (NZ), Hungarian (HU) and Malaysian (MLS) cohorts. Horizontal axis is the EGP estimated for each low minimum SI hours, Vertical axis is number of cases when it was changed (low minimum 35 hours)

3. ESTIMATING ENHANCED EGP

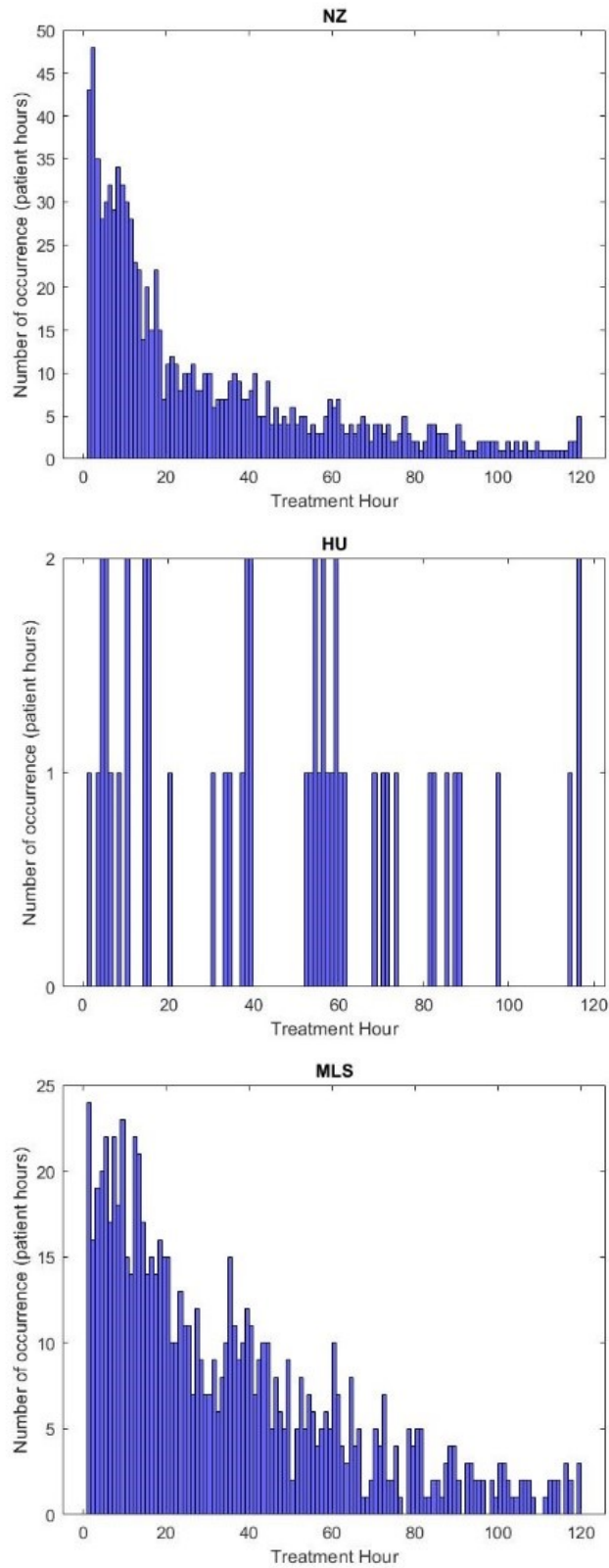


Figure 3.6: Occurrence in time of low minimum SI in the New Zealand (NZ), Hungarian (HU) and Malaysian (MLS) cohorts. (one histogram bin corresponds to 1 hour)

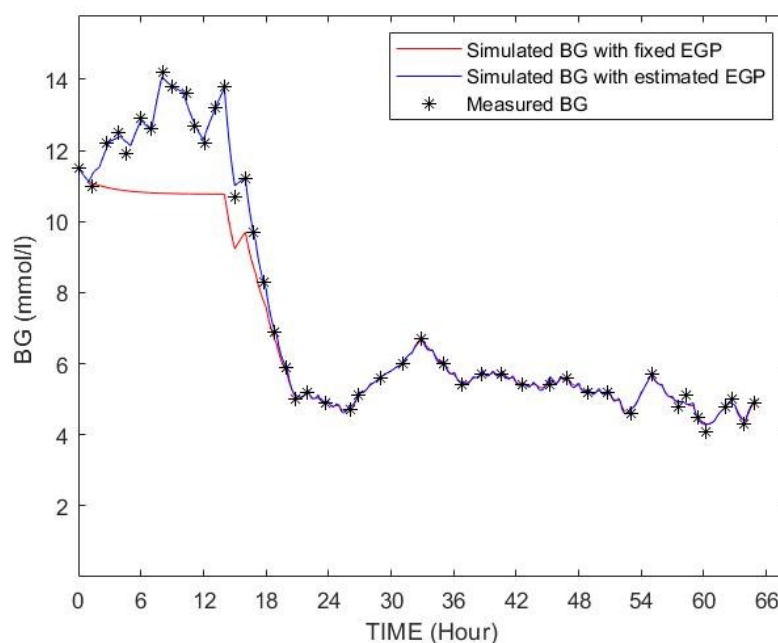


Figure 3.7: Example for a BG trajectory simulated by using the original EGP/SI values (shown as red) and the identified EGP/SI values (shown as blue) of the patient shown in Figure 3.1

dynamics, especially in the critical phases where there was a significant rise in BG levels resulting in a low minimum identified SI value using the fixed assumed value of 1.16 mmol/min. Table 3.2 shows BG errors per cohort for all patients where EGP was changed. Significant reductions in error in these cases where EGP was modified can be seen in all three cohorts using the proposed method. The greatest reduction was in the Malaysian cohort, which, following all other trends, was the most affected. The Hungarian cohort was the least affected. Median errors of 1.47-1.74% are within measurement errors.

Table 3.2: Median IQR of error per cohort and median IQR of maximum error per patient.

	NZ		MLS		HU	
	Fixed EGP	Est EGP	Fixed EGP	Est EGP	Fixed EGP	Est EGP
Absolute % BG error	7.43	0.43	10.63	0.65	6.77	0.79
per cohort Median [IQR]	[2.99, 16.10]	[0.14, 1.09]	[4.66, 19.33]	[0.17, 1.15]	[2.97, 15.67]	[0.52, 1.13]

3.4 Discussion

From the distribution of identified SI values for all 3 cohorts, there were significant differences in the proportion of hours where SI was constrained. The Hungarian cohort had the fewest (0.87%). However, considering the analysis of the treatment differences [Ste+16], the carbohydrate intake of the Hungarian cohort was higher. Equally, they have the highest identified SI, which would limit those situations in general, all else equal. These differences

may also reflect cohort differences in the incidence of greater complexity and level of critical illness, such as incidence of severe sepsis, in some cohorts, which can occur from the areas and types of patients treated, as well as from treatment selection or treatment failure bias [SC12; CS12]. The difference in insulin delivery using bolus or continuous infusion has no impact on the estimated insulin sensitivity value [Cha+09], and thus does not affect the results presented. However, no significant cohort-based differences in SI distribution across cohorts have been reported in previous studies [Ste+16].

Fasted patients could provide a better estimate than non-fasted patients, as EGP is the only input for fasted patients limiting any bias from data, clinical, or model errors. However, the patients who are not provided with enteral or parenteral nutrition are not consistent across or between cohorts. The number of hours where $SI = 1E-7$ L/mU/min at the lower limit and there was no enteral or parenteral nutrition given was 0% of affected hours for the HU cohort, 1.38% for the NZ cohort and 1.45% for the MLS cohort. These values make up 16% of the affected hours in the MLS cohort and 31% of hours in the NZ cohort, per Table 3.1, indicating the impact of having minimal nutrition in the model-based SI identification, a situation placing greater emphasis on the assumed EGP value [Dic+13; MR04a].

Changes in EGP appear well justified by the time of occurrence. 40-50% of hours where EGP is changed occur in the first 24 hours (Figure 3.6). This behavior matches clinical expectations and is due to the EGP surge often seen in the first 12-24 hours of the stay [MMB01; DBP09; Jee04], particularly in severe sepsis and septic shock patients [MMB01; And+04; Cha+00; Pre12; Jee04; Wae+08; Cha+08c], all of which match the metabolic variability seen in these first days of the stay [Uyt+17; Pre+12]. Thus, the timing of the hours where this phenomenon occurs qualitatively matches broad clinical expectations.

Fitting errors in these cases were larger or maximum as in Figure 3.1, and indicate EGP levels for a few select hours can be extremely high. These values would be well beyond the reported values used to justify the range in the model and the range used. However, they are possible, per the results in Table 3.2. This study thus shows the wide physiological range encountered in such patients. It is a major result of this analysis, which should be prospectively confirmed.

In this chapter, increasing EGP in the model not only reduces BG fitting error and allows the model to better follow the measured BG dynamics but also modifies the distribution of the SI values. These shifts are modest and will not affect the overall performance of STAR or its stochastic models, given the relatively low percentage of hours affected in Table 3.1. However, beneficial impacts may arise for STAR from improved predictions and thus more accurate GC during treatment for those hours affected.

The EGP estimation method starts only when a low minimum $SI = 1E-7$ L/mU/min is identified, and the new estimated EGP is kept until the end of the treatment. A follow-up study [YBC20a] for different practical application scenarios for estimating EGP considered only the hours affected and other constraints. In contrast, the results presented here are a maximum case for the occurrence and EGP level, where this follow-up study is a more conservative

estimate. Practically, in real-time implementation, every hour can thus be analyzed, and the EGP changed only as needed, starting each time from the assumed value. This approach is not terribly computationally heavy and can be performed well within the 10-30 seconds required to make a treatment decision. Hence, it is not likely to affect compliance or ergonomics [Cha+08b].

EGP estimation is an estimated value, which is a limitation of the work. EGP is very difficult and very invasive to measure directly, typically using tracers, and these direct measures can have significant errors. Thus, the estimated EGP values cannot be more fully validated. Further, the elevated values estimated are minimum estimates based on the criteria used to identify a need to modify the value from the estimated population constant. However, the values found are within measured ranges from a variety of limited independent studies in Table 2.3, where this study examines a very large number of patients.

Finally, The specific use of ICING model, namely fixing all the physiological parameters to a cohort-based constant value and using only insulin sensitivity (SI) – and in the case of this research EGP – as a time-varying model parameter, is a result of a compromise. This compromise enables using a patient-specific physiological model on the bedside, i.e. the model with these restrictions can be identified using the patient parameters available in the standard treatment. The ICING model and its use in this specific way have been extensively validated across several patient and ICU settings in many studies [Lin+11b].

Obviously, this solution results in modeling inaccuracies. However, it has been proven that the STAR protocol – using ICING in the way described above – provides safe and effective treatment of patients. It is already used in clinical practice in several Hospitals in New Zealand, Belgium, Hungary and Malaysia.

3.5 Conclusions

The study conducted was a further confirmation of the wide variability of EGP across ICU patient cohorts. Estimating a low EGP value can cause bias in the identified SI value, which can limit the accuracy of ICING model and potentially reduce the quality of GC treatment recommendation. In these cases, numbering 1-10% of possible hours in the three cohorts, the model was not able to follow the blood glucose dynamics. Estimating and adjusting EGP to a higher value using the novel methods presented shifted SI for these hours to physiologically realistic values and improved blood glucose fit to measured data. A further major result of this study, beyond the method presented, is the quantification of the potentially very wide range of EGP values in ICU patients, which may slightly exceed prior reports, and remain to be prospectively verified.

Related publications of the results of Thesis 1 which are presented in this Chapter 3 are the following: [j1; c4] .

Clinical application scenarios of the new EGP

4.1 Introduction

The accurate estimation of EGP plays a critical role in glycemic control, particularly those in intensive care unit in their early stages. However, the existing fixed cohort-based value assigned to EGP in the current settings of the STAR protocol may not adequately represent the true physiological value for certain patients. By addressing this limitation and proposing a new EGP estimation method, we can enhance the modeling accuracy and improve clinical outcomes.

In the prior chapter, we assessed the assumption that a low minimum SI value (constrained SI) is thus an indication that EGP needs to be raised to a higher value. Increasing EGP enabled the model to follow the observed BG dynamics and surpass this limitation, also showed impressive results in error reduction and change in the insulin sensitivity distribution.

In this study, practical application scenarios were suggested for the clinical implementation of estimating a higher EGP and the new EGP estimation method by analyzing the time occurrence and duration of these episodes, using the same clinical data of 717 patients from 3 different ICUs: New Zealand, Hungary and Malaysia.

The goal is to reduce the amount of times EGP is estimated, avoid overestimating the EGP levels of patients after their condition becomes stable, and reducing workload, without compromising the modeling accuracy and treatment quality.

4.2 Methods

4.2.1 Patient data /cohorts

In this study we selected the same data as the previous chapter of 717 patients from 3 different cohorts. 216 from the International Islamic University Malaysia Medical Centre, Malaysia, 408 from Christchurch Hospital, New Zealand, 93 patients from Kalman Pandy Hospital, Gyula, Hungary.

4.2.2 Analysis

In this chapter, in order to provide practical scenarios on how we can handle these low minimum SI situations. First, we analyzed the time of occurrence these episodes and Second, the duration (time lasting) of these episodes for the three different ICUs. By closely examining these temporal aspects, we will gain valuable insights into the patterns and frequency of these low minimum SI situations, allowing us to decide which way is more practical to adjust patient's EGP levels.

As a side research, we analyzed and compared different EGP upper limit values and the number of remaining constrained SI values using a cohort of 22 most affected Malaysian patients to test if EGP levels higher than the suggested upper-limit of 3.5 mmol/min are beneficial.

4.3 Results

4.3.1 Insulin resistance, constrained SI and low EGP

Figure 4.1 shows the distribution in time per day of the probability of occurrence of constrained SI for the 3 different cohorts. The overall trends for the New Zealand and Malaysian cohorts are exponential, with most episodes arising in the first 3-4 days, as expected given stress response physiology. The Hungarian cohort has quite a similar pattern except on the third day, where there was a rise in the rate of occurrence compared to the first 2 days.

Observational results from Figure 4.1, show ~ 24 -51% (24% in HU, 51% in NZ and 41% in MLS) of these situations happen in the first 24h (first day), ~ 36 -69% happen in the first 48h, ~ 61 -78% happen in the first 72h, and ~ 70 -83% happen in the first 96h across all cohorts. 17-30% of constrained SI occurrence occurs after the 4th day.

4.3.2 Duration of episodes

Figure 4.2 shows the duration in hours of constrained SI for the 3 different cohorts. All 3 cohorts have similar exponential trends, with most episodes lasting up to 4 hours.

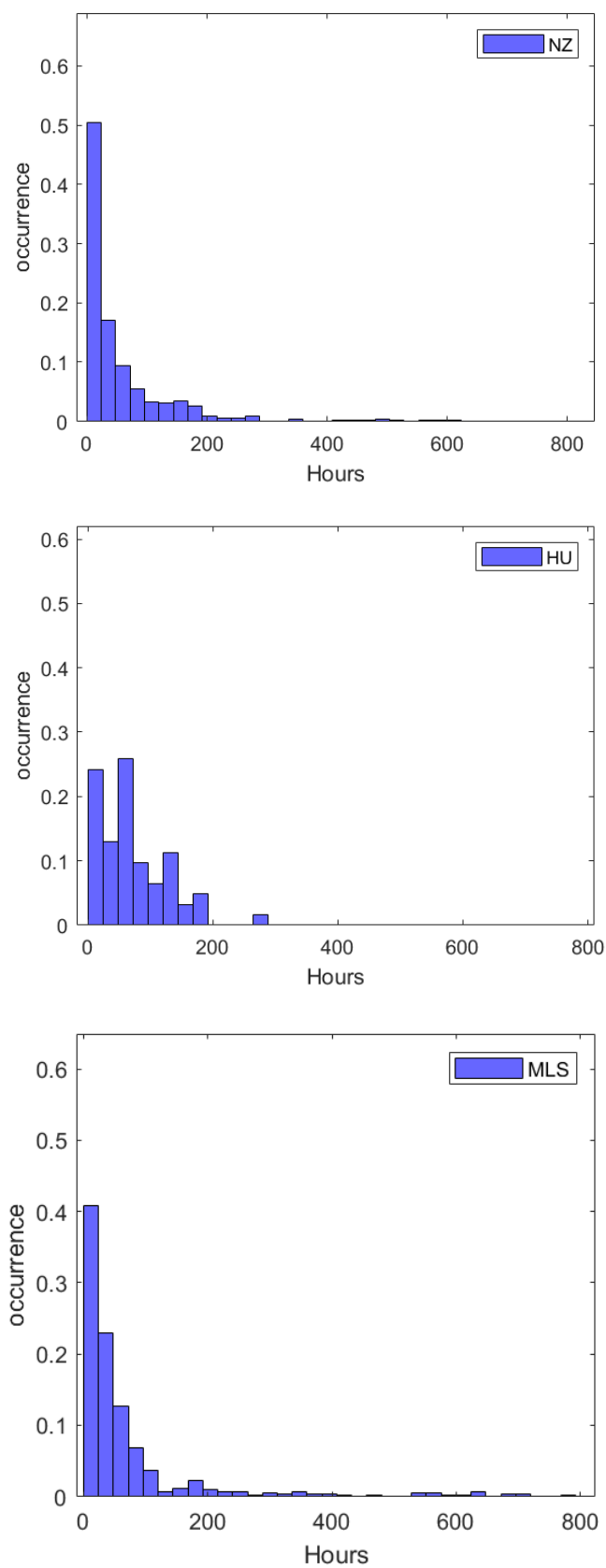


Figure 4.1: probability of occurrence of constrained SI per day (1bin= 24h, occurrence= probability of occurrence in %) for NZ (top), HU (middle) and MLS (bottom)

Table 4.1: Mean/max fitting error and remaining constrained SI values at different EGP upper-limit values in the 3 cohorts

EGP(mmol/min)	1.16		2.5		3		3.5		6	
Mean/Max	Mean	Max	Mean	Max	Mean	Max	Mean	Max	Mean	Max
Fitting Error (%)	18	48	2.03	16.89	1,04	6.38	0.77	2.33	0.63	2.33
N° of remaining constrained SI	468		18		9		6		3	

A small minority of New Zealand patients have constrained SI duration up to 18 hours, whereas in Hungarian and Malaysian patients, the maximum is 7-8 hours.

Observational results from Figure 4.2, show 53-71% of the insulin resistance situations last for 1 hour, 19-27% of the insulin resistance situations last for 2 hours and 5-11% of the insulin resistance situations last for 3 hours. Thus 89-95% of the insulin resistance situations last up to 3 hours across all the cohorts.

4.3.3 EGP parameter value limits, fitting error and remaining constrained SI values

Out of 216 Malaysian patients (the most affected cohort), we selected patients with the poorest BG fitting (BG error > 20%) to analyze the effect of applying different EGP upper limits mainly on modeling error (the result of the selection is 22 patients). Table 4.1 shows the Mean/Max fitting error and remaining constrained SI hours after increasing EGP with different limits compared to using a fixed EGP (1.16 mmol/min).

Using fixed EGP values comes with high fitting errors and a large number of constrained SI hours. Increasing the limit of EGP to 2.5 mmol/min shows a reduction of 96% in the constrained SI values but still has a slightly large maximum fitting error. In contrast, setting the limit of EGP up to 3.5 mmol/min shows a large reduction in BG fitting error to a very low value (2.33%) and a reduction of constrained SI values by 98%. Using EGP values higher than 3.5 mmol/min did not show any further improvement and using 6 mmol/min as a limit has similar results to using 3.5 mmol/min.

Forcing SI to take a non-negative value is a model limitation, and the identified constrained SI will result in a poor SI prediction in the real clinical application, which also will result in a poor BG prediction.

In the method presented in the chapter, there is a situation where the EGP values minimizing the BG fitting error results in also a constrained SI value (see Table 4.2). This leads to the idea of modifying the estimation method to prioritize the positive SI values over a constrained value with the acceptance of a small BG fitting error.

Results show over 98% of the constrained SI disappears when estimating EGP up to 3.5 mmol/min. This means no need for any further modifications of the current estimation

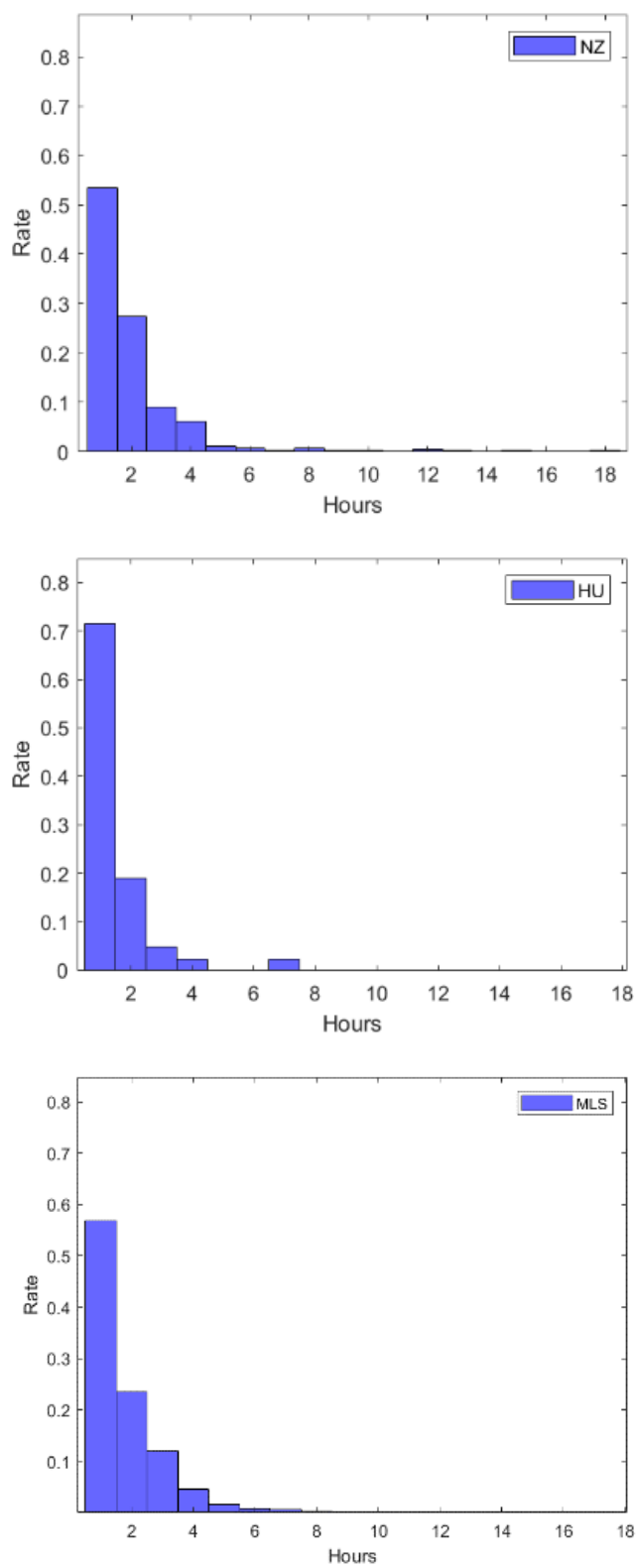


Figure 4.2: Rate of duration of constrained SI episodes when it occurs (how many times constrained SI lasted X hours), 1bin= 1h, rate= rate of duration in %), for NZ (top), HU (middle) and MLS (bottom) cohorts.

Table 4.2: The number of remaining constrained si in all the cohorts using fix EGP vs. Estimated EGP (est EGP)

	MLS		NZ		HU	
EGP value	Fix EGP	Est EGP	Fix EGP	Est EGP	Fix EGP	Est EGP
N°of constrained SI	1002	20	1117	11	63	1

method.

4.3.4 Preliminary experiment for using elevated EGP in the STAR protocol

As a preliminary experiment, the effect of using elevated EGP in the STAR protocol was tested. The primary question was whether changing the EGP in the case of constrained SI, the modified EGP would result in a modified treatment suggestion or the optimal treatment would not be affected. Thus, an in-silico simulation study was performed where the treatment option was recalculated in each case when contained SI was the result of the SI identification. In these cases, a new EGP value is calculated using the algorithm suggested in section 3.2.2. The results are summarized in Table 4.3. A patient cohort with 717 patients - described in section 2.6.1 - is used in this preliminary experiment.

Table 4.3: Result of the preliminary experiment of using elevated EGP in the case of constrained identified SI

N°of treatments with constrained SI and non-default EGP suggestion	167
N°of treatments with altered therapy suggestion	78
N°of treatments with altered insulin dosing	58
N°of treatments with altered nutrition dosing	20

4.4 Discussion

4.4.1 Insulin resistance and patient's condition relationship

For those hours where SI was hitting the lower limit, 70-83% of them occurred in the first 96 hours of stay for the Malaysian, New Zealand and Hungarian patients, as shown in Figure 3.1. This early occurrence is likely due to insulin resistance and to the surge in EGP seen particularly in severe sepsis and septic shock patients in the first 12-24 hours of the stay [CS12; SC12]. Thus, the location of these hours qualitatively matches broad clinical expectations, where severe sepsis is one of the leading causes of ICU admission [MMB01; Pre12].

41-51% of the constrained SI situation happens in the first 24H for Malaysian and New Zealand patients, whereas only 24% for the Hungarian cohort with the highest rate was on the third day of the ICU stay. These differences may also reflect cohort differences in the incidence of greater complexity and level of critical illness, such as incidence of severe sepsis, in

some cohorts, which can occur from the areas and types of patients treated, as well as from treatment selection or failure bias.

In a simple, in-silico simulation-based study, it was shown that using elevated EGP in the case of constrained identified SI will result in altered treatment suggestion in about 50% of the treatment cases (see Table 4.3). This shows the relevance of changing the default EGP in case of constrained SI and motivates the definition of protocol versions using temporary elevated EGP in the STAR treatment.

4.4.2 Handling EGP and constrained SI

Using a limit higher than 3.5 mmol/min shows no further improvement, and for that, there will be no reason to go above that limit. The 3.5 mmol/min limit of EGP is still an acceptable physiological value for a patient with a very high EGP.

The question now is, what should we do after we increase EGP? And For how long should we keep it high? Based on the results achieved, there are 3 different scenarios to handle EGP and the identified constrained SI in the clinical application of the STAR protocol after adapting the new EGP estimation method:

1) Set back EGP to the initial value after 72-96h of treatment: As 70-83% of the occurrence situations happen in the first 72-96h, this scenario tends to be logical because once we identify a patient with an insulin resistance (constrained SI) it is more likely to happen more frequently and it will continue until the 4th day where up to 83% of the situations happens within this time interval.

2) Set back EGP to the initial value after 3-4h each time after increasing it: As 90-95% of the cases last between 1 and 3 hours, it is possible to set back the estimated EGP to the initial value, which is 1.16 once 3 hours passed. However, the downside of this scenario is that frequent random occurrences of the constrained SI may lead to an 'increase-set back-increase again' loop also we will always be missing the first occurrence as the identification starts right after having the new BG measurements.

3) Keep EGP high for the entire treatment period: We assume once we identify a patient with a constrained SI it is more likely that it will happen again, and this patient will have a high EGP level during the entire stay in the ICU, the downside of this choice is we may overestimate the EGP level, especially after patient state stabilizes.

Based on the 3 scenarios mentioned above, the most optimal and practical way to handle EGP estimation is to use a mix of approaches 1 and 2: If the constrained SI happens in the first days of treatment, we keep the increased EGP value until the 4th day of stay. If it happens after the 4th day, we set back the initial EGP values after 3 hours each time we increase it.

The first reason behind this choice is that we know patients have a higher EGP in their first days after ICU admission, so we want to increase our estimation only for those four first

days. After that period, if we keep our high estimated value, we may end up overestimating the EGP level. The second reason is that after the first four days, a patient may have some spikes in EGP, as we saw in Figure 2.1, so increasing and keeping it for 3 to 4 hours before setting back to the initial value seems to be also a good solution.

4.5 Conclusion

Understanding the relationship between hyperglycemia, insulin resistance, and high endogenous glucose production has a huge impact on model-based control and treatment in intensive care units. Underestimating the EGP in situations where patients are experiencing insulin resistance showed poor modeling results. The estimation of the right EGP level, it significantly improves the simulation outcomes and surpasses the model limitation. The next step was to design a practical way of implementing the new EGP estimation method on the STAR clinical application.

Based on results, up to 83% of these constrained SI episodes happen within the first 96h and up to 95% of them last for 3h. For this the most practical scenario to handle these situations is to keep the increased EGP until 4 days of treatment passed, after that if it happens again we may set back EGP to the initial value after 3h each time we increase it. In summary, the clinical implementation of the EGP estimation method presented can effectively capture and handle patients' EGP variability, improve the model outcomes, enhance glycemic control and create a space for further development.

Related publications of the results of Thesis 2 which are presented in this Chapter 4 are the following: [j2; c4] .

Insulin sensitivity and blood glucose levels in the first 24h

5.1 Introduction

The first 24 hours following a patient's admission to the intensive care unit (ICU) are crucial for managing glycemic control. During this period, patients exhibit variability in their medical condition and experience insulin resistance, leading to elevated blood glucose levels known as hyperglycemia. As a result, maintaining stable glycemic control becomes highly sensitive and challenging during the initial stages of ICU treatment.

In order to better understand and address this issue, we conducted an extensive analysis of patients' insulin sensitivity levels (SI), the variability in SI (Δ SI), and their blood glucose levels (BG) across three distinct cohorts. The primary objective of this research is to examine both inter and intra-differences in SI levels, SI variability, and BG levels during the early phase of treatment (within the first 24 hours of ICU admission) compared to the subsequent treatment period. Additionally, we aim to investigate the changes in SI as the treatment progresses to evaluate its potential impact on model-based glycemic control.

By undertaking this study, we aim to introduce the concept of implementing a tailored model-based control system specifically designed for the initial phase of patient treatment. This customized approach will effectively address the challenges posed by patients' hyperglycemia, insulin resistance, and state variability during this critical period. Implementing such a model-based control system has the potential to significantly enhance glycemic control outcomes and improve patient care during the early stages of ICU treatment.

5.2 Methods

5.2.1 Patient data

In this study, we used a total of 702 patients data, 216 patients from Malaysia Medical Centre, 408 patients from Zeeland, Christchurch Hospital, and 93 patients from Hungary, Kalman Pandy Hospital.

The selection criteria for patients were: glycemic control of more than 5 days and insulin administration at the beginning of the glycemic control. Diagnosed diabetic patients were excluded.

5.2.2 Analysis

We analyzed patient's inter and intra-cohort model-based insulin sensitivity simulated and identified using the ICING model, SI variability and the measured blood glucose levels from the recorded data across the 3 different cohorts. Si variability (Δ) represents the hour-to-hour SI change in % as shown in (5.1). Using a percentage rather than the absolute change normalizes the metrics as patients have different SI levels:

$$\Delta\%SI = 100 * (SI_{k+1} - SI_k)/SI_k \quad (5.1)$$

where SI_k is SI at the kth hour.

We compared SI values, Si variability (ΔSI) and BG values for all patients in the first 24 hours of treatment to the values in the rest of the treatment (after the first 24h). We used cumulative distribution functions (CDF) to assess the distribution of values in Figures 5.1,5.2 and 5.3 and the mean/median values in Tables 5.1,5.2 and 5.3 consecutively.

Then, we compared SI values, Si variability, BG values for all patients in the first 5 days of treatment and assessed the day-to-day differences and changes in values. We exclude patients with a treatment time record of less than 120 hours and we end up with 11 patients from Malaysia, 50 patients from New Zealand and 26 patients from Hungary.

We used the cumulative distribution function (CDF) to assess the distribution of values in Figures 5.2,5.3 and 5.4 and the mean/median values in Tables 5.2,5.3 and 5.5 consecutively.

We also analyzed episodes of Insulin resistance (IR) where $SI < 10^{-5}$ L/mU/min and episodes of hyperglycemia (HG) where $BG > 10$ mmol/l, values are in % and are reported in Tables 5.2,5.3,5.4.

The t-test was employed to analyze and validate the observed difference in SI, SI variability and BG between two distinct time periods. Specifically, the two-sample t-test (ttest2) function

in MATLAB was utilized to compare values obtained during the first 24 hours with those obtained after the initial time period.

5.3 Results

5.3.1 SI in the first 24h vs. the rest of the treatment

Table 5.1: SI values (L/mU/min) comparison in the first 24h vs. Rest of the treatment for the 3 cohorts

Stats	Cohorts					
	NZ		HU		MLS	
	First 24h	After 24h	First 24h	After 24h	First 24h	After 24h
MEAN	$3.06 \cdot 10^{-4}$	$3.84 \cdot 10^{-4}$	$3.51 \cdot 10^{-4}$	$4.64 \cdot 10^{-4}$	$2.83 \cdot 10^{-4}$	$2.97 \cdot 10^{-4}$
MEDIAN	$2.17 \cdot 10^{-4}$	$2.82 \cdot 10^{-4}$	$3.01 \cdot 10^{-4}$	$3.91 \cdot 10^{-4}$	$2.04 \cdot 10^{-4}$	$2.25 \cdot 10^{-4}$
P-value	$1.3322 \cdot 10^{-37}$		$7.1446 \cdot 10^{-41}$		0.056802	

Figure 5.1 shows the distribution of insulin sensitivity (SI) of all patients under the New Zealand, Hungarian and Malaysian cohort in the first 24h (Blue) compared to the SI in the rest of the treatment time (Red). Table 5.1 contains stats values of SI for the 3 different cohorts in the first 24h of treatment vs. after 24h.

Inter-cohort SI values are lower in the first 24h compared to the rest of the treatment. The differences were noticeable in the Hungarian and New Zealand cohorts with median values of $3.01 \cdot 10^{-4}$ and $2.17 \cdot 10^{-4}$ consecutively in the first 24h which are 23% lower compared to 3.91 and 2.82 after, but not for the Malaysian cohort where the difference is small 10% between $2.04 \cdot 10^{-4}$ and $2.25 \cdot 10^{-4}$.

Given that the p-value is very small in the Hungarian and New Zealand cohorts $1.3322 \cdot 10^{-37}$ and $7.1446 \cdot 10^{-41}$, it provides strong evidence to reject the null hypothesis while it's not the case in the Malaysian cohorts with P-value >5%.

Intra-cohort Si values also vary, with the Malaysian cohort having the lowest SI values and the Hungarian cohort being the highest with a 33% difference between the two.

5.3.2 SI variability in the first 24h vs. the rest of the treatment

Figure 5.2 shows the distribution of SI variability (ΔSI) in % of all patients under the New Zealand, Hungarian and Malaysian cohort in the first 24h (Blue) compared to the SI in the rest of the treatment time (Red). Table 5.2 contains mean/median values of SI variability for the 3 different cohorts in the first 24h of treatment vs. after 24h.

5. INSULIN SENSITIVITY AND BLOOD GLUCOSE LEVELS IN THE FIRST 24H

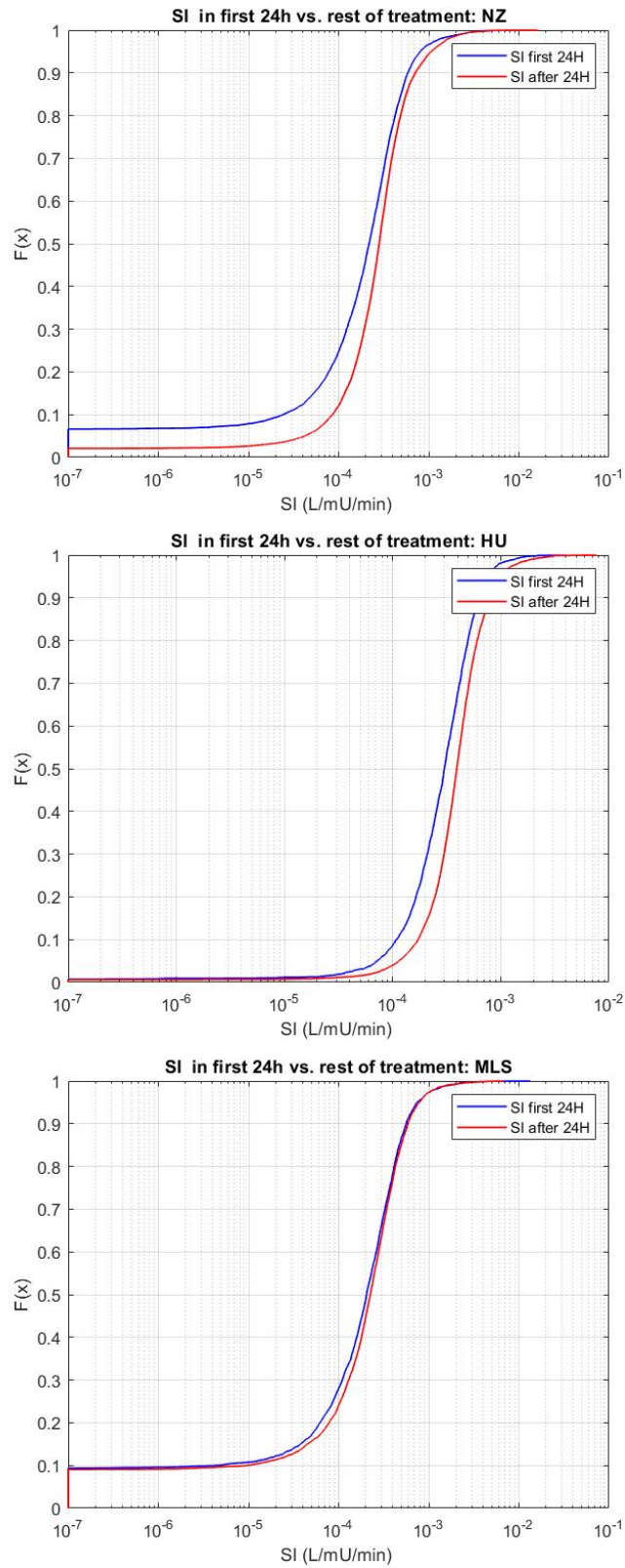


Figure 5.1: CDF of SI values in the first 24h compared to SI in the rest of the treatment for the 3 cohorts

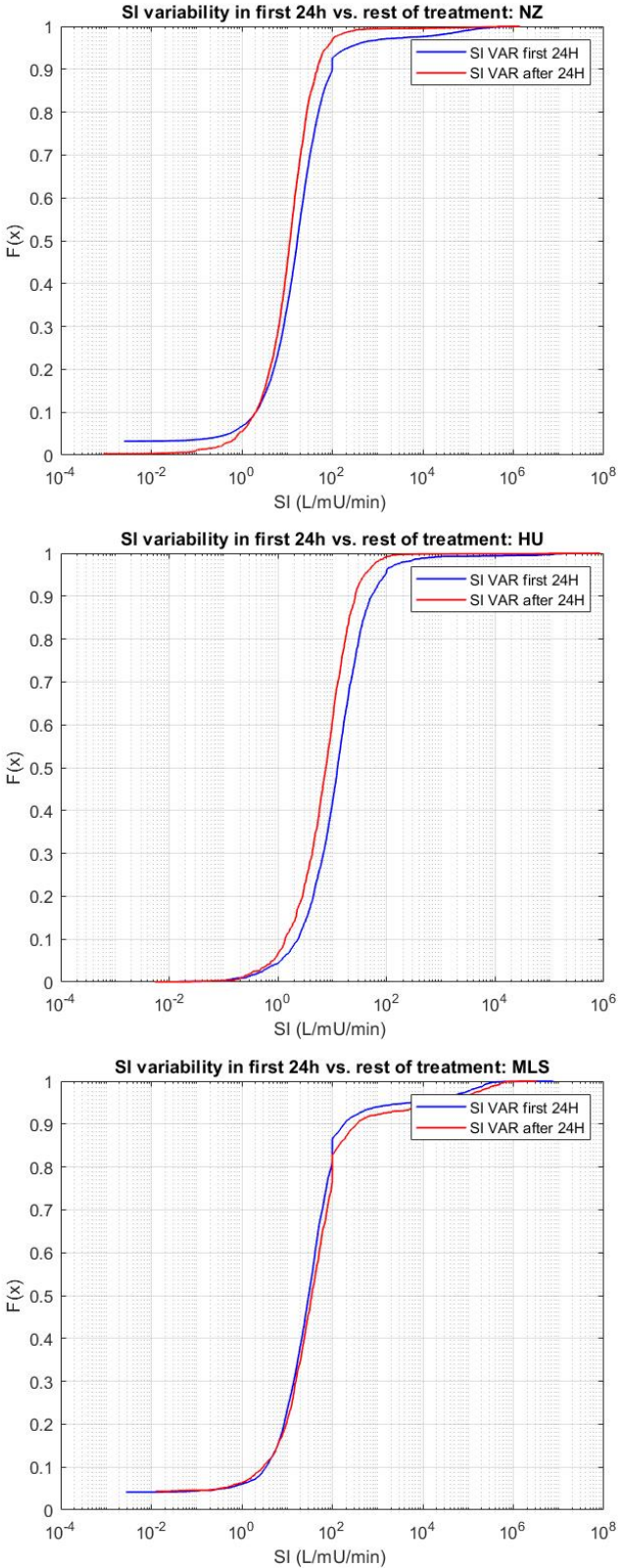


Figure 5.2: CDF of SI variability (ΔSI) values in the first 24h compared to SI in the rest of the treatment for the 3 cohorts

Table 5.2: SI variability values comparison Δsi in the first 24h vs. Rest of the treatment for the 3 cohorts

Stats	Cohorts					
	NZ		HU		MLS	
	First 24h	After 24h	First 24h	After 24h	First 24h	After 24h
MEAN	3.30%	9.50%	8.24%	2.14%	8.67%	1.27%
MEDIAN	16.8%	11.61%	12.46%	7.62%	30.17%	35.06%
P-value	$1.0832 \cdot 10^{-30}$		$5.4687 \cdot 10^{-4}$		$4.2542 \cdot 10^{-4}$	

Inter-cohort SI variability is higher in the first 24h compared to the rest of the treatment. The differences are 5% in terms of median values across all cohorts. Given that the p-value is very small in the 3 cohorts, it provides strong evidence to reject the null hypothesis.

Intra-cohort Si variability values also vary, with the Malaysian cohort having the highest SI median variability up to 35% and the Hungarian cohort being the lowest with a median value of 7.62%.

5.3.3 BG in the first 24h vs. rest of the treatment

Table 5.3: BG values comparison in the first 24h vs. rest of the treatment for the 3 cohorts

Stats	Cohorts					
	NZ		HU		MLS	
	First 24h	After 24h	First 24h	After 24h	First 24h	After 24h
MEAN	8.34	7.72	8.09	7.28	9.61	9.07
MEDIAN	7.80	7.40	7.60	6.90	9	8.70
P-value	$2.3527 \cdot 10^{-50}$		$1.1532 \cdot 10^{-29}$		$1.9878 \cdot 10^{-12}$	

Figure 5.3 shows the distribution of blood glucose measurements (BG) of all patients under the New Zealand, Hungarian and Malaysian cohort in the first 24h compared to the BG in the rest of the treatment time. Table 5.3 contains mean/median values of BG for the 3 different cohorts in the first 24h of treatment vs. after 24h.

Inter-cohort BG values are higher in the first 24h compared to the rest of the treatment. The differences were not significant in terms of absolute median values, which are 0.3-0.7 mmol/l in Table 5.3. However, the notifiable differences are in higher BG levels >10mmol/l, as it can be seen in Figure 5.3. Given that the p-value is very small in the 3 cohorts, it provides strong evidence to reject the null hypothesis.

Intra-cohort BG values also vary, with the Malaysian cohort having the highest median BG value (9/8.7 mmol/l) and the Hungarian cohort being the lowest (7.6/6.9 mmol/l).

5.3.4 Evolution of Insulin sensitivity in first 5 days of treatment

Table 5.4: Insulin sensitivity comparison in the first 24h vs. rest of the treatment for the 3 cohorts. %IR is the rate of insulin resistance hours episodes

Time period /Stats	Cohorts					
	NZ		HU		MLS	
	Mean	% IR	Mean	% IR	Mean	% IR
First 24h	$2.73 \cdot 10^{-4}$	4	$3.29 \cdot 10^{-4}$	1	$2.13 \cdot 10^{-4}$	15
24-48h	$3.33 \cdot 10^{-4}$	2	$3.56 \cdot 10^{-4}$	0	$3.04 \cdot 10^{-4}$	12
48-72h	$2.84 \cdot 10^{-4}$	3	$4.16 \cdot 10^{-4}$	1	$3.72 \cdot 10^{-4}$	12
72-96h	$3.20 \cdot 10^{-4}$	2	$3.62 \cdot 10^{-4}$	0	$2.48 \cdot 10^{-4}$	10
96-120h	$3.65 \cdot 10^{-4}$	1	$4.71 \cdot 10^{-4}$	1	$2.79 \cdot 10^{-4}$	7

Figure 5.4 shows the cumulative distribution function of insulin sensitivity (SI) of all patients under the New Zealand, Hungarian and Malaysian cohorts in the first 5 successive treatment days.

Based on SI daily mean values reported in Table 5.4, the lowest value was at the first 24h compared to the next four days of the treatment in all the three different cohorts, as low as $2.13 \cdot 10^{-4}$ in the MLS cohort, $2.73 \cdot 10^{-4}$ in the NZ cohort and $3.29 \cdot 10^{-4}$ in the HU cohort. The mean values start low and go up on the 2nd day in all cohorts. We also noticed a drop in SI mean values in the 3rd/4th days before they went up again the next day.

Episodes of insulin resistance (%IR) are higher in the first 24h compared to the four successive days. The Hungarian cohort has the lowest insulin resistance episodes of 1.07%, and the Malaysian cohort has the highest of 15.27%.

5.3.5 Evolution of Insulin sensitivity variability in first 5 days of treatment

Figure 5.5 shows the distribution of insulin sensitivity (SI) variability (ΔSI) in % of all patients under the New Zealand, Hungarian and Malaysian cohorts in the first 5 days of treatment days. Table 5.5 shows mean values of ΔSI for the first 5 days of treatment.

Based on ΔSI CDF and the daily mean values reported in Table 5.5, Values start at the highest value in the first 24 hours and it continues to drop for the following days, except for the Hungarian and Malaysian cohort, there was a sudden increase in the variability in the 5th day.

5.3.6 Evolution of blood glucose BG in first 5 days of treatment

Figure 5.6 shows the cumulative distribution function of Blood glucose (BG) of all patients under the New Zealand, Hungarian and Malaysian cohorts in the first 24h compared to SI in the four successive treatment days.

Table 5.5: Si variability Δ SI values comparison between the first five days of treatment for the 3 cohorts

Time period /Stats	Cohorts		
	NZ	HU	MLS
	Mean	Mean	Mean
First 24h	15%	11%	45%
24-48h	14%	8%	34%
48-72h	14%	10%	38%
72-96h	11%	9%	25%
96-120h	11%	11%	28%

Table 5.6: Blood glucose values comparison between the first five days of treatment for the 3 cohorts. %HG is the rate of Hyperglycemia hours episodes

Time period /Stats	Cohorts					
	NZ		HU		MLS	
	Mean	%HG	Mean	%HG	Mean	%HG
First 24h	8.68	24	7.82	14	10.20	45
24-48h	8.12	17	6.96	1	8.82	31
48-72h	7.99	16	7.00	5	8.71	35
72-96h	8	18	6.91	2	9.19	34
96-120h	7.64	12	7.16	7	8.83	32

Based on BG daily mean values reported in Table 5.6, the highest BG mean value was at the first 24h compared to the next four days of the treatment in all the three different cohorts, as high as 10.20 mmol/l in the MLS cohort. BG values drop by 6.5-13.5% on the 2nd day in all cohorts.

Episodes of hyperglycemia (%HG) are higher in the first 24h compared to the four successive days. The Malaysian cohort has the highest hyperglycemia episodes of almost half of the measurements (45.23%), and the Hungarian cohort has the lowest episodes with 14%.

5.4 Discussion

From the distribution of insulin sensitivity levels, SI variability and BG measurements for all 3 cohorts, there were noticeable differences between the first 24h and the successive days until the end of the treatment where the lowest SI values and the highest SI variability and BG values were always in the first 24h also the proportion of hours of insulin resistance and hyperglycemia. The Hungarian cohort had the highest SI and lowest SI variability/ BG but also had far fewer hours, and thus there may be a bias.

Early occurrence of insulin resistance and hyperglycemia episodes is likely due to the surge in EGP seen particularly in severe sepsis and septic shock patients in the first 12-24 hours of

the stay. This behavior matches clinical expectations and is due to stress, often seen in the first 24 hours of stay, particularly in severe sepsis and septic shock patients, all of which match the metabolic variability seen in the first 24h of stay. The low improving insulin sensitivity during patient treatment is likely due to the decline of counter-regulatory hormones as the acute phase of critical illness passes. Thus, this phenomenon occurs qualitatively matches broad clinical expectations.

Considering the analysis of the treatment difference, the CHO intake of the Hungarian cohort was significantly higher. On the other hand, the Malaysian cohort had the lowest SI and highest BG levels. These differences may also reflect cohort differences in the incidence of greater complexity and level of critical illness, such as incidence of severe sepsis, in some cohorts, which can occur from the areas and types of patients treated, as well as from treatment selection or treatment failure bias.

In the analysis of the first 5 days of treatment, we excluded patients with records less than 120 hours, this resulted in smaller cohorts and a reduction of 72-95% reduction in size, and only 5-28% of patients have a treatment time greater than 120 hours, this also may affect the results.

It's clear that the first 24h of patients ICU stay is crucial and difficult to manage and by implementing a customized model-based control designed explicitly for the early phase of patient treatment, exactly the first 24h that can potentially handle patients' variability, hyperglycemia, and insulin resistance episodes. Implementations that can be adopted are: higher glycemic target band, more frequent measurements, more modulated insulin/nutrition intakes and higher parameter estimation such as EGP. These beneficial impacts may arise for STAR or any other model-based protocol from improved predictions and thus more accurate GC during treatment for early-stage treatments.

5.5 Conclusion

Patients in the early stages of ICU have highly variable health state, low insulin sensitivity, and high blood glucose levels, as expected, given the stress response physiology. Results align with the clinical expectations were the lowest insulin sensitivity values and the highest variability and blood glucose levels tend to be in the first 24h in all cohorts.

Given the results, this study initiates the idea of implementing a customized model-based control designed explicitly for the early phase of patient treatment, exactly the first 24h that can effectively handle patients' variability, hyperglycemia, and insulin resistance. Implementations such as higher glycemic target band, frequent measurements, and more modulated insulin/nutrition intakes. Enhanced estimations resulting in more precise glycemic control (GC) during early-stage treatments can lead to positive outcomes not only for the STAR model but also for other model-based protocols.

Related publications of the results of Thesis 3 which are presented in this Chapter 5 are the following: [e6; e7; e9; e5] .

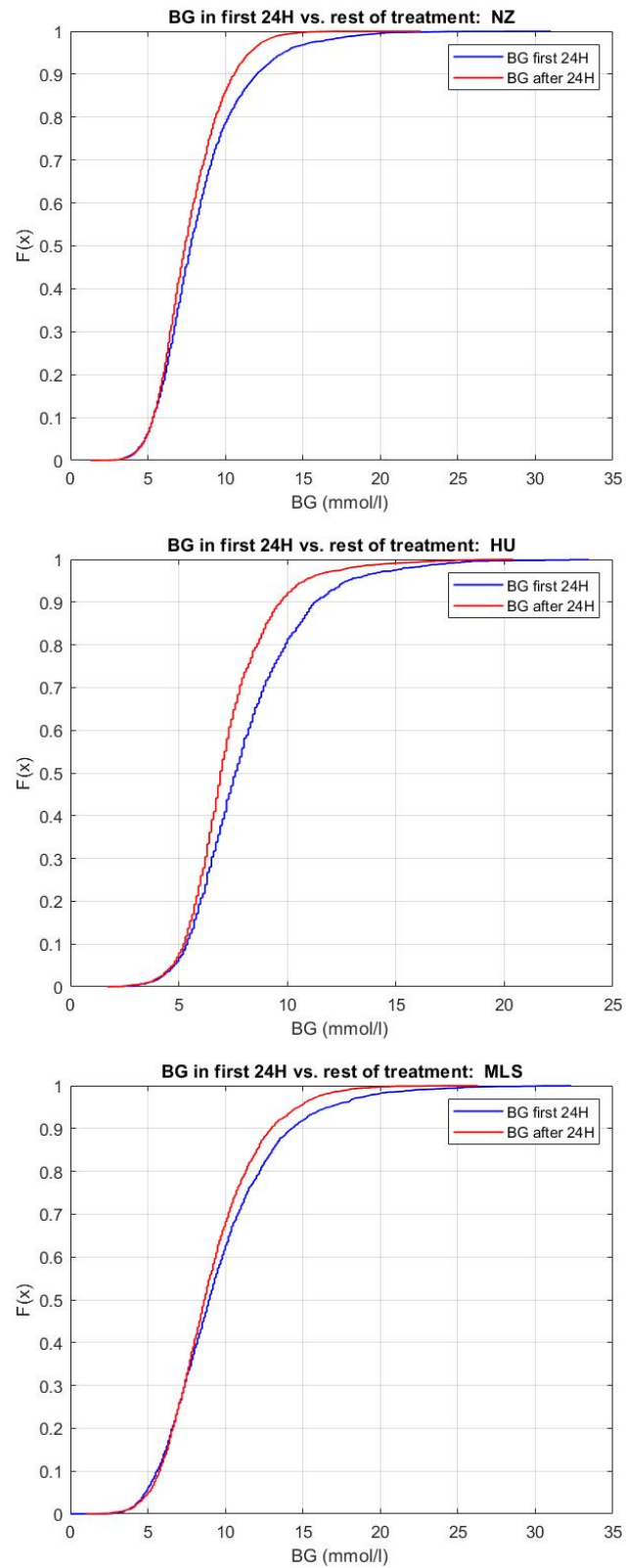


Figure 5.3: CDF of BG values in the first 24h compared to the rest of the treatment for the 3 cohorts

5. INSULIN SENSITIVITY AND BLOOD GLUCOSE LEVELS IN THE FIRST 24H

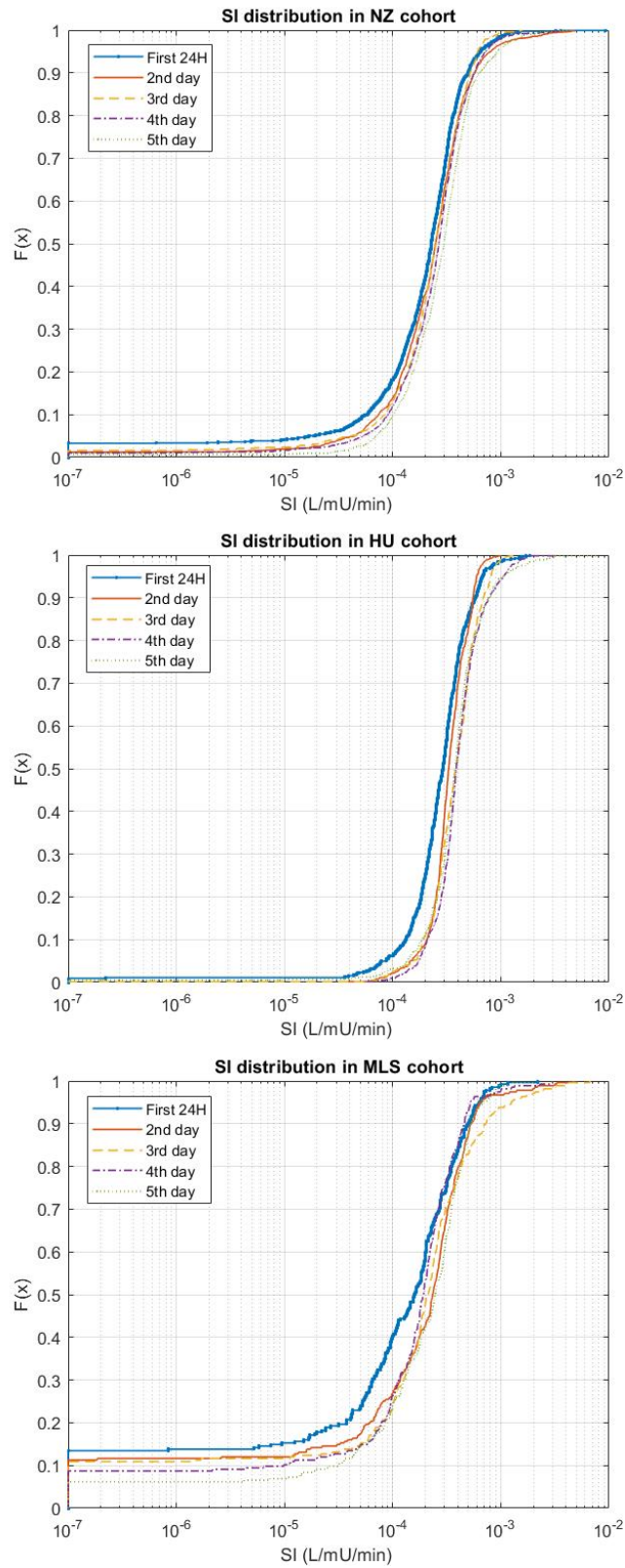
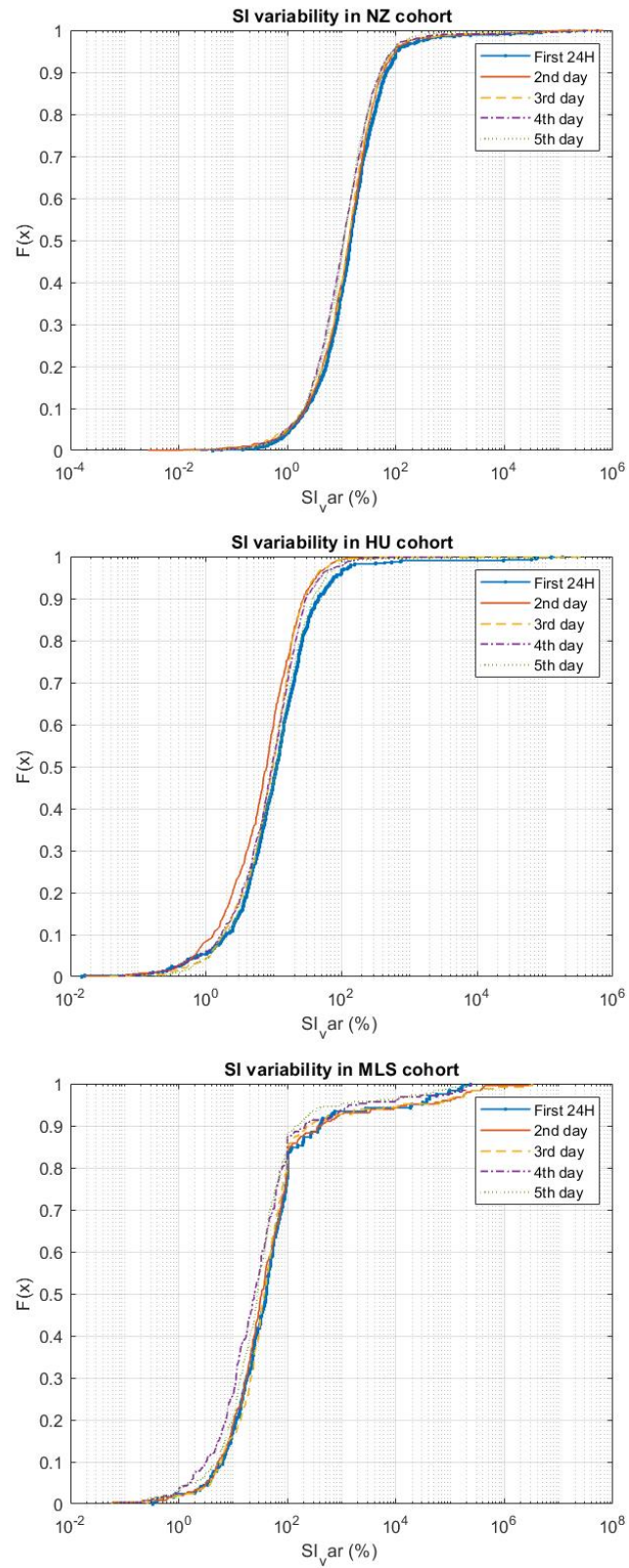


Figure 5.4: CDF SI values in the first 24h compared to the next four days for all cohorts

Figure 5.5: CDF of SI variability ΔSI for the first 5 days of treatment

5. INSULIN SENSITIVITY AND BLOOD GLUCOSE LEVELS IN THE FIRST 24H

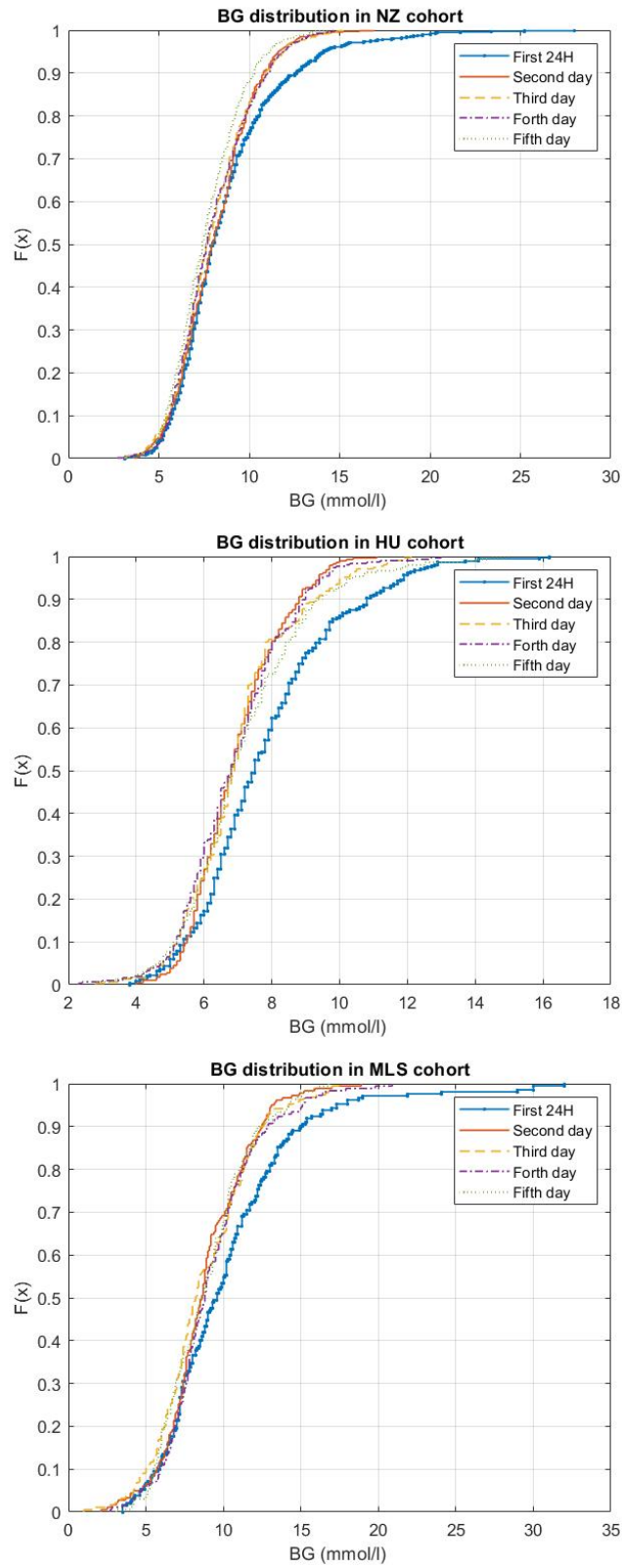


Figure 5.6: CDF of BG in the first 5 days of treatment

Stochastic ICING

6.1 Introduction

Most of the published models of human glucose-insulin system are deterministic ones, i.e., ordinary differential equations models which used to describe the physiological processes. These kinds of models are known as imperfect in the sense that modeling the uncertainty, system noise, and the stochastic nature of the physiological system are not taken into consideration [GPF11].

Intensive Care Insulin-Nutrition-Glucose (ICING) is one of the deterministic models that uses ordinary differential equations. This highly sophisticated model is used in model-based glycemic control for critically ill patients under the Stochastic TARgeted (STAR) protocol [Lin+11b; Eva+12; Fis+12].

In the STAR glycaemic control protocol the ICING model parameters are fixed to a cohort-based constant value except for the insulin sensitivity (SI) parameter [Eva+12]. As a result of this parameter setting SI will represent the ‘whole body’ metabolic state condition as a single parameter. The identification of the SI was achieved via an integral-based method. In this way all the dynamic errors were lumped into the SI profile which frequently caused high variability in the SI profiles and indirectly in the blood glucose levels. To solve this problem and try to regularize the SI profile, an additional stochastic term was suggested in the glucose equation, which can capture the unmodulated dynamics and measurement noise [Eva+12].

Palancz et al in [Pal+16] investigated the stochastic Ito version of the ICING model (ICING SDE) equations with parametric stochastic noise term. The computation of the system trajectories and their statistical futures were carried out using Runge-Kutta method with Wiener-type diffusion process term. Parameter estimation is achieved via the maximum likelihood technique. This type of stochastic model allows not only the characterization of the noise integrated into the stochastic term but also enables the reduction of the modeling error.

In this analysis study, the accuracy of the new stochastic version of ICING model was examined to assess its potential use and implementation in the STAR protocol. The modeling error was calculated and compared with the original version of the model (ICING) with a clinical data set collected during the treatment of 60 patients from three different ICU's in Belgium, Hungary, and New Zealand.

6.2 Methods

6.2.1 ICING model stochastic extension

In the stochastic version of the ICING model (ICING SDE) an additional stochastic term was suggested in the glucose equation incorporating a stochastic behavior of the human metabolic system, like modeling error, unmodulated dynamics, and system noise, etc. [Pal+16].

ICING SDE can be considered as an extension of the ICING model by introducing a system noise in the form of Wiener processes in Equation (6.1):

$$\begin{aligned} dG(t) = & - \left(p_G G(t) + S_I(t) G(t) \frac{Q(t)}{1 + \alpha_G Q(t)} \right) dt \\ & + \left(\frac{P(t) + EGP - CNS}{V_G} \right) dt + \sigma(t) dW(t) \end{aligned} \quad (6.1)$$

where $\sigma(t)$ is the diffusion term depending on time and $W(t)$ is a Wiener process, also known as Brownian motion, a continuous-time random walk, practically an integrated white noise process:

$$\frac{dW}{dt}(t) = \mathcal{N}(t). \quad (6.2)$$

6.2.2 Patient data/cohorts

The clinical data used in this study were collected from three independent cohorts of 60 critically ill patients. Patients are from 3 different ICUs: Belgium, Hungary, and New Zealand with 20 patients from each hospital.

6.2.3 Identification of SI and stochastic term with ICING SDE

ICING SDE can generate unlimited numbers of blood glucose trajectories for a given SI(t) profile. Thus, it is more difficult to estimate the model parameters based on experimental observations which represent only one trajectory of the stochastic model. For this maximum likelihood estimation (MLE) method was used to identify SI and $\sigma(t)$ [Pal+16].

$SI(t)$ and $\sigma(t)$ were considered as step-wise functions that are constant in each half-hourly interval. The parameter estimation was achieved on the basis of the linear approximation of the not equidistant blood glucose measurements. The total treatment time has been divided into half-hourly sections $\delta(i)$ and in every section, a new insulin sensitivity value $SI(i)$ and diffusion term value $\sigma(i)$ were estimated. The identification method in detail with the equations can be found in [Pal+16].

6.2.4 Virtual trial (simulation)

Also known as in-silico simulation, virtual trials are a stage where in-silico protocols performance can be verified before clinical testing. Numerical simulations of both models with the estimated parameter profiles and the virtual patient data were carried out using an ordinary differential equation solver for ICING and Runge-Kutta method for ICING SDE with a fixed step size of one minute.

During the simulation in the case of ICING SDE the number of the realizations of the stochastic trajectories varied between 100 and 500. The analysis considers the mean of the simulated trajectories.

6.2.5 Error analysis/comparison

Performance was defined as fitting errors between the simulated BG outputs for both models and the real blood glucose measurement in the clinical data. The relative error was calculated in order to consider the over/underestimation of BG levels for both models and the absolute error to measure the size of the error. In order to have an extended analysis of the error, the median and the interquartile range (IQR) of the model error were also calculated.

6.3 Results

6.3.1 Identification result of SI profile and sigma

As mentioned in the previous section, SI identification is the first step in forming a virtual patient. The $\sigma(t)$ profiles are also identified for the ICING SDE model. The result of the identification of a typical patient is shown in Figure 6.1 and Figure 6.2.

6.3.2 BG outputs

After the patient's parameter identification phase has been completed, the next step is to simulate the blood glucose (BG) values using the two models, referred to as the ICING model and the ICING SDE model. This simulation will be conducted on a total of 20 patients, with each patient undergoing two simulations.

The purpose of this simulation is to generate two BG trajectories for each patient, one for each model. These trajectories can then be plotted as time series functions and compared

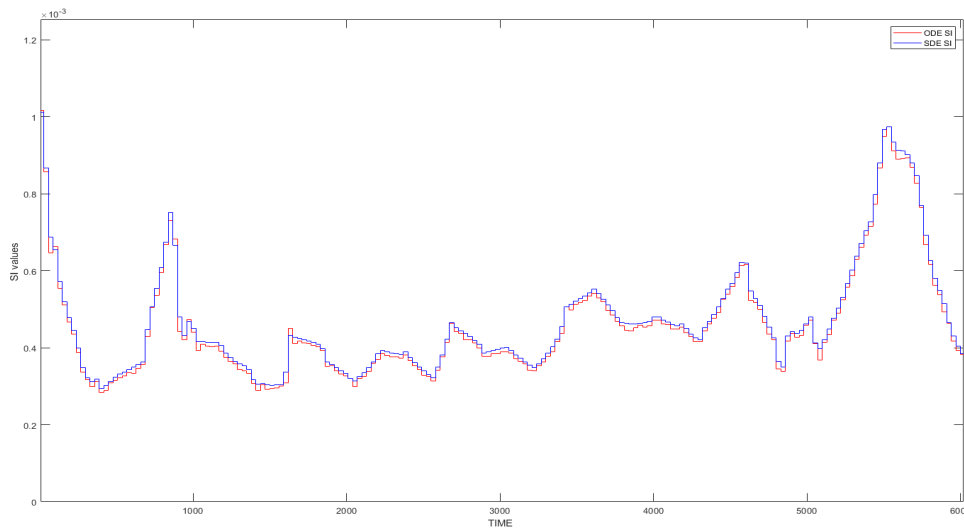


Figure 6.1: Stepwise time series function of the identified SI by ICING (blue) vs. ICING SDE (red)

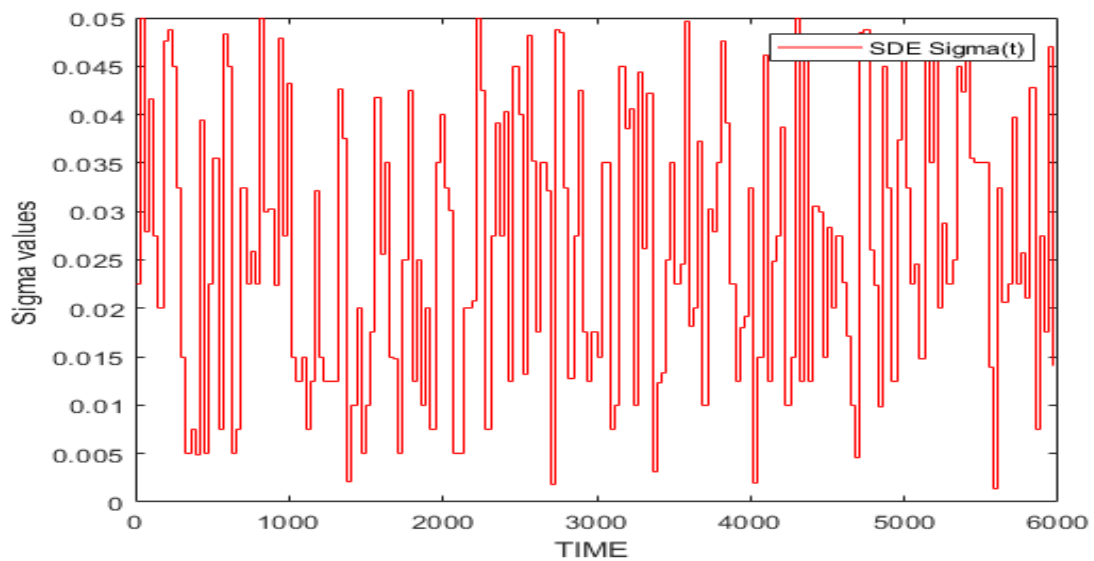


Figure 6.2: Stepwise time series function of the identified $\sigma(t)$ by ICINC SDE

to the real BG values obtained from clinical data. By visually analyzing these plots, we can identify any similarities and differences between the predicted BG levels and the actual BG levels. This comparison is useful in evaluating the accuracy and reliability of the two models in predicting BG levels in patients.

An example of this plot for a single patient is shown in Figure 6.3. It is important to note that this analysis is conducted on a representative sample of patients, and the results may not necessarily be applicable to all individuals. However, this analysis can provide valuable insights into the performance of the ICING and ICING SDE models and inform future research in this field.

The average simulation run-time for one patient with an average of 120 treatment hours for the original ICING is 7-13 seconds. The simulation run-time for SDE were not measured, but the fact that the SDE has to generate 100-500 BG trajectories at each hour point makes it significantly time and resource intensive.

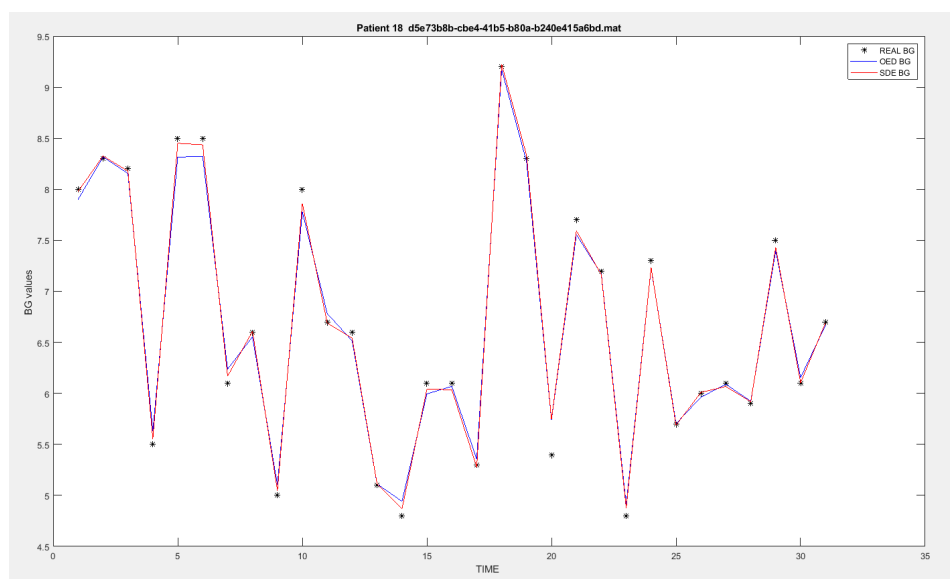


Figure 6.3: The mean of trajectories of ICING SDE (red) vs. the trajectory of ICING (blue) with the measurements points

6.3.3 Error calculation/comparison

To better understand the accuracy of the observational results, it is important to convert them into a numerical evaluation. One way to do this is to calculate the relative and absolute errors. This allows for a more objective analysis of the data and enables the identification of the model with a lower modeling error. Additionally, this numerical evaluation can inform clinical treatment decisions and potentially lead to improvements in patient care.

The relative error is a useful metric for examining the extent to which the BG levels are underestimated or overestimated. This is important because deviations from the true BG levels can result in hyperglycemia or hypoglycemia in the clinical application of the models. By analyzing the relative error at each measurement point, as shown in Figure 6.4 for a representative patient, we can gain insights into the performance of the models and identify areas for improvement.

Overall, the calculation of relative and absolute errors provides valuable information for evaluating the accuracy of the models and informing future research in this field.

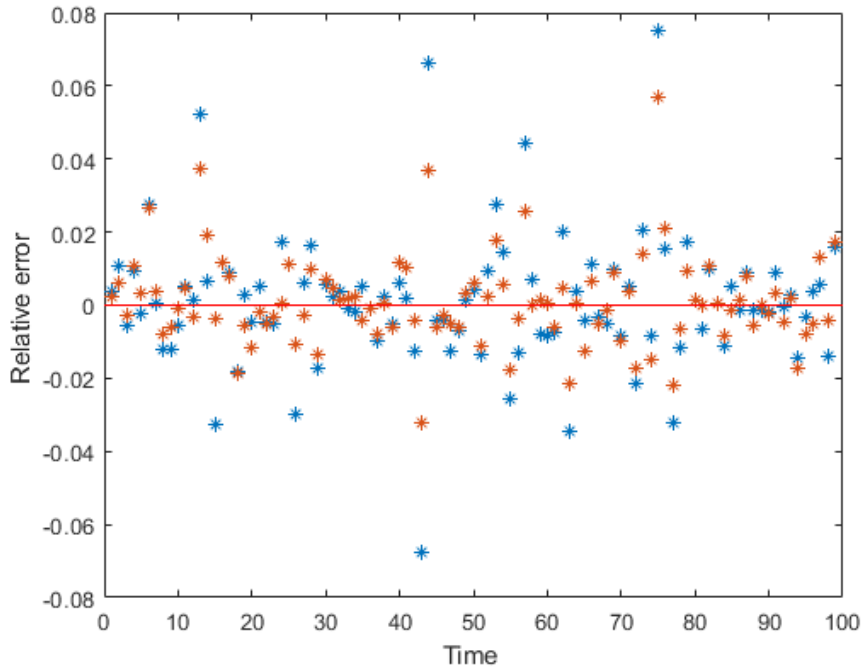


Figure 6.4: The relative error of ICING (blue) vs. ICING SDE (red) for one selected patient

To further assess the accuracy of the models, the absolute error for both models was compared across all three simulations for the 20 patients at each measurement point (corresponding to the real BG values). The percentage of times that each model had a smaller error (i.e., a better estimation) was then calculated. These results are summarized in Table 6.1. This analysis allows for a direct comparison of the performance of the two models and helps to determine which model is more accurate overall.

6.4 Discussion

Insulin sensitivity (SI) is a crucial parameter that reflects the state of a patient. In order to evaluate the performance of the ICING and ICING SDE models, we conducted a series of experiments to assess their ability to accurately capture changes in SI.

Figure 6.1 shows an example of the SI functions obtained using the two models and their respective identification methods (integral-based versus likelihood method). It is clear that the two SI functions are very similar to each other, which was consistently observed in all patients across the three different cohort simulations. This demonstrates that the two identification methods yield similar physiological parameters and accurately describe the patient's state, with only slight differences observed.

Table 6.1: The absolute error comparison of SDE vs. ODE for entire 3 cohorts in %

Cohorts ICING version	BE		HU		NZ	
	ODE	SDE	ODE	SDE	ODE	SDE
P1(B/H/NZ)	33	67	35	65	42	58
P2(B/H/NZ)	48	52	32	68	33	67
P3(B/H/NZ)	41	59	44	56	47	53
P4(B/H/NZ)	40	60	26	74	36	64
P5(B/H/NZ)	39	61	32	68	20	80
P6(B/H/NZ)	45	55	40	60	50	50
P7(B/H/NZ)	41	59	13	87	21	79
P8(B/H/NZ)	50	50	26	74	31	69
P9(B/H/NZ)	64	36	25	75	26	74
P10(B/H/NZ)	45	55	29	71	36	64
P11(B/H/NZ)	41	59	35	65	41	59
P12(B/H/NZ)	46	54	15	85	42	58
P13(B/H/NZ)	47	53	29	71	35	65
P14(B/H/NZ)	33	67	42	58	31	69
P15(B/H/NZ)	38	62	43	57	63	37
P16(B/H/NZ)	26	74	31	69	37	63
P17(B/H/NZ)	46	54	36	64	44	56
P18(B/H/NZ)	25	75	26	74	42	58
P19(B/H/NZ)	20	80	24	76	25	75
P20(B/H/NZ)	40	60	28	72	35	65
Average:	40%	60%	31%	69%	37%	63%

Overall, these results support the conclusion that the ICING and ICING SDE models are reliable for capturing changes in SI and accurately describing the patient's state. This information is valuable for informing clinical treatment decisions and improving patient care.

The simulation phase generated two BG trajectories, which enabled the evaluation of the accuracy of both models and the comparison of the simulated outputs to the real BG values obtained from clinical data. The modeling error was calculated as the difference between the simulated and measured BG values. Figure 6.3 presents the time series of the BG trajectory produced by the ODE model and the mean of the SDE trajectories, along with the real BG measurement points. It is evident that the ICING SDE model is more flexible in closely approximating the real measurement points compared to the ICING model.

From a physiological perspective, it is important to determine whether the model-predicted BG values tend to underestimate or overestimate the actual BG values. This is because deviations from the true BG levels, particularly hypoglycemia, can have serious consequences for patient treatment within a short period of time.

Figure 6.4 supports the observations made in Figure 6.3 and shows that the ICING SDE model

has a slightly smaller relative error than the ICING model in both cases of BG value underestimation and overestimation, particularly in highly variable patient states (where the modeling error is high).

Table 6.1 presents the results of a comparison of the absolute error at each real BG measurement point and the percentage of times that each model had a smaller error at that particular measurement. These results indicate that the SDE model was more precise and had a smaller modeling error than the ICING model in 93% of the patients, with an average rate of 64%.

While the above analysis suggests that the ICING SDE model may be more accurate at predicting BG levels in most patients, the difference in accuracy is not significant enough to potentially impact treatment decisions and clinical outcomes. Additionally, it is important to consider that the ICING SDE model is more resource and time intensive, requiring the generation of 100-500 BG stochastic trajectories when simulating BG levels. This puts it at a disadvantage compared to the original ICING model in the clinical application, where the original ICING model only generates one deterministic BG trajectory.

Given these factors, it is not yet advisable to replace the original ICING model with the ICING SDE model. The trade-off between the small improvement in modeling accuracy and the increased complexity and resource requirements may not necessarily result in improved treatment outcomes. Further research is needed to fully assess the potential benefits and drawbacks of the ICING SDE model.

6.5 Conclusion

The goal of this work was to analyze the stochastic ICING model, an extension of the original ordinary differential equation-based ICING model using a large clinical data set. The patient records were collected from three geographically distinct cohorts treated in Belgium, Hungary, and New Zealand.

The modeling error was calculated by creating virtual patients at first and then using in-silico simulation where the blood glucose trajectories simulated by the two versions of the ICING model were compared to the real measurements.

The results indicate that the ICING SDE model exhibits slightly lower modeling error compared to the original ICING model. However, the impact on treatment quality is not significant enough to justify the increased computational demands and complexity of the stochastic modeling approach. Therefore, we conclude that further improvements and research are necessary before the ICING SDE can be considered a viable replacement for the ICING model.

Related publications of the results of Thesis 4 which are presented in this Chapter 6 are the following: [e5; e11].

Summary of the Research Results

7.1 Estimating enhanced EGP

Underestimating the patient's endogenous glucose production (EGP) level where insulin sensitivity (SI) is close to the minimum value - which means the patient is experiencing an insulin resistance situation - can cause bias in the identified SI value, which can limit the accuracy of ICING model and potentially reduce the quality of GC treatment recommendation.

According to the study presented, these cases where SI is constrained to a low minimum value, numbering 1-10% of possible hours and 23-63% of total patients in the three cohorts: Malaysian, New Zealand and Hungarian. 24-50% of these cases occur in the first 24 hours and 60-75% occur within in the first 72 hours.

In those treatment periods where constrained SI is found in the patient records the EGP value is estimated by a method proposed in Chapter 3. 80% of the new estimated EGP values range was between 1.25-2 mmol/min, where fewer differences were seen in the rest 20% of higher range (2-3.5 mmol/min).

Estimating higher EGP significantly improved blood glucose fit to measured data and modeling accuracy, reducing the fitting error by 90% .

A further major result of this study, beyond the method presented, is the quantification of the potentially very wide range of EGP values in ICU patients, which may slightly exceed prior reports, and remain to be prospectively verified.

7.2 The new EGP estimation method's clinical applications

Understanding the relationship between hyperglycemia, insulin resistance, and high endogenous glucose production is of great importance in model-based control and treatment of pa-

tients in intensive care units (ICUs). Previous models have often underestimated endogenous glucose production (EGP) in situations where patients are experiencing insulin resistance, leading to poor modeling results and suboptimal glycemic control. Accurate estimation of EGP is crucial for improving outcomes and overcoming model limitations. In this study, we aimed to design a practical way for implementing the new EGP estimation approach (proposed in Chapter 3) in the STAR clinical application.

To evaluate the feasibility of the proposed method, we analyzed data from patients in the ICU who were experiencing insulin resistance. Our results showed that 96% of constrained insulin sensitivity (SI) episodes occurred within the first 96 hours of treatment and 95% lasted for 3 hours. Based on these findings, we determined that the most practical scenario for handling these situations is to maintain increased EGP for the first 4 days of treatment, and then reset EGP to the initial value after 3 hours each time it is increased if necessary.

The first reason behind this choice is that we know patients have a higher EGP in their first days after ICU admission, so we want to increase our estimation only for those four first days. After that period, if we keep our high estimated value, we may end up overestimating the EGP level. The second reason is that after the first four days, a patient may have some spikes in EGP, so increasing and keeping it high for 3 to 4 hours seems to be also a good solution.

The clinical implementation of the proposed EGP estimation method has the potential to effectively capture and manage patients' EGP variability, improve model outcomes, and enhance glycemic control. In addition, this approach provides a foundation for further development and refinement of model-based glycemic control in the ICU setting. Future research could include the investigation of the long-term effects of the proposed method on patient outcomes, as well as the development of additional strategies for accurately estimating EGP in patients with insulin resistance.

7.3 Insulin resistance and hyperglycemia in the first 24 hours of model-based glycemic treatment

Patients in the early stages of intensive care unit (ICU) treatment often have a highly variable health state, low insulin sensitivity, and high blood glucose levels, as expected due to the physiological stress response. Our results align with clinical expectations, showing that the lowest insulin sensitivity values and the highest SI variability and blood glucose levels tend to occur in the first 24 hours in all patient cohorts.

Based on these findings, we propose the idea of implementing a customized model-based control approach specifically designed for the early phase of patient treatment, specifically the first 24 hours. This approach could effectively handle patients' variability, hyperglycemia, and insulin resistance through strategies such as a higher glycemic target band, more frequent measurements, and more modulated insulin and nutrition intake. These benefits may

arise from improved predictions and more accurate glycemic control (GC) during early-stage treatment for protocols such as STAR or other model-based approaches.

Given the significant impact of hyperglycemia, insulin resistance, and EGP on model-based control and treatment in the ICU, it is important to optimize the management of these factors during the early stages of treatment. By implementing a customized model-based control approach specifically designed for the first 24 hours of treatment, we can effectively address the high levels of variability, insulin resistance, and hyperglycemia that are commonly observed in this time period. This approach has the potential to improve patient outcomes and enhance the overall effectiveness of model-based control in the ICU setting.

7.4 New stochastic version of ICING

We assessed the accuracy and reliability of the stochastic ICING model, an extension of the original ICING model based on ordinary differential equations, using a large clinical data set collected from three geographically distinct patient cohorts treated in Belgium, Hungary, and New Zealand. To evaluate the performance of the models, we conducted in-silico simulations by creating virtual patients and comparing the blood glucose trajectories simulated by the two versions of the ICING model to the real measurements.

The results of this analysis showed that the ICING SDE model had slightly lower modeling errors compared to the original ICING model. While this finding suggests that the ICING SDE model may be a more accurate tool for predicting blood glucose levels in some cases, the difference in accuracy was not significant enough to significantly impact treatment decisions and clinical outcomes.

Additionally, it is important to consider the increased computational demands and complexity of the stochastic modeling approach, which may not be justified given the relatively small improvement in modeling accuracy. Therefore, we conclude that further research and improvements are needed before the ICING SDE model can be considered a viable replacement for the original ICING model.

Publications

Number of publications:	11
Number of peer-reviewed journal papers (written in English):	3
Number of articles in journals indexed by WoS or Scopus:	3
Number of publications (in English) with at least 50% contribution of the author:	2
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Number of peer-reviewed publications:	3
Number of independent citations:	9

Publications Linked to the Theses

	Journal papers	International conference and workshop papers	Local conference and workshop papers
Thesis 1	[j1]*	[c4]*	—
Thesis 2	[j1]*, [j2]	[c4]*	—
Thesis 3	[j3]	—	[e6],[e7],[e9],[e5]
Thesis 4	—	—	[e5],[e11]

* These publications are attached to multiple theses.

This classification follows the faculty's Ph.D. publication score system.

Journal Papers

- [j1] Anane Yahia, Ákos Szlávecz, Jennifer L Knopp, Normy Norfiza Abdul Razak, Asma Abu Samah, Geoff Shaw, J Geoffrey Chase, and Balazs Benyo. Estimating enhanced endogenous glucose production in intensive care unit patients with severe insulin resistance. *Journal of diabetes science and technology* 16(5), 2022, pp. 1208–1219.
- [j2] Anane Yahia, Balazs Benyo, and J Geoffrey Chase. Clinical application scenarios to handle insulin resistance and high endogenous glucose production for intensive care patients. *IFAC-PapersOnLine* 53(2), 2020, pp. 16299–16304.

- [j3] Balázs Benyó, Béla Paláncz, Ákos Szlávecz, Bálint Szabó, Yahia Anane, Katalin Kovács, and J Geoffrey Chase. Artificial intelligence based insulin sensitivity prediction for personalized glycaemic control in intensive care. *IFAC-PapersOnLine* 53(2), 2020, pp. 16335–16340.

International Conference and Workshop Papers

- [c4] Yahia Anane, Balázs Benyó, Ákos Szlávecz, Chris Pretty, and J Geoffrey Chase. Endogenous glucose production parameter estimation for intensive care patients. In: *2019 Scientific Meeting on Electrical-Electronics & Biomedical Engineering and Computer Science (EBBT)*, pp. 1–4. 2019.

Local Conference and Workshop Papers

- [e5] Yahia Anane, Balázs Benyó, A Szlávecz, Béla Paláncz, and Geoff Chase. Potential use of the stochastic icing model in star protocol. In: *Proceedings of the Workshop on the Advances of Information Technology: WAIT 2019*, pp. 33–37. 2019.
- [e6] Yahia Anane, Balázs Benyó, and Geoff Chase. Insulin sensitivity and blood glucose levels analysis of hungarian intensive care patients under model-based control. In: *Proceedings of the Workshop on the Advances of Information Technology (WAIT) 2021*, p. 123. 4. 2021.
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- [e9] Yahia Anane, Balázs Benyó, and Geoff Chase. Insulin resistance in intensive care patients under model-based glycaemic control. In: *Proceedings of the Workshop on the Advances of Information Technology 2020 : WAIT 2020*, pp. 138–141. 2020.
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