Risk and reward trade-off of glycaemic control in intensive care units

Auteur : Seret, Marie
Promoteur(s) : Desaive, Thomas; Uyttendaele, Vincent
Faculté : Faculté des Sciences appliquées
Diplôme : Master en ingénieur civil biomédical, à finalité spécialisée
Année académique : 2022-2023
URI/URL : http://hdl.handle.net/2268.2/17706

University of Liège - Faculty of Applied Sciences

Risk and reward trade-off of glycaemic control in intensive care units

Master thesis conducted by

Marie Seret

with the aim of obtaining the degree of Master in Biomedical Engineering

Under the supervision of

Prof. Thomas Desaive
Dr. Vincent Uyttendaele

Academic Year 2022-2023

Abstract

Stress-induced hyperglycaemia is a frequent glycaemic complication in critically ill patients. The resulting elevated blood sugar levels are associated with increased mortality and morbidity in intensive care units. Glycaemic control (GC) has been used to regulate stress-induced hyperglycaemia and is mostly achieved through insulinotherapy. The Stochastic TARgeted (STAR) protocol is a model-based GC protocol modulating both insulin and nutrition minimising risk for the BG levels to be outside a pre-set target range.

STAR has been clinically validated and provides safe and effective control for nearly all patients. However, one of the main identified drawback from the implementation of STAR in clinical environment is the possible increased workload compared to some intensive care units (ICU) local practice. This work aims at investigating solutions to reduce this workload and the insulin dosing variability also affecting nurse's compliance to the protocol. The solutions are studied by means of virtual trials on virtual patients allowing to assess and validate likely outcomes prior potential clinical trial, ultimately saving clinical time and costs.

The first solution investigated aims at increasing measurement intervals in STAR from 1-3 hourly to 1-6 hourly. New stochastic models are built to forecast insulin sensitivity variability over 1-6 hours intervals. These models are first validated using five-fold cross-validation, then used in virtual trials to validate their impact on simulated BG outcomes. Results obtained show a risk and reward trade-off with, as expected, a reduced workload for longer time intervals at the cost of reduced safety. However, both performance and safety remains very high confirming the results obtained for a virtual trial performed on an older version of the stochastic models. These results should be further confirmed by conducting clinical trials.

To further reduce workload, new treatment selection processes are considered in the STAR framework. Different modifications are implemented on the current version allowing longer treatment intervals and reducing insulin dosage variations between interventions. Results obtained from the different virtual trials performed with these modifications once again highlight risk and reward trade-offs with reduced workload and median insulin variations at the expense of respectively reduced safety and nutrition, and increased workload. Their combination results in a safe and effective control, but should be clinically validated after some further optimisations.

Acknowledgments

This master thesis is the first work of this magnitude I ever had to carry out. Many people contributed directly or indirectly to the realisation of this work. Their support has been invaluable and I would like to thank all of them.

First of all, I would like to express all my gratitude to my supervisors Prof. Thomas Desaive and Dr. Vincent Uyttendaele. I would like to thank them for giving me the opportunity to work on such an interesting topic. I would also like to thank them for their availability to answer my questions, their precious advice and for guiding me all along this work.

Then, I would like to thank the members of my jury for taking the time to read my thesis and assist at my defense.

Finally, I am thankful to my family and my friends. They have encouraged me throughout all my studies and in particular throughout this thesis. Their support has been unfailing throughout these years and I am grateful for it.

Contents

Table of Figures

List of Tables

Table of abbreviations

BG	Blood Glucose
CI	Confidence Interval
CNS	Central Nervous System
GC	Glycaemic Control
ICING	Intensive Control Insulin-Nutrition-Glucose
ICU	Intensive Care Unit
IQR	Interquartile range
SI	Insulin Sensitivity
SIH	Stress-induced Hyperglycaemia
SPRINT	SPecialized Relative Insulin and Nutrition Tables
STAR	Stochastic TARgeted
TGC	Tight Glycaemic Control

Chapter 1

Introduction

About 30-50% of critically ill patients experience stress-induced hyperglycaemia (SIH) on their admission in the intensive care unit (ICU) [1]. This metabolic condition results from stress and inflammatory response to severe injury, responsible for a dysregulation of their glucose homeostasis leading to a transient hyperglycaemia [2]. It results from the release of humoral mediators including inflammatory cytokines and counter regulatory hormones affecting the glucose regulatory system [1].

SIH and glycaemic variability are associated with increased mortality and morbidity in critically ill patients [2, 3]. Glycaemic control (GC) has been introduced to reduce the blood glucose (BG) levels and stabilise them in a certain range [2]. It is achieved through protocols essentially modulating insulin. Recent studies have shown the importance of protocol designs accounting for inter- and intra-patient variability to provide safe and effective control for all [4, 5].

The Stochastic TARgeted (STAR) GC protocol is a model-based control protocol modulating both insulin and nutrition. It uses a combination of a physiological and a stochastic model to provide intervention recommendations minimising the risk of BG levels to be outside a pre-set target band. STAR provides a unique risk-based dosing approach [6]. The key parameter of STAR is insulin sensitivity (SI), characterising patient-specific response to insulin. By predicting its future distribution using the stochastic model, STAR can forecast likely future BG levels using the physiological model [7].

STAR has been clinically validated [8]. It provides a safe and effective control by accounting for both inter- and intra-patient variability. Two versions of the stochastic model used by STAR have been developed to date leading to two versions of the protocol denoted STAR-2D and STAR-3D. Both versions have been clinically shown to provide safe and effective control with better control than other GC protocols, but STAR-3D provides a more patient-specific control

thanks to tighter, more patient-specific, SI predictions given by the 3D stochastic model [9, 10].

However, the workload associated with the use of STAR GC protocol can represent a clinical burden for the nurses impeding its implementation in some intensive care units. This was especially reported in units with lower nurse per patient ratio [11]. In these units, nurses cannot manage regular measurements and interventions frequency from every hour to every 3 hours with the current protocol [12]. In addition, cognitive workload can also impact protocol adoption. For example, it is possible, based on predictions, that changes in treatment have minimal impact on BG outcomes while requirement changes treatment. Nurses see this variability as a possible cause of glycaemic variability affecting their confidence in the protocol. These two factors affect the nurse compliance to the protocol and, therefore, impact clinical outcomes [13].

The aim of this master thesis is to investigate in silico two potential solutions to reduce the workload associated with the protocol and increase nurse's confidence in STAR. The first solution consists in extending the measurement and treatment intervals from 1-3 hourly to 1-6 hourly. This solution has already been assessed in virtual trials on the 2D version of STAR and was shown to still provide safe and effective GC for all patients [14]. This work studies the risk and reward trade-off of the extension to the 3D version of STAR. The second solution is an optimisation of the way STAR considers the different possible treatments, i.e. the treatment selection process. Two propositions are investigated, one aims at maximising the time interval (STAR-TIM) and the other at minimising the variability of the treatments recommended (STAR-IVM). Both propositions are also considered together in a global optimisation (STAR-GO).

First, the physiological basis of stress-induced hyperglycaemia and the concept of glycaemic control and protocols are presented in Chapter 2. Then, the GC protocol used all along this work, STAR GC is presented and developed in detail in Chapter 3. The goal of this work is to assess the risk and reward trade-off associated with different changes implemented in STAR on the performance, safety and workload of GC. This is done by conducting virtual trials which are described in Chapter 4. This Chapter also presents the cohort of virtual patients and the metrics used to quantify the impact of GC. Chapter 5 develops the 3D stochastic models used in this work. They are based on retrospective data from the cohort considered. Then, two Chapters present the results of the virtual trials performed on new versions of the protocol. Chapter 6 studies the impact of longer treatment intervals and Chapter 7 considers the new treatment selection processes. Finally, Chapter 8 draws conclusions from this work and gives indications for possible future work.

Chapter 2

Glycaemia and glycaemic control

This Chapter presents the biological and physiological background required to understand the work conducted in this master thesis. The first part focuses on glycaemia, including glucose metabolism, hyper- and hypoglycaemia and a well-known pathology in critically ill patients, stress-induced hyperglycaemia. The second part describes the concept of glycaemic control and the protocols used to achieve it. More specifically, it defines the SI parameter and develops the concept of model-based protocols such as STAR that will be used in this work.

2.1 Glycaemia

2.1.1 Metabolism

Glucose is the most common monosaccharide (simplest carbohydrate with as molecular formula a multiple of CH2O) [15] present in the human body and is the most important source of energy for our metabolism [16, 17]. About 80% of blood glucose (BG) is consumed by the central nervous system (CNS) while the remaining 20% by the skeletal muscles [18]. The concentration of blood glucose (BG) is referred to as glycaemia [15].

Normal persons present large glycaemic variations over the day. These variations have to do with nutrition and fasting periods that a person experiences over the day. Typically, the concentration of BG increases after a meal due to exogenous glucose ingestion during the meal. Conversely, it decreases between the meals and typically during the night as the glucose is used by the tissues and there is no or less glucose entering the blood. Glucose balance (glucose homeostasis) is then important to control and regulate the BG level [16, 19].

Glucose homeostasis is controlled by two antagonist pancreatic hormones of the endocrine system, insulin and glucagon [16, 17] (Figure 2.1). Hormones are used by the organism to

regulate metabolic function [15, 16]. In particular, insulin and glucagon are released into interstitial fluid by pancreatic cells for BG level regulation. They promote respectively catabolic and anabolic reactions taking place in four tissues: the liver, the kidneys, the muscles and the adipose tissues [7, 19, 20].

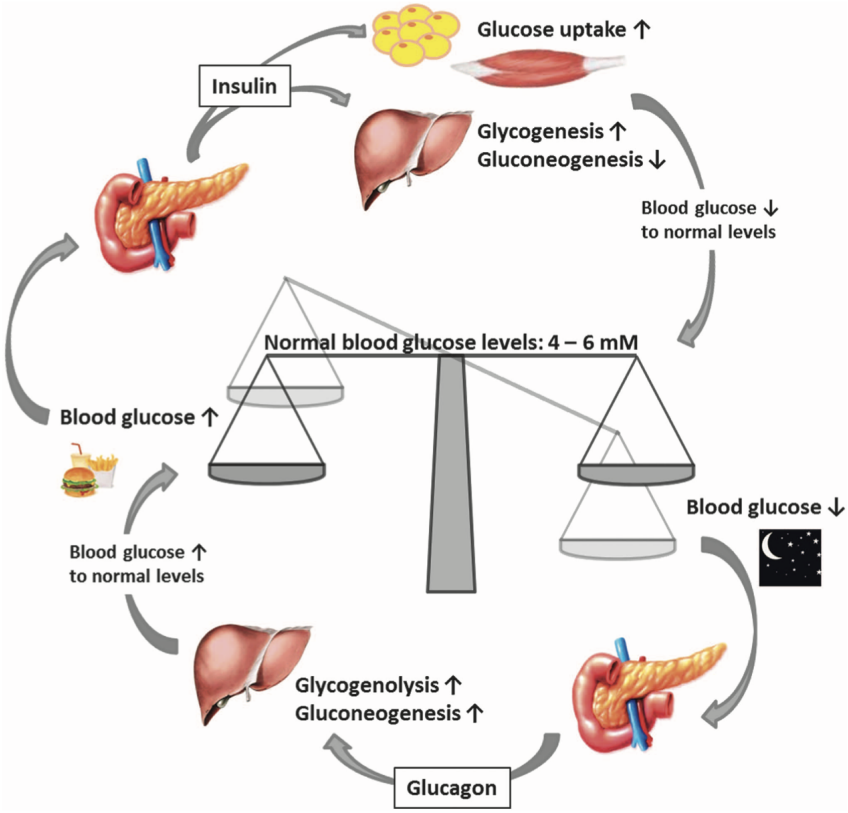


Figure 2.1: *Blood glucose homeostasis by insulin and glucagon [19].*

Glucagon is secreted by pancreatic α-cells when BG levels are low [15, 17], typically during the night or between meals [19]. It promotes anabolic reactions whose effect is to increase BG levels (lower part in Figure 2.1) [20]. Anabolic reactions are the hepatic glucose synthesis from glycogen (glycogenolysis) and the hepatic and renal formation of glucose from substrates: pyruvic acid, lactic acid, glycerol and amino acid (gluconeogenesis) [15, 17, 19, 21]. These reactions correspond to endogenous glucose production [20]. Other hormones, such as cortisol, catecholamines and growth hormone also promote glycogenolysis and gluconeogenesis [18]. These hormones and glucagon are called counter-regulatory hormones [7]. Epinephrine also intervenes, but its action is negligible compared to that of glucagon [22].

Insulin is secreted by pancreatic β-cells [15, 17]. Insulin release is stimulated by elevated BG levels which occurs generally after a meal [19]. It promotes catabolic reactions to stimulate glucose degradation use and storage to lower BG levels (upper part in Figure 2.1) [19]. Those reactions are the transport of blood glucose to the cells, the transformation of glucose into adenosine triphosphate and pyruvic acid in all body cells (glycolysis), the transformation of glucose into glycogen in the liver and muscles (glycogenesis) and into fat or lipids by hepatic and adipose cells (lipogenesis). The other action of insulin is to inhibit glycogenolysis

and gluconeogenesis [17, 21]. In addition to these hyperglycaemic effects, opposed to that of glucagon, insulin also exerts non-glycaemic actions. It has anti-inflammatory, anti-thrombotic, anti-apoptotic and anti-oxidant effects [23].

The secretion of insulin and glucagon is regulated following a negative retroaction mode. Their secretion is stimulated or inhibited by BG levels fluctuations as a control feedback loop [15, 17].

2.1.2 Hyper-, hypoglycaemia and their medical consequences

It is important for glycaemia to stay in a certain range to maintain a constant energy supply for the brain and other organs and tissues as glucose is their main source of energy [15]. Normal fasting BG levels are generally between 4.4 and 6.1 mmol/L [17]. This safe range is called normoglycaemia. The bounds of this range can vary a bit from one physiology reference book to another but remain in the same range [15, 16]. When BG levels are below this range, it is called hypoglycaemia, while elevated BG levels above this range are called hyperglycaemia [7, 20].

There is no strict threshold defining hyper- and hypoglycaemia [7]. As this work is a continuation of another work [7], the same values and ranges will be used to define hyper-, and hypoglycaemia. A BG level between 8.0 and 10.0 mmol/L corresponds to moderate hyperglycaemia. A BG level above 10 mmol/L is referred to as severe hyperglycaemia. Moderate hypoglycaemia is defined between 2.2 and 3.9 mmol/L and severe hypoglycaemia below 2.2 mmol/L.

Both hyper- and hypoglycaemia have adverse effects on the metabolism [7]. Hyperglycaemia can affect fluid balance, immune function, inflammation and can lead to multiple organ failure [20, 23]. Typical symptoms are polyuria and exacerbated hunger and thirst [17]. Hypoglycaemia can affect the brain and the heart by inducing irreversible injuries, trembles, seizures and cardiac dysfunctions [7, 22]. Symptoms from hypoglycaemia are fatigue, feeling of warmth, formal thought disorders, behavioural changes, emotional lability and eventually seizures and coma [17, 22].

As any other system in the human body, glucose homeostasis can suffer from dysregulation. The most common glucose homeostasis impairment in everyday life is diabetes. Diabetes or diabetes mellitus is a syndrome caused by a lack of insulin secretion or a reduced sensitivity of the tissues to insulin, leading to a sustained hyperglycaemia [15, 16]. The symptoms of diabetes are the same as the ones of hyperglycaemia but as it is a sustained state, it can lead to more serious problems such as heart attack and stroke, increased utilisation of fats and metabolic acidosis and depletion of body's proteins [16]. Different types of diabetes caused by different pathologies exist: type I, type II, gestational diabetes and other less common types of diabetes [24].

Type I diabetes is an autoimmune disorder also called insulin-dependent diabetes mellitus. It is caused by the destruction of the β-cells secreting the insulin by the immune system. This diabetes generally appears abruptly in a few days or weeks during childhood [15, 16, 17, 24]. Contributing factors to develop type I diabetes are genetic and environmental factors [17, 24].

Type II diabetes is much more common than type I as it affects 90% of all people with diabetes and is called non-insulin dependent diabetes mellitus. It consists in insufficient synthesis of insulin and increased insulin resistance of the target tissues. This induces a compensatory response by the β-cells, an increased plasma insulin concentration. This diabetes is diagnosed in most cases after 40 years old and develops gradually. Its incidence increases with age. Obesity plays an important role in the apparition of this type II diabetes which can cause alterations in cell receptors [15, 16, 17, 24].

The last main type of diabetes mellitus is gestational diabetes. As mentioned in its name, this diabetes occurs during pregnancy. During pregnancy, women experience accelerated starvation, glucose fluctuations, additional insulin secretion by the placenta and increased insulin resistance by the end of the first trimester. All these factors together can lead to diabetes. Generally, this type of diabetes resolves at the end of the gestational period but it can lead to some complications, including an increased risk of mortality for both the mother and the foetus [24].

Diabetes is not the only dysregulation of glucose regulatory system. Another type of glucose dysregulation is stress-induced hyperglycaemia (SIH). It generally occurs in intensive care units (ICU) as it is part the body response to severe trauma. This stress-induced hyperglycaemia (SIH) is a current problem in ICU as it increases patient mortality and morbidity [18]. It is the dysregulation of interest in this master thesis and will therefore be discussed in more details in the next Section.

2.1.3 Stress-induced hyperglycaemia

Patients admitted in ICU have just experienced severe trauma and their body is constantly under physiological stress. This stress is the systemic response to critical injury and consists in an hypermetabolic state [18] which corresponds to an unusual high metabolic activity, inflammation and hyperdynamic cardiovascular state [25]. This hypermetabolic state can cause important neuroendocrine and humoral changes [23]. It involves the release of humoral mediators called inflammatory cytokines and counter regulatory hormones [1, 26]. Glucose uptake is also impaired [1]. All these mechanisms affect the glucose regulatory system in the patients whether or not they have pre-existing diabetes. The dysregulation of the glucose homeostasis leads to a transient hyperglycaemic condition in critically ill patients called stress-induced hyperglycaemia (SIH) [2]. This condition is common in ICU and particularly in the first 48 hours of ICU admission [1].

Inflammatory cytokines such as tumour necrosis factor-α (TNF-α) and interleukins (IL-1, IL-6) cause the inhibition of insulin release and insulin resistance [1, 18]. TNF-α also stimulates glucagon production [2, 26]. Hepatokines such as Forkhead Box O (FOXO) also cause insulin resistance [1].

Counter regulatory hormones (cortisol, catecholamines and growth hormone) promote the activation of pancreatic α-cells which results in an increased gluconeogenesis (increased glucose production). They also inhibit insulin release and glucose utilisation and increase insulin resistance [1].

The action of cytokines inhibitors and counter regulatory hormones involves increased endogenous glucose production and impairment of the insulin signalling pathway leading to an alteration of glucose metabolism. This alteration results in increased BG levels, insulin resistance and low levels of insulin leading to SIH (Figure 2.2) [1, 26, 27].

Insulin resistance is frequent in critically ill patients [23]. As previously explained, several components are responsible for its development. TNF-α reduces the expression of the insulin receptors in cells and induces the phosphorylation of insulin receptor substrates [18]. Catecholamines inhibits insulin binding to insulin receptors. The different actions of TNF-α and catecholamines induce insulin resistance [2]. It results in an inability to suppress hepatic glucose production and promotes a catabolic state [26]. Its associated mechanisms are altered insulin receptor binding and signal transduction, glucose synthesis, increased hepatic glucose production and decreased peripheral glucose uptake [23].

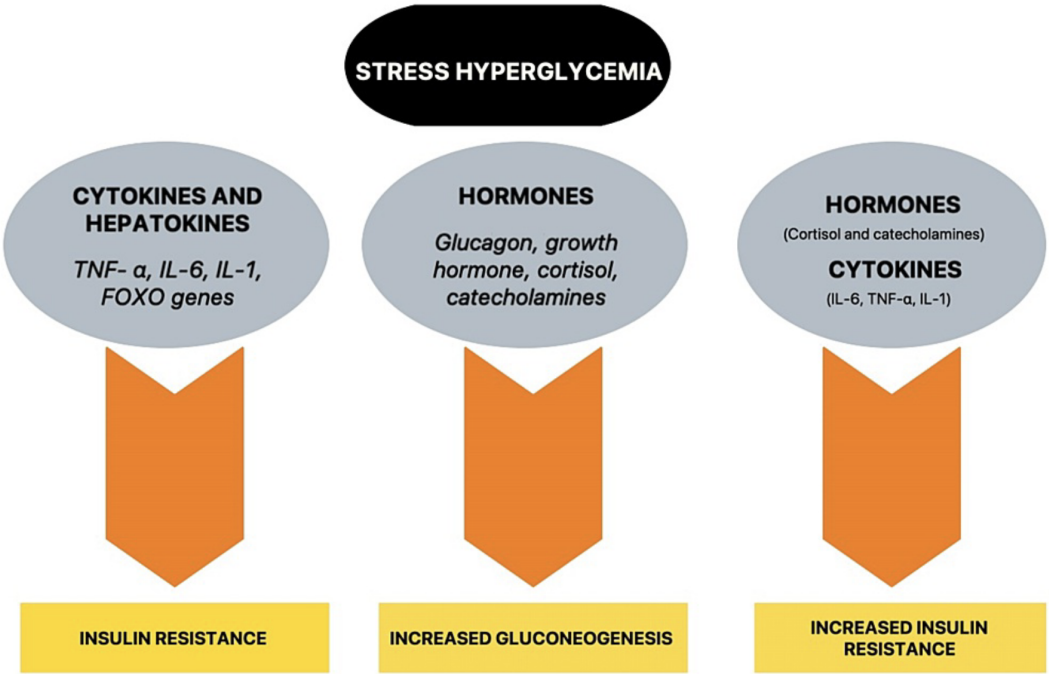


Figure 2.2: *Pathophysiology of the stress-induced hyperglycaemia [1].*

In addition to the hypermetabolic state associated with stress, other endogenous and exogenous factors influence stress-induced hyperglycaemia: severity of the disease, parenteral administration of nutrition and therapeutic interventions [2, 27]. First, severity of the disease or trauma impacts the stress response and therefore the dysregulation of the glucose metabolism [18, 26]. Then, patients receive enteral and parenteral nutrition during their stay in ICU which consists in an exogenous glucose supply [20]. In addition, parenteral nutrition is not so well managed by the liver as ingested glucose and represents an even more important supply [18]. A consequence of this exogenous supply is an increase of BG levels [20]. Finally, many drugs administered to critically ill patients are diluted in glucose solutions [28]. They consist in other exogenous glucose supply and induce an increase in BG levels. Some treatments can also contain counter regulatory hormones which directly influence glucose metabolism [26]. There also exist some complicating factors such as pre-existing diabetes mellitus, cirrhosis, pancreatitis, drugs, hypokalaemia, long stay in bed and age [18].

Stress-induced hyperglycaemia is associated with poor outcomes in critically ill patients. Hyperglycaemia is not itself responsible for poor outcomes but it affects the fluid balance, immune function and inflammation in diabetic and nondiabetic patients particularly after myocardial infarction, stroke, surgery or other trauma [1, 23]. Those effects are ultimately associated with increased mortality and morbidity in ICU patients and even more in nondiabetic patients [2, 27]. SIH can also increase the incidence of type 2 diabetes after recovery and this is more present in men than in women [1].

Finally, a major problem associated with SIH is that it is self-sustained. Indeed, hyperglycaemia itself induces cytokines release, inflammatory and stress responses that will increase the BG level [26]. This self-sustained loop has to be broken as hyperglycaemia is associated with poor outcomes [7, 20]. The only way to do so is by using exogenous insulin which will lower BG levels [26].

2.2 Glycaemic control

2.2.1 Principles of glycaemic control

Besides stress-induced hyperglycaemia, glycaemic variability is also associated with worse outcomes in critically ill patients [2, 3, 29, 30]. Glycaemic variability can be expressed as the standard deviation around the mean glucose value or by the mean amplitude of glycaemic variations [2]. It resulted from studies that this variability is different between patient with SIH and with normoglycaemia and is the strongest predictor for mortality and morbidity in critically ill patients [27].

Reducing SIH and glycaemic variability are important points to focus on to reduce mortality and morbidity in ICU. This is the goal of glycaemic control (GC) [2, 27]. This control should be adaptive and patient-specific [31]. GC also has to account for inter- and intra-patient variability which is challenging because it can generate glycaemic variability and an increased risk of hypoglycaemia [7, 32, 33].

A typical way to achieve GC is by the administration of exogenous insulin bolus or infusion. It allows to overcome the stress-induced insulin resistance by helping to lower glycaemia as the pancreatic insulin is not sufficient. Safe and effective glycaemic control is associated with several beneficial effects such as limiting the risk of infections [20]. Insulin is not only responsible for lowering the BG level. As listed in Section 2.1.1, insulin also has non-glycaemic effects which can be mediated thanks to the control of the BG levels and which can reverse the effects of SIH [18, 23]. In addition to insulin, nutritional inputs can also be used to help control glucose when insulin only is not sufficient to lower BG levels [31].

There are two main types of glycaemic control: conventional and intensive or tight glycaemic control (TGC). They differ by their BG level target. TGC has a control target consisting in lower BG levels while conventional GC targets higher BG levels [7, 34].

Using insulin therapy for GC increases the risk of hypoglycaemia, particularly for TGC targeting lower BG ranges [2, 22, 29, 35]. It results from a combination of factors: insulin excess, inadequate nutritional support, insufficient exogenous glucose and features of critical illness. Hypoglycaemia in the ICU is also associated with worse outcomes in ICU patients such as seizures and death which are the most severe complications [2]. Ensuring a high safety from hypoglycaemia also has to consist in one of the goals of GC as the risk of hypoglycaemia is one of the factors impeding effective GC implementation [2, 20, 22].

Different studies have been carried out to compare conventional and tight GC have shown controversial results [4]. Some of the studies highlighted the fact that TGC allowed to reduce the risk of infections and both mortality and morbidity by more than 40% [3, 23, 36, 37]. However, these effects seem to be really beneficial in patients who stay for more than 3-5 days in ICU [23]. Below this length, insulin administration can worsen the outcomes as hyperglycaemia is a transient state that resolves with the resolution of the critical state [2, 23]. In contrast, other studies failed to replicate these results and showed that TGC increased the absolute risk of death [29, 34]. Nevertheless, further investigations of these studies suggested that their results might be explained by the poor compliance to the protocol used [4].

Because of these controversial results, the optimal target band is still debated in the ICU as GC should respect the well-known "first do not harm" medical principle [7].

2.2.2 Glycaemic control protocols

Many insulin therapy protocols have been developed with the ultimate to achieve safe and effective GC. There are probably as many protocols as there are ICUs [20]. Those protocols are typically developed by groups of clinicians. They contain guidelines defining the BG target, insulin and nutrition dose adjustment, and the monitoring frequency [2]. Protocol design must overcome the factors impeding safe and effective GC implementation which are the dynamic patient condition, the risk of hypoglycaemia and the increased nurse staff workload. This translates into protocols that should be safe (minimising hypoglycaemia), effective (efficient BG regulation), easy to use, and accounting for patient variability by providing an adaptive control [20]. If they are well-designed, the protocols allow to have a safe and accurate control, a treatment that is not a trial and error and interventions prior to hypoglycaemia. It also allows a decrease of glycaemic variability [2].

Most protocols aim at maintaining the BG levels below 6.1 mmol/l [23]. However, as mentioned in Section 2.2.1, the optimal target band for GC has also still not been fixed [7]. Therefore, the different protocols are currently using different targets depending on the degree of control sought [27].

There currently exist three categories of protocols: flowchart-based protocols, formula-based protocols and model-based protocols [38].

Flowchart-based protocols consist in the administration of intravenous insulin infusion or bolus depending on empirical rules [26, 27]. The rules also give the measurement frequency. These protocols have a limited efficiency as they are based on clinical practice and do not take into account patient-specificity [20]. They are based on a "one size fits all" method [7].

Formula-based protocols are based on empirical formulae to administrate exogenous insulin. In this case, the measurement frequency follows the flowchart-based rules. As flowchart-based protocols, formula-based protocols lack patient-specificity [20].

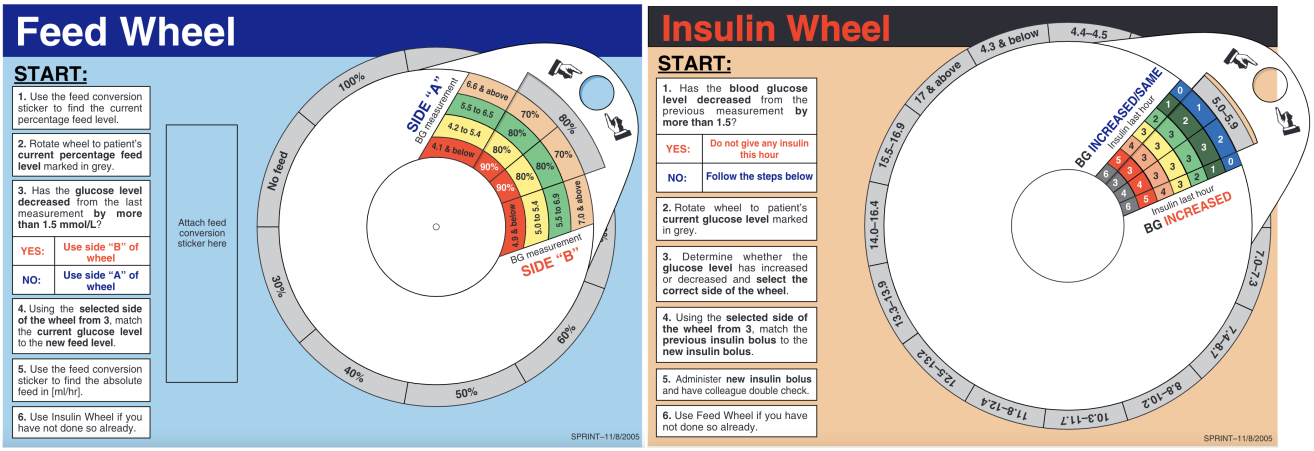
Model-based GC protocols are protocols based on physiological models describing the insulin-glucose dynamics. Such system allows us to identify some key parameters representing a patient metabolic state. Model-based protocols can thus adapt to the dynamic state of the patient and deliver patient-specific control [7, 20]. They directly account for inter- and intra-patient variability [7]. Model-based approaches can also better control highly dynamic patients as they require more frequent measurements [31, 37, 39].

The primary control input of such protocols is the administration of exogenous insulin [37]. Nutrition can also consist of a second control input but it is less used as nutrition is often considered completely independently from GC. However, using nutrition in GC represents an

advantage as for patients with high insulin resistance, insulin is not sufficient to reduce the BG levels [31, 37, 39]. Such protocols have been shown to provide a tighter control than the ones modulating insulin only [39]. Moreover, most of the model-based protocols calculate the intervention assuming that the insulin sensitivity (SI), an important parameter representing patient metabolic response to insulin, is constant from one intervention to the other. However, SI can actually evolve significantly during the early and late acute phase of stress, as well as during the recovery phase. Some model-based protocols such as STAR adapt the control with respect to the SI variations [6]. Finally, model-based protocols allow the conduct of virtual trials which help in developing the protocol before its implementation in ICUs [40].

Model-based protocols can also be divided in different types of control. They differ in their metabolic model and the control method they use. However, they are all based on the same "one method fits all" approach [31].

The specialised relative insulin and nutrition tables (SPRINT) protocol is a table-based version of one of the model-based protocols [39, 40]. SPRINT is based on computerised glucose control trials and patient simulations. It is represented by two wheels (Figure 2.3): one dedicated to the enteral nutrition optimisation (Figure 2.3a) and the other to the insulin bolus administration (Figure 2.3b). Based on the current blood glucose level, the previous hour feed level and insulin bolus size and the trend that follows the BG level, the wheels are used to determine the insulin bolus and the rate of feed to administrate to the patient to reach the BG target which is in this case 4.4-6.1 mmol/l [39]. Although SPRINT was shown to provide the tightest control in several studies, it is relatively inflexible and its target glycaemia cannot be changed even for specific clinical needs or highly dynamic patients. In addition, the choice of measurement interval is not free [6].



(a) *Feed wheel* (b) *Insulin wheel*

Figure 2.3: *The SPRINT nutrition (a) and insulin (b) wheels. BG values are in mmol/L, nutrition in percentage of goal feed and insulin in U/h [39].*

Another recently developed model-based protocol is the Stochastic TARgeted (STAR) protocol. It is a unique risk-based dosing approach that provides insulin and nutrition recommendations

while ensuring a certain risk of hypoglycaemia. It is composed of two main elements: a physiological model describing the glucose-insulin dynamics and a stochastic model used to make predictions on insulin sensitivity (SI) variations and then on BG outcomes [6, 40, 41]. As mentioned, STAR is the first protocol to consider SI variations in its control. It then provides a patient-specific approach accounting for both inter- and intra-patient variability. STAR is the protocol used in this thesis. Its different components and framework are discussed more in details in Chapter 3 [41].

2.2.3 Insulin sensitivity

Insulin sensitivity (SI) is the main parameter used in the glucose-insulin system models developed to represent the patients and describe the patient-specific metabolic condition [7, 20]. It characterises the cell's ability to uptake glucose through the mediation of insulin and so quantifies the response of the body to the insulin [7]. A reduced SI results from an impaired binding between insulin and cell insulin receptors [20].

This parameter is the reciprocal of insulin resistance which is more commonly used. Increased SI corresponds to reduced insulin resistance. Critically ill patients generally present a low insulin sensitivity which results in a reduced insulin action and leads to increased BG levels. SI is influenced by different factors such as stress, exercise and temperature [20], but is treatment independent [42].

It is important to determine insulin sensitivity for glycaemic control. This parameter is patient-specific and time-varying. Its identification in real time for each patient allows it to assess patient's response to insulin to better determine the insulin dose to administer for safe GC [4]. In addition, its variability establishes the overall controllability of the patient [4]. Accounting for SI and its variability over time in GC allows then to consider inter- and intra-patient variability [32].

2.3 Summary

This Chapter first presented the biological and physiological concepts around glycaemia. Glucose homeostasis is important as glucose is the main source of energy for our metabolism. However, it can be subjected to dysregulations leading to hyper- and hypoglycaemia. A characteristic dysregulation in critically ill patients is stress-induced hyperglycaemia mediated by cytokines and counter regulatory hormones. Stress-induced hyperglycaemia is associated with increased mortality and morbidity.

Secondly, it described the glycaemic control used in ICUs to regulate the stress-induced hyperglycaemia and reduce glycaemic variability. Protocols are used to achieve this control and can be of different types. Model-based protocols provide the best control as they account for

inter- and intra-patient variability. The Stochastic TARgeted (STAR) protocol, the protocol of interest in this master thesis, is one of them.

Lastly, insulin sensitivity, the key parameter of GC was developed. This parameter is patient-specific and time-varying, accounting for it allows to further improve GC.

Chapter 3

STAR risk-based glycaemic control

This chapter fully presents, details and describes the STAR GC protocol used and studied in this thesis. STAR is the successor of the table-based SPRINT protocol and uses a combination of a physiological and a stochastic model to provide a unique risk-based dosing approach in GC [7, 41]. The different components are detailed in this Chapter as well as the STAR framework and the different retrospective results.

3.1 Introduction

The Stochastic TARgeted (STAR) protocol is a model-based GC protocol that provides a unique patient-specific, risk-based dosing approach [7, 41]. STAR uses the combination of a physiological glucose-insulin model and a population-based stochastic model to provide optimal insulin and nutrition interventions for ICU patients [40, 41]. The stochastic model accounts for metabolic variability and predicts likely future distribution of SI [10]. Based on these predictions, STAR forecasts the range of future likely BG outcomes for a specific intervention. It finally provides recommendations of insulin and nutrition intervention guaranteeing a pre-set, clinical level of risk for this range to be outside a clinically pre-set target band [6, 7].

STAR is the first protocol modulating both insulin and nutrition to provide improved GC outcomes. The modulation of nutrition interventions has been shown to provide better GC performance (longer time in the target band), to be safe (decreased risk of hypoglycaemia) and to reduce clinical workload [43].

The main advantage of STAR is that it allows to achieve adaptable and optimised care to meet patient-specific needs [6, 10]. The protocol is flexible, safe and induces lower clinical workload compared to other protocols previously developed [6].

Moreover, using stochastic models allows to have better predictions of BG evolution over longer intervals. It provides an enhanced control with guaranteed risk level of hyper- and hypoglycaemia at the cohort level and this risk is optimised. Finally, protocol is fully generalisable as the target ranges and risk level can easily be specified to adapt to specific clinical needs [6].

3.2 Physiological model

The physiological model used by STAR is the clinically validated Intensive Control Insulin-Nutrition-Glucose (ICING) model [6, 44]. The model is composed of three different compartments and metabolic pathways characterising glucose or insulin pharmacodynamics in blood and interstitial fluid volumes. The compartment model is illustrated in Figure 3.1 and described below [7, 44].

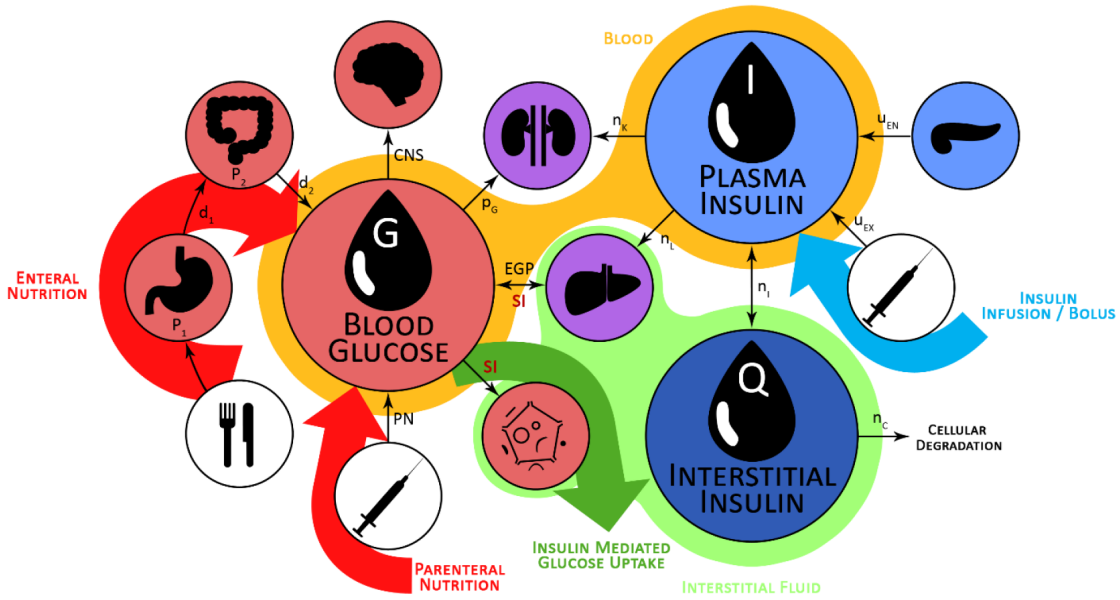


Figure 3.1: *Schematic representation of ICING model representing the compartments and metabolic pathways [7].*

Firstly, the glucose compartment (G) is impacted by insulin and non-insulin mediated glucose transfers. The insulin mediated transfer is the clearance influenced by SI and the non-insulin mediated transfers are absorption through exogenous inputs, endogenous glucose production, kidney clearance and central nervous system uptake.

Secondly, the plasma insulin compartment (I) is influenced by plasma insulin appearance from exogenous and pancreatic endogenous insulin and by plasma insulin clearance through the kidneys and the liver.

Thirdly, the interstitial insulin compartment (Q) is impacted by interstitial insulin appearance from plasmatic insulin transport and by interstitial insulin clearance through cellular degradation.

Each of the compartments is governed by a balance equation which leads to a system of three ordinary differential equations modelling the glucose-insulin dynamics [4, 40, 44]:

$$\dot{G} = -p_G \cdot G(t) - S_I \cdot G(t)\frac{Q(t)}{1+\alpha_G \cdot Q(t)} + \frac{P(t) + EGP - CNS}{V_G} \tag{3.1}$$

$$\dot{I} = -n_K \cdot I(t) - n_L \frac{I(t)}{1+\alpha_I \cdot I(t)} - n_I(I(t) - Q(t)) + \frac{u_{ex}(t)}{V_I} + (1 - x_L)\frac{u_{en}(G)}{V_I} \tag{3.2}$$

$$\dot{Q} = n_I(I(t) - Q(t)) - n_C \frac{Q(t)}{1+\alpha_G Q(t)} \tag{3.3}$$

where

$$P(t) = \min\left(d_2 P_2, P_{\max}\right) + PN(t) \tag{3.4}$$

$$\dot{P}_2 = -\min\left(d_2 P_2, P_{\max}\right) + d_1 P_1 \tag{3.5}$$

$$\dot{P}_1 = -d_1 P_1 + D(t) \tag{3.6}$$

$$u_{en}(G) = min(max(u_{min}, k_1 G(t) + k_2), u_{max}) \tag{3.7}$$

The different variables of the model are G(t), the blood glucose level (mmol/L), I(t), the plasma insulin concentration (mU/L), Q(t), the interstitial insulin concentration (mU/l), P(t), the glucose appearance in plasma (mmol/min), P_2, the glucose level in gut (mmol), P_1, the glucose level in the stomach (mmol) and $u_{en}(G)$, the pancreatic insulin secretion (mU/min). The other parameters and endogenous variables of the model are gathered and defined in the Tables A.1 and A.2 [6, 10, 36].

The advantage of this model is that it accounts for insulin sensitivity (SI), the key parameter in GC [4, 36]. SI is a patient-specific and time-varying parameter [4]. It is the only unknown parameter of the equations [7]. Its units are (L/mU/minute) and consist in rate units as it assesses the rate of insulin mediated glucose removal depending on current insulin concentration [4]. Patient-specific SI profiles can be obtained from the model thanks to an integral-based fitting that determines SI hourly from patient data (current and past BG levels, past insulin and nutrition data) which accounts for inter-patient variability [4, 9, 32].

3.3 Stochastic model

As mentioned in previous Sections, SI is a time-varying patient-specific parameter. In the context of GC, it is important to consider its variations. This is done by the means of a stochastic model, the second component of STAR assessing intra-patient variability [9, 45].

The stochastic model is based on ICU population data and aims at forecasting future SI distributions knowing the current identified patient-specific metabolic condition (SI) and the cur-

rent intervention itself based on observed parameter variations. It describes the hour-to-hour changes in SI levels [10, 36, 46]. Thanks to the model, a 90% confidence interval (CI) of the future SI distributions is obtained. These distributions in conjunction with the ICING model are then used to obtain a 90% CI of future likely BG distributions in response to a specific insulin and nutrition intervention [10, 36]. These predictions of BG will then be used to select the adequate treatment ensuring a less than 5% risk of hypoglycaemia [10, 46].

Two versions of the stochastic model were constructed for STAR, the 2D and the 3D stochastic models. They are both based on a kernel-density estimation method. This method provides a probability density function of future SI evolution. In the 3D model, future values of SI depend on its current and anterior values [36]. In addition, SI can be considered as a Markov chain, a sequence of random variables for which the state at one time depends on the state in the previous time(s) [47], and its variations are handled as a Markov process [36].

3.3.1 2D stochastic model

The 2D stochastic model uses a bi-variate kernel-density estimation method to predict changes in SI at hour n+1 depending on SI at hour n. The estimation method provides a model that describes the transition from one hour to the next and that considers how the existing data behave. The result obtained with this method is a bi-variate probability density function predicting the potential future SI values [36, 45].

In the 2D stochastic model, SI can be treated as a first-order Markov chain. It means that the state of the variable SI at the time n+1 depends only on the prior state at the time n [47]. The conditional probability of SI_{n+1} is then obtained using the Markov property and given by:

$$P\left(SI_{n+1} = y \mid SI_n = x\right) = \frac{p\left(SI_n = x, SI_{n+1} = y\right)}{p\left(SI_n = x\right)} \tag{3.8}$$

The right-handed term composed of the joint probability density function and the probability density function of SI at time n can also be developed and give a final expression providing the probability of SI_{n+1} knowing SI_n [36]:

$$p\left(SI_{n+1} = y \mid SI_n = x\right) = \sum_{i=1}^{n} \omega_i(x) \frac{\phi\left(y; y_i, \sigma_{y_i}^2\right)}{p_{y_i}} \tag{3.9}$$

$$\omega_i(x) = \frac{\phi\left(x; x_i, \sigma_{x_i}^2\right) / p_{x_i}}{\sum_{j=1}^{n} \phi\left(x; x_j, \sigma_{x_j}^2\right) / p_{x_j}} \tag{3.10}$$

where ϕ is the normal probability density function centred at individual data points normalised in the positive domain by:

$$p_{x_i} = \int_0^{\infty} \phi\left(x; x_i, \sigma_{x_i}^2\right) \tag{3.11}$$

$$p_{y_i} = \int_0^{\infty} \phi\left(y; y_i, \sigma_{y_i}^2\right) \tag{3.12}$$

σ is the variance, function of the local data density in a centred and orthonormalised space at each data point [36]. The resulting 2D stochastic model in 3D is represented in Figure 3.2. From this graph, considering a certain SI at the hour n, it is possible to have the probability distribution of possible SI_{n+1}. It is shown by the red line in Figure 3.3.

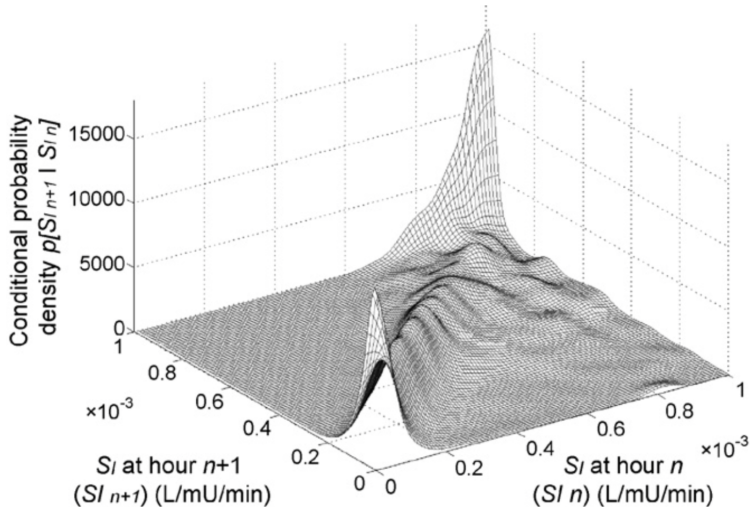


Figure 3.2: *2D stochastic model of SI variability [36].*

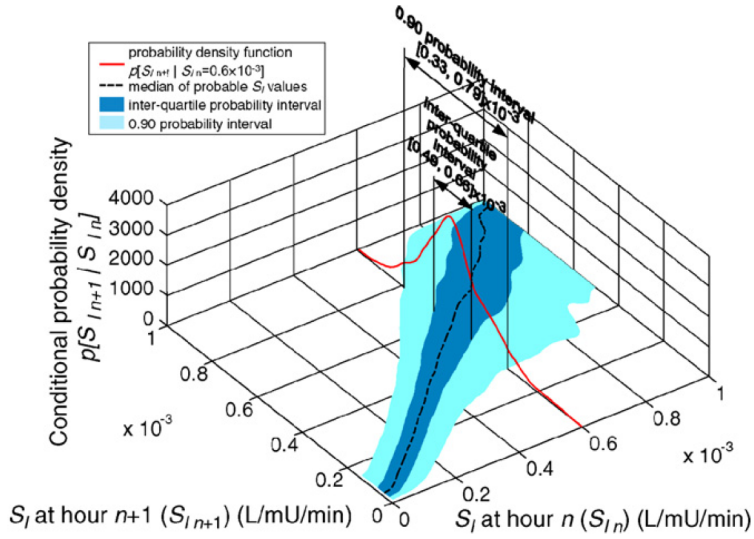


Figure 3.3: *Probability density function of likely future SI obtained from Figure 3.2 [36].*

The bi-variate kernel-density estimation as illustrated in Figure 3.4 creates a smooth, continuous model surface. Every slice of this surface along the axis on SI_{n+1} gives the probability distribution of SI_{n+1} given SI_n [36, 45].

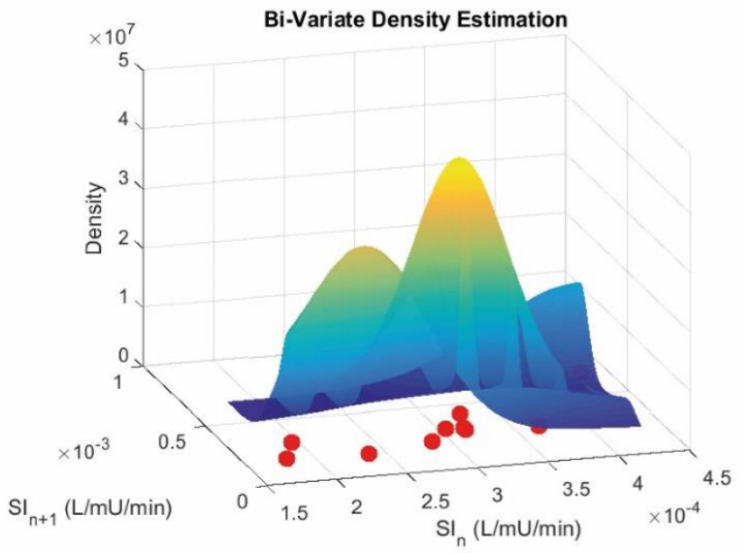


Figure 3.4: *Example of bi-variate kernel-density estimation for 10 data pairs [10].*

3.3.2 3D stochastic model

A second version of the stochastic model, the 3D stochastic model, has been built in order to provide higher patient-specificity, improved SI prediction and, thus, more tailored treatments [9, 10]. The 3D stochastic model has itself two versions but the most recent one is detailed here. It uses a tri-variate kernel-density estimation method which is similar to the 2D version. This model uses 2 inputs, SI_{n-1} and SI_n, to forecast future SI, SI_{n+1}, distribution [9, 10].

For the 3D model, SI is considered as a second order Markov chain, its state at the time n+1 depends on the two prior states at time n-1 and n [10, 47].

The conditional probability distribution is also obtained using the Markov property and is expressed [10]:

$$P\left(SI_{n+1} = z \mid SI_n = y, SI_{n-1} = x,\right) = \frac{p\left(SI_{n+1} = z, SI_n = y, SI_{n-1} = x\right)}{p\left(SI_n = y, S_{n-1} = x\right)} \tag{3.13}$$

The joint probabilities of the right-handed expressions can be estimated using kernel-density methods and bi- and tri-variate Gaussian kernel-density functions. It finally provides the probability of SI_{n+1} taking a specific value knowing SI_{n-1} and SI_n [10]:

$$\frac{P\left(SI_{n+1} = z \mid SI_n = y, SI_{n-1} = x\right)}{P\left(SI_n = y, SI_{n-1} = x\right)} = \frac{\frac{1}{N}\sum_{i=1}^{N} \frac{K_{hx_i}\left(u_{x_i}\right)}{p_{x_i}} \frac{K_{hy_i}\left(u_{y_i}\right)}{p_{y_i}} \frac{K_{hz_i}\left(u_{z_i}\right)}{p_{z_i}}}{\frac{1}{N}\sum_{j=1}^{N} \frac{K_{hx_j}\left(u_{x_j}\right)}{p_{x_j}} \frac{K_{hy_j}\left(u_{y_j}\right)}{p_{y_j}}} \tag{3.14}$$

where $K_h(u) = \frac{1}{\sqrt{2\pi}h} e^{\frac{-1}{2}\left(\frac{u}{h}\right)^2}$, the Gaussian kernel-density function centred on u with variance h and N, the number of data points available.

The variance h is determined using the Silverman's general rule of thumb (ROT):

$$h = 0.9686\sigma \left(\frac{mR^3 N^{\frac{3}{7}}}{Z} \right)^{-\frac{1}{7}} \tag{3.15}$$

where σ is the standard deviation of the data, m the number of data point inside a radius of $N^{\frac{-1}{7}}$ after orthonormalisation, R, the radius from the origin including Z*N data ($0 \leq Z \leq 1$) [10].

Each kernel-density function $K_h(u)$ in Equation 3.14 is normalised by the area under each Gaussian curve:

$$p_x = \int_0^\infty K_x(u)dx, \quad p_y = \int_0^\infty K_y(u)dy, \quad p_z = \int_0^\infty K_z(u)dz \tag{3.16}$$

An example of a tri-variate kernel-density estimation is shown in Figure 3.5.

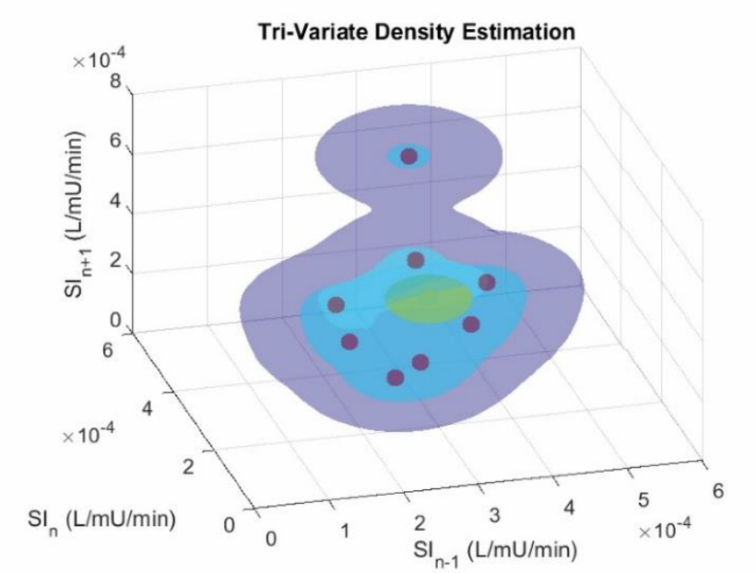


Figure 3.5: *Example of tri-variate kernel-density estimation for 10 data triplets [10].*

3.4 STAR GC protocol

STAR uses the ICING and stochastic model to ensure that the 5$^{\text{th}}$ and 95$^{\text{th}}$ percentiles of the predicted BG are inside the pre-set target range (4.4-8.0 mmol/L) [6, 9, 10, 40, 43]. The stochastic model is used to give a 90% confidence interval (CI) of future predictions of SI values based on its current and previous value. These predictions and the equations of the ICING

model are then used in conjunction to obtain a 90% CI of future likely BG predictions for a specific insulin and nutrition intervention. It is important to mention that the percentile values of SI correspond to the reversed (100-percentile) values of BG. This is because high SI values produce low BG levels [36]. The conversion between the percentiles of SI values to the percentiles of BG levels is shown in Figure 3.6. From the CI of BG predictions, STAR chooses the adequate insulin and nutrition intervention ensuring the 5th percentile of BG predictions to be above the lower band of the target range.

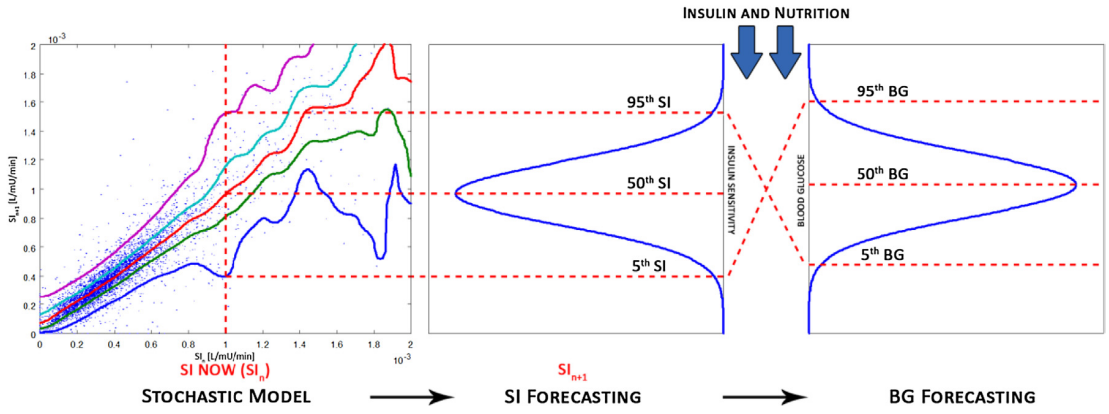


Figure 3.6: *SI forecasting using stochastic models and BG forecasting for given insulin and nutrition intervention. BG percentiles are obtained from reversed SI percentiles [9].*

It is a target to range approach. This allows a pre-set risk of only 5% of the BG of the patient to be below the lower band and to maximise the likelihood of BG in the desired target range [6, 41]. To reach this, STAR follows some guidelines and is composed of several steps.

First of all, it includes a starting and stopping criterion. The starting criterion for STAR is to have two successive BG measurements over 8.0 mmol/L within a 4-hour period [9, 40, 43]. The stopping criterion is to have BG levels inside the target band for at least 6 hours and with insulin rates less than 2.0 U/h. This suggests patients are stabilised and do not need intensive insulin therapy anymore but may require subcutaneous insulin [9].

Moreover, insulin and nutrition interventions are titrated following some rules. The dose of insulin administered varies from 0.0 to 6.0 U/h with increments of 0.5 U (excluding 0.5 U/h) [6, 9, 41]. This increment cannot be more than +2.0 U/h at a time for safety reasons [9]. An additional 1-3 U/h of continuous infusion can also be administered to highly resistant patients [6, 9, 41]. Nutrition intervention must be between 30 and 100% of the total caloric goal feed. The standard 100% goal feed is calculated for each patient individually based on age, and sex and corpulence using the reference of 25 kcal/kg/day [6, 8, 10, 48]. The increments are of 5% [6, 41] and the maximum change between two interventions is ± 30% [41, 48]. Such limits provide more robustness and hyperglycaemia is reduced gradually [6]. There is also a preference for increasing insulin before reducing nutrition. Nutrition is reduced if insulin is not sufficient to safely lower BG levels, what typically happens for highly resistant patients [9, 48].

STAR proceeds in four main steps to determine the optimal insulin and nutrition rates to administer to the patients. The different steps are shown on Figure 3.7 and detailed below [7].

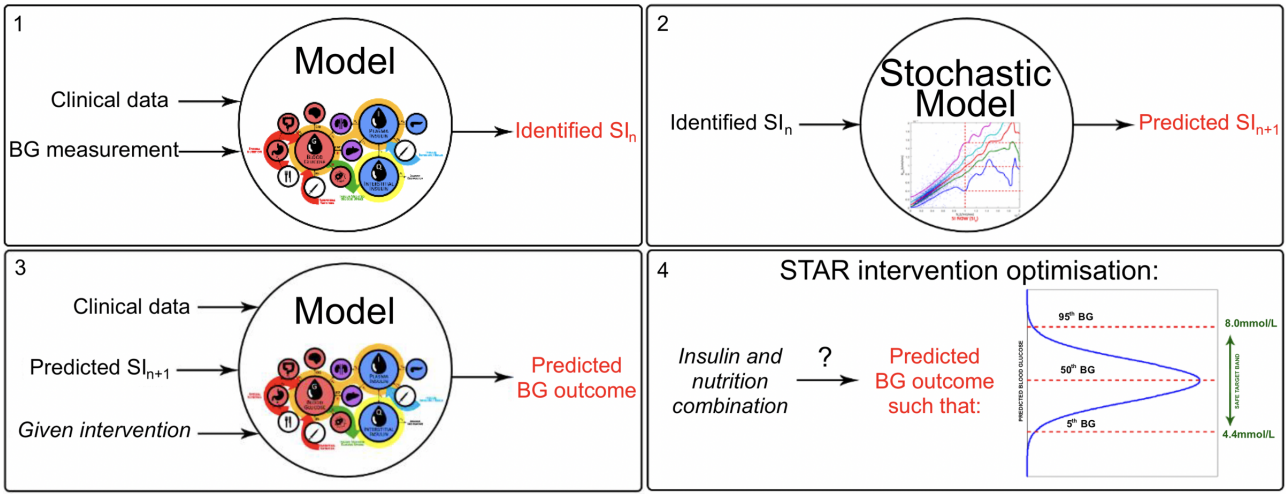


Figure 3.7: *4 steps of STAR GC framework. 1) SI identification from BG measurement and clinical data, 2) SI variability prediction by the stochastic model, 3) treatments and BG outcomes assessment from SI prediction using ICING model and 4) treatment choice providing optimal control and low risk of hypoglycaemia. Inspired from [7].*

1. SI identification

Current SI (SI_n) is evaluated from previous and current BG measurements and clinical data using the ICING model and integral-based methods [41]. Patient clinical data, BG measurements, insulin and nutrition interventions and model parameters are set up. A fitting window of 60 minutes is used to determine SI. This step accounts for inter-patient variability as SI is determined hourly for each patient [20]. SI is assumed to be independent of insulin and nutrition interventions [42]. (See Figure 3.7.1)

2. SI variability prediction

The stochastic model is used to determine distribution of possible future SI values for the different treatment intervals [41]. It uses the current identified SI values (SI_n) to obtain probability distribution functions. The 5th, 25th, 50th, 75th and 95th percentile predictions are given by the model. They are controlled to ensure the safety of the patient. This step accounts for intra-patient variability as the potential evolution of SI is based on patient-specific values. The range of possible SI values is wider for longer treatment intervals. This is synonymous with higher potential variability and so higher risks of hyper- and hypoglycaemia [7]. (See Figure 3.7.2)

3. Treatments and BG outcome assessment

All the possible treatments (insulin and nutrition) are assessed. For each of them, a predicted BG outcome is calculated from the 5th-95th prediction range of SI using the physiological model [9, 41]. In this case, SI is known and BG is unknown. The model gives the predicted 5th-95th percentile BG range simulated over a time period (last measurement + time interval) and the different BG ranges are retained and analysed in the last step [7]. (See Figure 3.7.3)

4. Treatment choice
The BG outcomes are checked to verify that the 5^{th} and 95^{th} percentiles of BG predictions lie in the specified target range. The 5^{th} percentile of BG predictions should not be below the lower limit of the target band (4.4 mmol/L) to ensure a risk of hypoglycaemia of maximum 5% [9, 41]. The treatment ensuring the best overlap of the target band and the required risk of hypoglycaemia is chosen [7]. (See Figure 3.7.4)

The last two steps are part of the treatment selection process of STAR. The different treatments possible are considered and it is checked that the corresponding BG predictions comply with some conditions. As mentioned in Chapter 1, this part will be modified and studied in Chapter 7.

Predictions and treatment selections are performed for the different time intervals, currently 1, 2 and 3 hours. The 2 and 3 hours time intervals are considered when there is a certain BG stability in the target range and when safety from hypoglycaemia is ensured [6, 9]. If treatments associated to different time intervals are acceptable, the nurses are free to choose between the different intervals, but the treatment associated with the longest time interval should be chosen to minimise the clinical workload. However, when the BG level is outside the target range, the time interval is fixed to 1 hour for patient safety [6]. Nurses are also free to reject all recommendations and adapt rates based on their clinical judgment [7].

In the choice of the optimal intervention, patient safety is the first priority. That means that a maximum risk of hypoglycaemia of 5% is ensured. The second priority is reaching 100% of the goal feed [8, 48]. To achieve that, nutrition is modulated less dynamically than insulin. Nutrition rates are reduced only if increasing insulin is not sufficient to reduce BG levels and inversely. If different interventions are acceptable, the protocol selects the one with the greatest nutrition administration [6].

As mentioned in Section 3.1, STAR is fully generalisable. In addition to the target range and the risk level, other parameters can be changed: nutrition regimes (enteral or parenteral), insulin administration (by bolus or infusion), maximum insulin and nutrition rates and measurement frequency [7, 20]. The treatment proposed by STAR is only a suggestion. Clinicians are free to make some changes with respect to the recommendations. Those changes are recorded and used by STAR for the future treatment calculations [7].

3.5 Performances and limitations

STAR was shown to provide safe and effective control for ICU patients. In a clinical trial performed on actual clinical data of patients coming from Christchurch Hospital, New Zealand and Gyula Hospital, Hungary [8], patients under STAR-2D, the version of STAR using the

2D stochastic model, showed more than 86% of the time in the target band and very few occurrences of severe hypoglycaemia (1.5 and 4.3% of patients respectively). STAR provided a safe and effective control with reduced time on protocol and workload [8]. In another trial [9], these results were compared with another clinical trial using STAR-3D, the version of STAR using the 3D stochastic model. The two versions were shown to provide similar, high, quality of control. However, STAR-3D provides improved GC outcomes with reduced incidence of hypoglycaemia and increasing nutrition delivery [9].

On the one hand, the 2D version is only based on the current identified current SI value to forecast future SI distribution. The model is then not able to accurately capture and forecast SI variability as well as to capture the direct measurement or identification errors directly impacting the SI predictions [10, 46, 49]. As a result, STAR-2D may be over-conservative for stable patients by providing wide prediction bands. Even if this conservation allows to reduce the risk of hypoglycaemia, it also limits insulin dosing and therefore the ability of the controller to bring BG to the normorange, directly impacting efficacy. At the same time, it may be under-conservative for less stable patients and gives narrow prediction bands. This will increase the risk of hypoglycaemia with aggressive insulin dosing [10, 46].

On the other hand, in STAR-3D, the stochastic model leads to tighter prediction bands. Insulin is thus administered with more certainty and its dosing is more aggressive, while still ensuring a low risk of hypoglycaemia (safety). The 3D model was shown to provide tighter predictions more than 70% of the time leading to a greater patient-specificity. The prediction ranges are even tighter when the hour-to-hour variation (%ΔSI) is within $\pm$ 20%. This result suggests that previous metabolic state of the patients has a direct impact on future SI. The stable patients tend to remain stable and the more variable patients are likely to have bigger metabolic variations [10]. STAR-3D therefore improves predictions to provide optimal dosing, offering a higher safety and effective control, while significantly increasing caloric intake, all associated with improved outcomes. These observations are true cohort-wide and at a per-patient perspective. It also provides a more patient-specific GC by better considering inter- and intra-patient variability [9, 10, 46].

However, more data is required to build the 3D stochastic model and STAR-3D engenders an increased workload as more measurements per day are required (13.7 vs 12.9 measurements per day [8, 9]) [9, 10]. More globally, the STAR protocol presents some limitations. Parameters used to define the physiological model are approximations or coming from the literature which can be a source of error. The stochastic model is based on patient data and might not be able to characterise some specific behaviours, although it is based on thousands of hours of data [7].

3.6 Summary

This Chapter presented and detailed the STAR GC framework. STAR provides a unique risk-based dosing approach and is fully generalisable. The protocol is based on the combination of a physiological and a stochastic model. They are both successively used to determine the combination of insulin and nutrition interventions to ensure patient safety, nutrition closest to 100% of the goal feed and a minimum clinical workload.

Two versions of the stochastic model and therefore of STAR were developed and the 3D-version offers the best outcomes with the greatest patient-specificity, efficiency and safety though it requires more data and generates more workload.

The 3D-version will be used in this master thesis to respond to the different objectives detailed in Chapter 1.

Chapter 4

Virtual trials and virtual patients

This Chapter presents the tools used to assess and compare the different versions of the STAR protocol studied in this thesis. Virtual trials are used to design and validate GC protocols on virtual patients. Such trials have been validated and generalised for GC in ICU patients [50]. They allow to compare different protocols on the same cohort of patients before their clinical implementation. Virtual trials are performed on virtual patients. The cohort of virtual patients used to do the different analysis is also presented in this Chapter. Virtual patients are created based on retrospective data of patients from two different ICUs. The different metrics used to compare and assess GC safety performance and workload are also briefly detailed.

4.1 Virtual patients

Virtual trials are performed on virtual patients based on retrospective clinical data. More specifically, each virtual patient is characterised by a unique SI(t) profile obtained using an integral based fitting method and the physiological ICING model [40, 42]. The model uses patient-specific BG measurements and given insulin and nutrition inputs to derive SI(t) profiles. SI is time varying and is identified hourly from those clinical data. The patient-specific profiles obtained were shown to be independent of the clinical inputs used to create them [42]. They fully characterise the patient metabolic state and its evolution over time [40, 50].

Using real patient data to create the virtual patients allows for the best possible imitation of the behaviours observed in the clinical environment [40].

4.2 Virtual trials

Virtual trials are a clinically validated tool used to design, assess and validate GC protocols. They have emerged with the model-based protocols. These in-silico trials allow to assess the

performance and safety of different protocols by comparing them on the same cohort of patients [50]. This is useful in order to help the clinicians to choose the most efficient protocol design prior to its clinical implementation [6, 40].

Virtual trials are performed on virtual patients preventing any predictable and avoidable adverse effect to appear after the clinical implementation and then avoidable risks on actual patients [6].

The use of virtual trials is time and cost saving in the development of GC protocols. They allow to optimise the protocol virtually and to assess its performance and safety on virtual patients prior to costly clinical trials, and before its clinical implementation, leading to more robust protocols [40, 42].

In the context of this thesis, the trials are simulated on MATLAB using a JAVA version of STAR. The SI(t) profiles of the virtual patients are used to create the stochastic models used for the different trials performed on the same cohort of patients. The protocol is simulated on the cohort of virtual patients. The stochastic models and the virtual trials are performed using five-fold cross-validation [40, 42]. The cohort of virtual patients is divided in five random groups. Then, STAR is simulated on one group (the validation group) by using the stochastic model built based on the four other groups (the training groups). This is repeated for each group. At the end of the simulations, the results for each group are gathered and results at the whole cohort level are obtained.

However, virtual trials are not sufficient to validate GC protocols. Indeed, they generally represent ideal conditions with full compliance of the nurse to protocols which is not the case in clinical conditions. Results in terms of protocol performances and patient safety may be biased compared to the ones obtained clinically due to the imperfect compliance and the potential clinical errors present in clinical practices [51]. More specifically in the simulation of the virtual trials, the longest treatment is always chosen if different recommendations are available. In the clinical reality, nurses are free to choose between the different possibilities according to other factors, not considered in virtual trials and can also reject the treatment suggested [7]. Clinical trials must then be conducted in addition to the virtual ones to completely validate the different GC protocols [7, 20].

4.3 Cohorts and episodes

Different virtual trials are performed in this thesis. They are all based on retrospective data of 603 critically ill patients treated with either STAR or SPRINT and coming from different ICUs. There are 292 patients treated with SPRINT. They were treated between July 2005 and May 2007 in Christchurch Hospital, New Zealand. The patients with STAR were treated from June

2011 to May 2015. They come from two 2 ICUs, 264 of them were admitted in Christchurch Hospital, New Zealand and 47 in Kalman Pandy Hospital, Hungary. More specific information concerning the cohorts are available in a previous work [7].

In total, 820 GC episodes corresponding to 68 629 hours of control are considered. The number of GC episodes is superior to the number of patients in the cohorts as a same patient can experience several episodes of SIH and require several episodes of GC during his stay in ICU. This happens when the patient is stabilised and then experiences a new BG dysregulation or when GC is stopped for a clinical exam or surgery and restarted after [7].

From the initial number of episodes, only the ones lasting more than 10 hours and with an initial BG level above 7 mmol/L are retained. This allows to discard the episodes that may not be representative of typical GC patients. There remains 681 GC episodes and 59 439 hours of control from this selection. From these episodes, a cohort of 681 virtual patients is built.

4.4 Virtual trials comparison analysis

To be able to analyse the results obtained from the different trials and assess the performance and safety of the different versions of STAR studied, different metrics are used. The metrics used here are the same as the ones used for the study of the extension on STAR-2D and correspond to metrics usually used in GC studies [14]. The different protocols are compared in terms of performance, safety and workload.

The performance is assessed by the median and interquartile range (IQR) of hourly resampled BG (mmol/L) and %BG in different bands (4.4-8.0 mmol/L and 4.4-7.0 mmol/L). It is also possible to assess the performance by looking at the time spent in the different bands and in this case at the number and percentage of patients with more than 50%BG in the bands.

Safety is analysed using the %BG outside the target band (%BG $<$ 4.4 mmol/L and %BG $>$ 8.0 mmol/L), the %BG below the limit of severe hypoglycaemia (%BG $<$ 2.2 mmol/L) and the number of patients experiencing severe hypoglycaemia.

Finally, workload is compared by looking at the number of measurements per day. The median and interquartile range of per-patient insulin (U/h) and nutrition rates (%GF) are also compared.

In addition to these metrics, other results will be used to assess the performance of the new treatment selection processes studied in Chapter 7. The percentage of unchanged nutrition and insulin rates interventions as well as the per-patient median [IQR] insulin rate (U/h) and time interval (min) variations will be also compared. Performance of GC will also be assessed by

studying the glycaemic variability. Low variability has been associated with improved outcomes in GC [29, 30, 52]. Glycaemic variability is assessed by the median [IQR] BG level variation.

Those different metrics will be used to assess the risks and rewards associated with the different versions of STAR developed and studied in this thesis. They will allow to discuss and conclude on the different versions tested.

4.5 Summary

This Chapter presented the tools that will be used to assess the performance and safety of the different versions of STAR GC protocol studied in this master thesis. First, virtual trials allow the protocol to be simulated on virtual patients. The protocol can then be optimised before its clinical implementation avoiding unnecessary risks for patients.

Chapter 5

3D Stochastic models

The aim of this Chapter is to build and validate the stochastic models that will be used for the different virtual trials performed in this thesis. 3D stochastic models are used as they were proven to provide improved SI predictions, thus, resulted in improved GC outcomes [9, 10, 46]. They are developed using a tri-variate kernel-density method and are validated using a five-fold cross-validation.

5.1 Introduction

SI is a patient-specific parameter representing patient metabolic response to insulin. STAR predicts SI variability using a stochastic model. These predictions are used to optimise patient treatment minimising predicted risk of hypoglycaemia. SI is considered to be constant over a 1 hour period but is time-varying, changing from hour to hour. As intra-patient variability is not patient-specific [4], the stochastic models are built on ICU patient data to forecast future SI distributions. The predictions can then be used to predict future BG levels in response to a certain nutrition and insulin intervention [10, 36, 46].

As discussed in Chapter 3, different versions of the stochastic models have been developed for STAR. Compared to the original 2D model using only the current identified SI to forecast variability, the 3D version also uses prior temporal information to better characterise future potential variability [10]. This new version has been clinically proven to provide tighter prediction ranges and improved GC outcomes compared to the 2D version [9, 10]. The 3D version of the stochastic models has then been chosen to be used in the different trials of this master thesis.

One of the main goals of this thesis is to assess the risk and reward trade-off of an extension of STAR to measurements intervals up to 4-, 5-, or 6-hourly. Six stochastic models are needed,

one for each of the different time intervals considered. They will also be validated using cross-validation methods.

5.2 Models construction

5.2.1 Patients and cohort

Stochastic models are built based on patient data. The cohort of patients used is described in Chapter 4. The GC episodes considered are the ones remaining after the selection process, i.e. only the episodes lasting more than 10 hours and with a starting BG level above 7.0 mmol/L. In total, 681 GC episodes totalling 59 439 hours of control and coming from two different ICUs (Christchurch, New Zealand, and Gyula, Hungary) are considered.

SI is the only patient-specific parameter required to build the stochastic models. Patient-specific SI profiles are created by identifying SI hourly for each patient using the ICING model and an integral-based fitting method as described in Chapter 3. The identified SI profiles are then transformed into triplets (SI_{n-1}, SI_n, SI_{n+i}) where i is the time interval (i=1 to 6).

5.2.2 Models creation for different time intervals

To consider an extended version of STAR to longer time intervals (1-6 hourly), stochastic models must be created for the different intervals considered. In total, six different stochastic models are built. They are all built upon the same cohort of patients and only the values of SI_{n+i} in the triplets change between the models. For each of the time intervals, the corresponding triplets of the virtual patients (SI_{n-1}, SI_n, SI_{n+i}, i=1 to 6) are gathered into a different matrix. These matrices are the input elements of the models.

The 3D stochastic models are built using kernel-density methods. In particular, a tri-variate kernel-density estimation method is used with the triplets of patient data. The development of the method has been detailed in Section 3.3.2. Future SI predictions, SI_{n+i}, are obtained by knowing current and previous SI values (SI_n and SI_{n-1}). For each pair of (SI_{n-1}, SI_n), there is a conditional probability density function giving the forward predictions of SI_{n+i}. The model obtained provides, for any pair (SI_{n-1}, SI_n) the different predicted percentiles (5^{th}, 25^{th}, 50^{th}, 75^{th}, 95^{th}) for SI_{n+i}.

Each percentile of the model can be represented by a surface giving the corresponding percentile prediction of SI_{n+i} from a pair of (SI_{n-1}, SI_n). An example is shown in Figure 5.1 for the 5^{th} and 95^{th} percentiles of predictions for the model with a 6-hourly time interval.

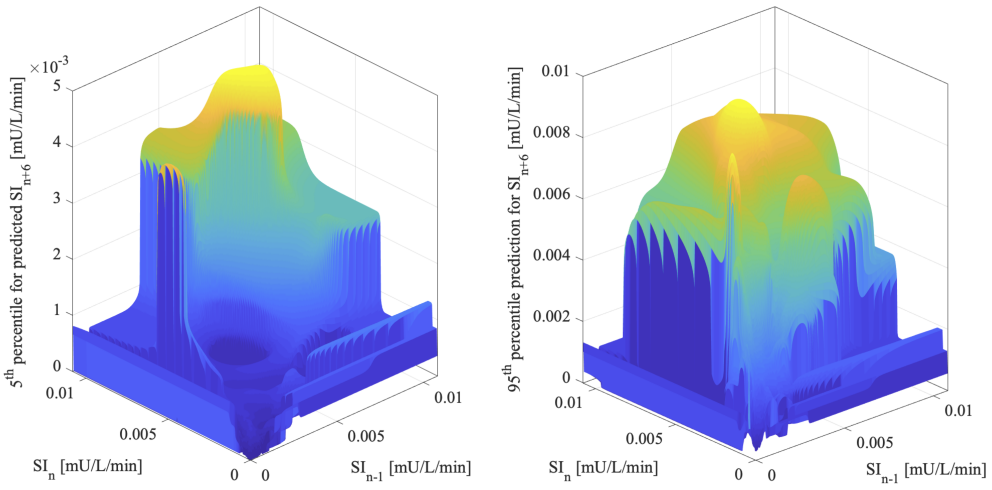


Figure 5.1: *Comparison between the* 5^{th} *(left) and* 95^{th} *(right) percentile prediction for 6-hourly 3D stochastic model.*

5.2.3 Cross-validation

Cross-validation is used to validate the capacity of the model to accurately predict SI variations on a completely different cohort of patients. More specifically, the different models are built using a five-fold cross-validation. Models are built using 80% of patients and validated on the remaining 20% of patients [42, 53].

The cohort of virtual patients considered in this thesis is thus divided in five random groups of similar size (136 or 137 patients). These groups were randomised such that the number of SI triplets identified is similar. Four of these groups (544 patients) are used to build the model to be validated on the last group (136 or 137 patients). This allows the ability of the stochastic model to predict the actual SI of ICUs populations to be assessed. In total, 5 models are thus built and validated, and thus each patient data is only used once for validation.

The validation is done by comparing the prediction accuracy of the model built on the training group on the data triplets in the validation group. The percentages of data triplets within the predicted 5^{th}-95^{th} and 25^{th}-75^{th} prediction ranges are assessed. The prediction in the 5^{th}-95^{th} percentile range is expected to contain 90% of the SI_{n+i} values, 50% for the 25^{th}-75^{th} percentile range. These percentages are assessed for the different stochastic models.

5.3 Validation and comparison results

The models are compared in terms of prediction accuracy but also in terms of the predicted range width.

5.3.1 Comparison between the different time intervals

A representation of the evolution of SI and the 3D predictions ranges for the different 1-hourly and 6-hourly time intervals for one specific virtual patient is shown in Figure 5.2. From this Figure, it can be observed that the prediction range is much wider for longer time intervals. This is shown more globally for the whole cohort and for all the time intervals with the median width [IQR] of the 5^{th}-95^{th} prediction range reported in Table 5.1. The 5^{th}-95^{th} prediction range width constantly increases for longer time intervals from a median width [IQR] of 2.5e-04 [2.0e-04 3.6e-04] L/mU/min for 1-hourly time interval to 5.2e-04 [4.1e-04 7.7e-04] L/mU/min for 6-hourly time interval. These results clearly reflect the increased potential variability behaviour as time intervals are longer. Potential hyper- and hypoglycaemic risks are thus higher, and the resulting treatments will be more conservative with less aggressive insulin dosing than for lower time intervals with higher confidence.

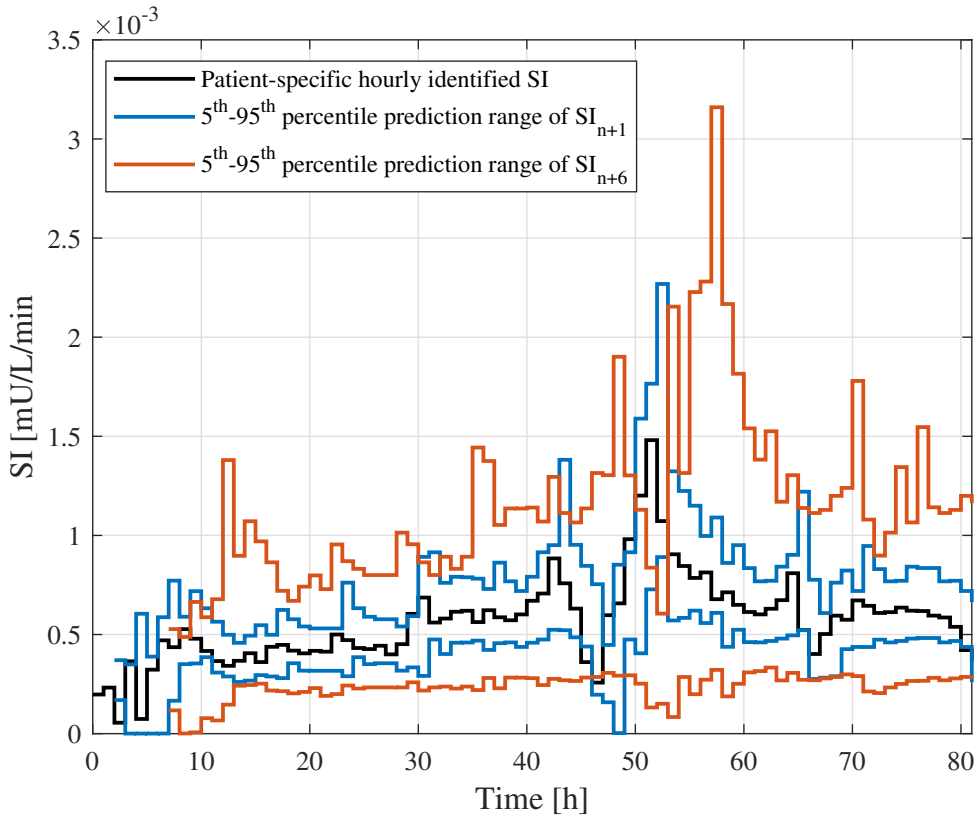


Figure 5.2: *Representation of hourly identified SI evolution and corresponding 1-hourly (blue) and 6-hourly (red) 3D prediction ranges for one specific virtual patient.*

	1-hourly	**2-hourly**	**3-hourly**	**4-hourly**	**5-hourly**	**6-hourly**
5^{th}-95^{th} prediction width median [IQR] (L/mU/min $\times 10^{-4}$)	2.5 [2.0 3.6]	3.4 [2.6 5.0]	3.9 [3.1 5.9]	4.4 [3.3 6.7]	4.8 [3.7 7.3]	5.2 [4.1 7.7]

Table 5.1: *Prediction range width comparison between 3D stochastic models for different time intervals (1-6 hourly).*

Another observation that can be made from Figure 5.2 is that there is an increased mismatch between the prediction range and the patient-specific identified SI as the time interval increases. This is particularly noticeable for sudden big changes in SI as in the hour 52. The identified SI value is outside of the prediction range of the model corresponding to a 6-hourly time interval. The model was not able to predict such variability, based solely on information from 6 hours before where SI was actually decreasing, thus explaining the lower predicted range. This suggests that the use of these models can lead to BG level predictions and treatment recommendations not well suited for highly variable patients, although the very high prediction accuracy suggests this does not occur very often. This can be associated with increased risk of unpredicted extreme BG values and then reduced safety as the time interval increases.

In these models, only two values are needed to predict future SI. Ideally, more values would be needed to predict future SI for longer time intervals. This would give a better representation of the overall evolution of the patient whether its SI is increasing, decreasing or stable and would decrease the mismatch observed. For example, it would be better to use the previous 3 values to predict SI_{n+3}, the previous 4 values to predict SI_{n+4}, and so on. However, this is computationally really hard.

While the prediction range width increases, the relative increase decreases as the time interval increases. This is represented by Figure 5.3 and Figure 5.4. These Figures represent the ratio of the 5^{th}-95^{th} percentile prediction ranges between the 1-hourly and the 3-hourly 3D models (Figure 5.3) and between the 4-hourly and the 6-hourly 3D models (Figure 5.4). Figure 5.3 shows that the 1-hourly 3D model provides tighter prediction ranges than the 3-hourly and in particular between $\pm 20\%\Delta SI$ meaning that the 1-hourly 3D model leads to more specificity and particularly for stable patients. In Figure 5.4, the 4-hourly 3D model also provides tighter prediction ranges than the 6-hourly 3D model but, in this case, the ratio remains more or less the same for any $\%\Delta SI$. These observations corroborate the ones obtained with Figure 5.2 and Table 5.1. The ratio is closer to 1 for the 4-hourly versus the 6-hourly ratio meaning that these two models provide approximately the same specificity. This is not the case for the 1-hourly versus the 3-hourly. From these observations, it can be concluded that the difference in prediction range width decreases between the models as the time interval increases and so the loss of specificity also decreases.

5.3.2 Cross-validation results

The percentage of SI_{n+i} values of the virtual patients contained in the 5^{th}-95^{th} and 25^{th}-75^{th} percentile prediction ranges is computed for the different time intervals and is reported in Table 5.2. Approximately 90% and 50% of the values are respectively contained in the 5^{th}-95^{th} and 25^{th}-75^{th} percentile prediction ranges given by the 3D stochastic models for all the time intervals. These percentages coincide with what was expected by building the models. Those results allow to conclude that the different models represent well how SI evolves in ICU patients

and can be generalised to other patient cohorts coming from different protocols and ICUs. They can be used to give specific predictions of SI values even for large time intervals.

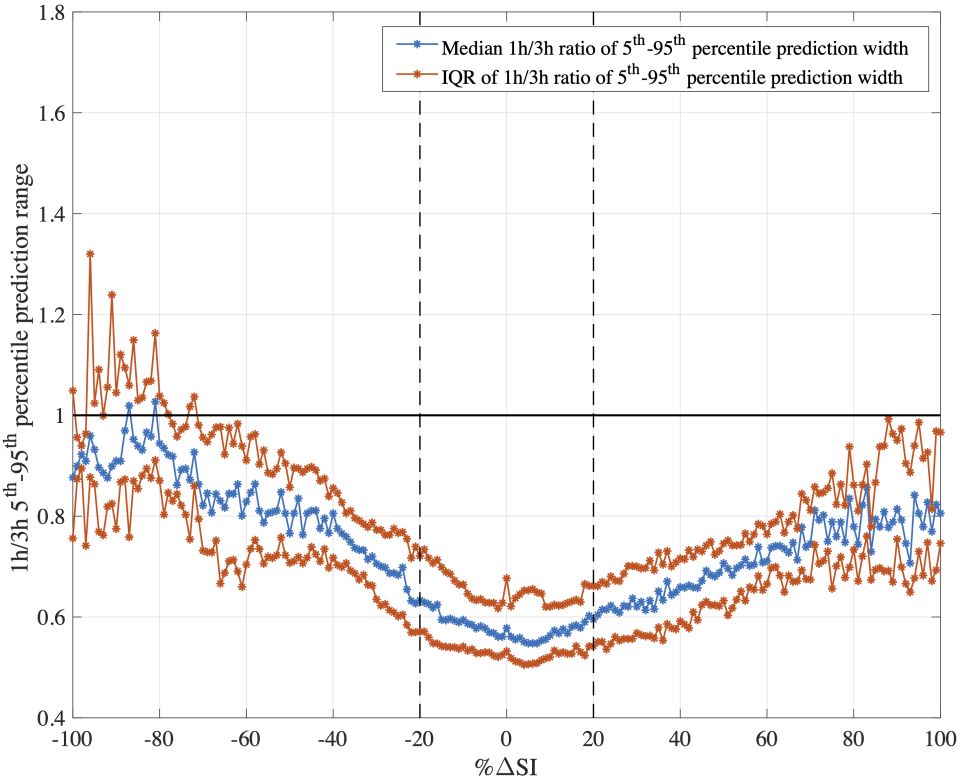


Figure 5.3: *Median [IQR] ratio of* 5^{th}-95^{th} *percentile prediction width between the 1-hourly and 3-hourly 3D stochastic model as a function of the hour-to-hour percentage change in SI.*

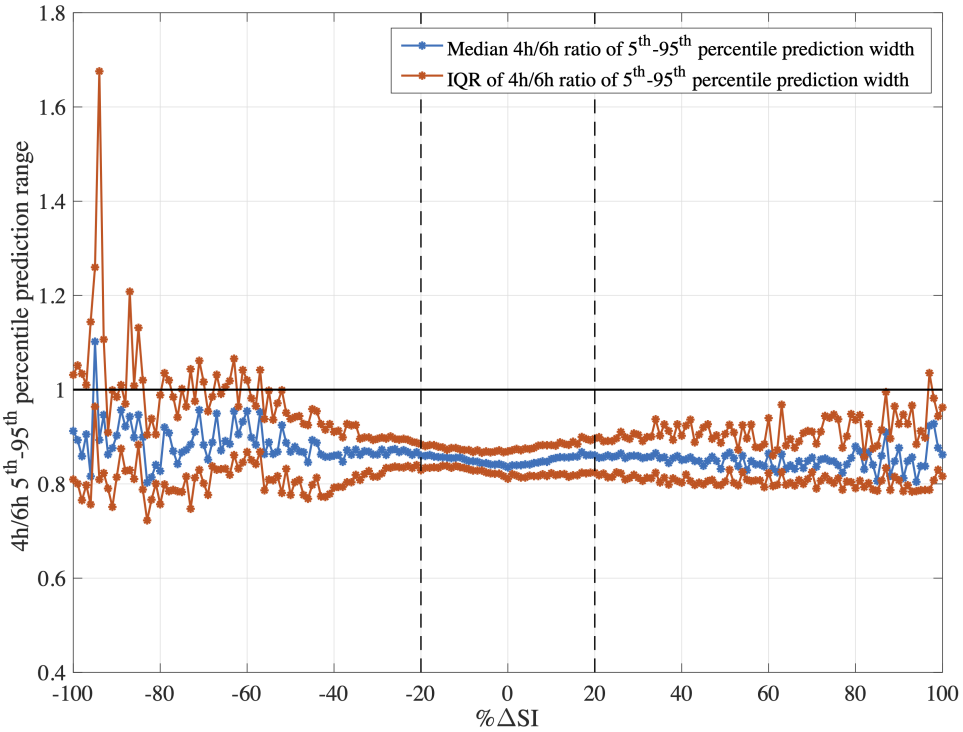


Figure 5.4: *Median [IQR] ratio of* 5^{th}-95^{th} *percentile prediction width between the 4-hourly and 6-hourly 3D stochastic model as a function of the hour-to-hour percentage change in SI.*

Another observation is that the percentage of predictions decreases as the time interval increases while remaining very close to the expected 90% and 50%. This can be explained by the mismatch described in the previous Section that appears between the identified SI profile and the prediction ranges for higher time intervals. As the models for higher time intervals may fail to predict greater variability, less percentage of identified values is contained in the prediction ranges.

	1-hourly	**2-hourly**	**3-hourly**	**4-hourly**	**5-hourly**	**6-hourly**
Total number of triplets	58082	57401	56720	56039	55358	54677
% predictions in 5^{th}-95^{th} range	91.1	90.8	90.8	90.7	90.7	90.6
% predictions in 25^{th}-75^{th} range	53.8	52.4	51.8	51.4	51.0	51.0
% identified SI above 5^{th}-95^{th} prediction range	3.0	3.6	3.9	4.1	4.2	4.3
% identified SI below 5^{th}-95^{th} prediction range	5.8	5.6	5.3	5.2	5.1	5.1

Table 5.2: *Five-fold cross-validation results summary of prediction power comparison between 3D stochastic models for different time intervals (1-6 hourly).*

The cross validation also allows the mismatch highlighted in Section 5.3.1 to be quantified. This is done by computing the percentages of identified SI values above and below the **5^{th}-95^{th}** range. Identified values above the range mean higher risk of hypoglycaemia and conversely, values below the range show a risk of hyperglycaemia. For the different time intervals, the risk of hyperglycaemia is higher than the risk of hypoglycaemia (5.1% vs. 4.3% of identified SI respectively below and above the predicted range for 6-hourly time intervals). While the mismatch increases with the time interval (Figure 5.2), the actual risk obtained only slightly increases. This is related to the increased width of the prediction compensating for the mismatch.

5.4 Summary

This Chapter developed and validated the stochastic models that will be used for the different virtual trials performed in this thesis. The new clinically validated 3D stochastic model method was used to build new stochastic models for different time intervals (1-6 hourly).

The different models were compared and some observations could be made. Particularly, models built for longer time intervals provide wider prediction ranges. They seem to be less specific and

thus more conservative. They could then be associated with reduced safety for the patients. However, the loss of specificity decreases as the time interval increases and so the loss of safety may stabilise for longer time intervals. These different observations will be checked and possibly confirmed with virtual trials performed in the next Chapter.

The models were also validated using a five-fold cross-validation. It resulted that they represent well ICU patient's intra-variability and can then be generalised to other patient cohorts from different ICUs and protocols.

Chapter 6

Virtual trial on STAR extension to 4-, 5-, and 6-hourly intervals

This Chapter aims at quantifying the impact of the extension from 1 to 3-hourly to 1 to 4-, 5-, and 6-hourly of the measurement and treatment intervals on the performance of STAR in GC. The protocol uses the six stochastic models developed in Chapter 5.

The risk and reward trade-off of the extension is studied by conducting a virtual trial on STAR-3D adapted to allow longer measurement and intervention intervals. Performance, safety and workload are compared between each protocol. The results obtained are also compared with previously virtual trial results of STAR using the old 2D stochastic model [14].

6.1 Introduction

The current version of STAR uses 1 to 3-hourly prediction intervals to determine 1 to 3-hourly treatment intervals while ensuring a certain risk of hyper- and hypoglycaemia, representing an average of 12 BG measurements per day [14]. Nurse's workload in ICU is directly linked with the safety and quality of care of the patients [13]. This workload is easier to manage in ICUs where the nurse per patient ratio is relatively high as it is the case at the Christchurch Hospital, New Zealand. However, in other ICUs where the nurse per patient ratio is lower such as the University Hospital Center of Liège, Belgium, the same workload can represent a critical clinical burden [2, 14, 51]. The relatively elevated workload was specifically reported as a barrier to adoption following a clinical trial of STAR in Liège [12]. The excessive burden of frequent BG measurements may lead to a poor protocol compliance. Protocol compliance directly impacts BG outcomes, and, therefore, associated clinical outcomes [13, 51, 52]. There is thus a need to decrease the workload of the nurses and in this context of GC to improve their compliance to protocols and GC outcomes. A first approach would be to reduce the number

of measurements and interventions per day by extending the measurement and intervention interval to 1 to 6-hourly.

A virtual trial quantifying the risk (reduced safety and performance) and reward (reduced workload) trade-off of an extension of the measurement and intervention interval to 1 to 6-hourly has already been conducted using the old 2D stochastic model [14]. This study concluded that longer time intervals are associated with reduced workload but slightly increased risks of hyper- and hypoglycaemia. However, performance and safety of the extended version of STAR remain much better than the ones of other major protocols. It highlights a clear risk and reward trade-off between the workload and the GC outcomes even if STAR stays robust to adaptation to longer time intervals, but requires further clinical validation to confirm these results [14].

The goal of this Chapter is to study the impact of an extension of the 1 to 3- to 4-, 5- and 6-hourly measurement and intervention interval of STAR-3D GC framework. STAR-3D is chosen as it was proven to better account for inter- and intra-patient variability providing more patient-specific GC [9]. These results are a consequence of the use of 3D stochastic models basing their predictions on current and previous SI values. The model provides tighter predictions leading to an optimal dosing with higher safety and effective control than STAR-2D [9, 10]. It is assumed that the same risk and reward trade-off highlighted by the trial on STAR-2D will be observed with the risk being reduced performance, safety and nutrition administration and a reduced workload as the reward.

To be able to assess the impact of the extension of the time interval on the performance and safety of STAR-3D presented in Chapter 3, validated virtual trials are used. Using virtual trials allows the safety and performance of the different protocols to be compared on the same cohort of patients. This trial is performed on the cohort of virtual patients described in Chapter 4. The results obtained from the trial are compared using the metrics described in the same Chapter.

6.2 Protocol extension

Few changes were required in STAR protocol design to adapt it to 1 to 6-hourly measurement and intervention intervals. The main change consisted in allowing the protocol to suggest longer treatment intervals if it meets the safety requirements. The treatment selection process remains unchanged and the same constraints on the 5^{th} and 95^{th} percentiles of BG prediction are used.

Another important part of the protocol that was changed was the creation of the corresponding stochastic models. Six 3D stochastic models were built, one for each time interval, giving the 5^{th}-95^{th} percentile prediction ranges for 1 to 6-hourly intervals. Those models were built using a tri-variate kernel-density estimation method.

6.3 Results

6.3.1 STAR-3D virtual trial results

STAR-3D virtual trial results are gathered in Table 6.1. The number of GC hours increases as the time interval increases for the same number of GC episodes. This depends on what happens at the end of the simulation. For the same patient, the control can last longer for a last 6-hourly treatment interval than for a 3-hourly treatment interval. This adds 3 hours in the number of GC hours for this patient. Extending this to the whole cohort, the number of GC hours differs between the versions of the protocol and increases as the measurement and treatment interval increases.

	STAR-3D-3H	**STAR-3D-4H**	**STAR-3D-5H**	**STAR-3D-6H**
# GC episodes	681	681	681	681
# GC hours	59209	59522	59701	60054
# BG measurements	29903	25471	22951	20696
# BG measurements/day	12.1	10.3	9.2	8.3
Median BG (mmol/L)	6.4 [5.8 7.2]	6.6 [6.0 7.4]	6.7 [6.1 7.5]	6.8 [6.2 7.5]
Median insulin (U/h)	3.5 [2.0 5.0]	3.0 [2.0 4.0]	2.5 [2.0 3.5]	2.5 [1.7 3.0]
Median nutrition (%GF)	99.7 [84.5 100.0]	94.7 [78.8 100.0]	89.4 [74.5 97.3]	85.3 [70.1 94.7]
%BG in 4.4-8.0 mmol/L	83.8	82.9	82.0	81.4
%BG in 4.4-7.0 mmol/L	67.5	62.9	58.8	56.3
%BG > 8.0 mmol/L	14.5	15.5	16.4	16.9
%BG < 4.4 mmol/L	1.7	1.7	1.6	1.6
%BG < 2.2 mmol/L	0.03	0.03	0.05	0.05
# patients ≥50%BG in 4.4-8.0 mmol/L (%)	591 (86.8%)	592 (86.9%)	586 (86.0%)	584 (85.7%)
# patients ≥50%BG in 4.4-7.0 mmol/L (%)	479 (70.3%)	457 (67.1%)	432 (63.4%)	398 (58.4%)
# patients min BG < 2.2 mmol/L (%)	12 (1.8%)	14 (2.0%)	19 (2.8%)	23 (3.4%)

Table 6.1: *Virtual trial results for STAR-3D for 1 to 3-, 4-, 5-, and 6-hourly intervals.*

Different observations concerning the performance can be made from the results as the measurement and treatment interval increases. The %BG in the target band (4.4-8.0 mmol/L) slightly decreases from 83.8% for STAR-3D-3H to 81.4% for STAR-3D-6H. The difference is more significant in the 4.4-7.0 mmol/L band with a transition from 67.5% for STAR-3D-3H to 56.3% for STAR-3D-6H. This decrease is related to the shift upward in median [IQR] BG from 6.4 [5.8 7.2] to 6.8 [6.2 7.5] mmol/L. This tendency is also represented by the number of patients having more than 50%BG in the different bands.

Concerning safety, there is an increased incidence of both hyper- and hypoglycaemia with increased time intervals (14.5 (3-hourly) vs. 16.9 (6-hourly) %BG $>$ 8.0 mmol/L and 0.03 (3-hourly) vs. 0.05 (6-hourly) %BG $<$ 2.0 mmol/L). The number of patients experiencing severe hypoglycaemia also increases from 12 to 23 patients. The workload significantly decreases as the time interval increases from 29 903 BG measurements for STAR-3D-3H to 20 696 BG measurements for STAR-3D-6H corresponding respectively to 12.1 and 8.3 measurements per day.

Regarding insulin and nutrition rates, they both decrease as the time interval increases which is correlated with the increased risk of hyperglycaemia. However, the median [IQR] nutrition remains quite high with 85.3 [70.1 94.7] %GF for STAR-3D-6H.

6.3.2 STAR-3D virtual trial results once target band is reached

The results of the virtual trials can also be expressed from the time where the patients have reached the target band, i.e. the time at which the BG level falls back into the pre-set target band. These results are gathered in Table 6.2. From the initial cohort, 671 (98.5%) patients have reached the target band. The time to reach the target is the same for all the measurement and treatment intervals (2.0 [1.0 3.0] h). At their entry in GC, patients are not yet stabilised. The protocol is then constrained to propose 1-hourly measurement and treatment intervals to stabilise the patient. In the initial hours under GC, there is also less nutrition and more insulin administered as the BG level needs to decrease.

The performance is slightly higher in this case. However, the decrease in %BG in the target bands occurring when the time interval increases remains the same. Indeed, the discarded hours are hours where BG is outside and above the target band. The median [IQR] BG is barely impacted with a very slight decrease for 6-hourly intervals with respect to the raw data by considering the entire GC length (6.7 [6.1 7.4] mmol/L once the target band reached vs. 6.8 [6.2 7.5] mmol/L for the raw data).

The incidence of hypoglycaemia and the number of patients experiencing severe hypoglycaemia did not change. However, the incidence of hyperglycaemia decreased as the hours discarded are hours of initial hyperglycaemia (10.7% for STAR-3D-3H once the target band reached versus 14.5% for STAR-3D-3H in raw data) and this is directly linked with the slightly lower median BG. The change in safety between the different time intervals did not change. The workload also slightly decreased by 1 measurement per day for each protocol by discarding initial hours. The first hours of control require higher measurement and treatment intervals because they are often constrained to 1 hour while outside the target band, representing the very acute phase of metabolic stress and SIH.

The median [IQR] insulin is slightly decreased, directly impacted by the discarded hours and the median [IQR] nutrition in %GF is increased (89.4% [74.5% 94.7%] for STAR-3D-6H once the target is reached versus 85.3% [70.1% 94.7%] for STAR-3D-6H with raw clinical data).

Overall, the changes between the protocols are identical. GC performed during the discarded hours seems to be independent of the measurement and treatment interval allowed and changing it has no impact on what happens during these hours.

	STAR-3D-3H	**STAR-3D-4H**	**STAR-3D-5H**	**STAR-3D-6H**
# GC episodes	671 (98.5%)	671 (98.5%)	671 (98.5%)	671 (98.5%)
# GC hours	56639	56941	57106	57446
# BG measurements	27353	22924	20404	18149
# BG measurements/day	11.6	9.7	8.6	7.6
Time to target (h)	2.0 [1.0 3.0]	2.0 [1.0 3.0]	2.0 [1.0 3.0]	2.0 [1.0 3.0]
Median BG (mmol/L)	6.4 [5.8 7.1]	6.6 [6.0 7.2]	6.7 [6.1 7.4]	6.7 [6.1 7.4]
Median insulin (U/h)	3.0 [2.0 4.5]	2.5 [1.5 3.5]	2.5 [1.5 3.0]	2.5 [1.5 3.0]
Median nutrition (%GF)	99.9 [89.4 100.0]	95.4 [84.4 100.0]	90.7 [79.1 99.3]	89.4 [74.5 94.7]
% BG in 4.4-8.0 mmol/L	87.5	86.5	85.6	85.0
% BG in 4.4-7.0 mmol/L	70.5	65.7	61.4	58.8
% BG > 8.0 mmol/L	10.7	11.7	12.7	13.3
% BG < 4.4 mmol/L	1.8	1.8	1.7	1.7
% BG < 2.2 mmol/L	0.03	0.03	0.05	0.06
# patients ≥50%BG in 4.4-8.0 mmol/L (%)	621 (92.5%)	623 (92.8%)	620 (92.4%)	620 (92.4%)
# patients ≥50%BG in 4.4-7.0 mmol/L (%)	527 (78.5%)	493 (73.5%)	468 (69.7%)	431 (64.2%)
# patients min BG < 2.2 mmol/L (%)	12 (1.8%)	14 (2.1%)	19 (2.8%)	23 (3.4%)

Table 6.2: *Virtual trial results for STAR-3D for 1 to 3-, 4-, 5-, and 6-hourly intervals once target band is reached.*

6.3.3 Performance, safety and workload comparison between STAR-2D and STAR-3D

The results of the virtual trials performed with STAR-2D in [14] and STAR-3D presented before are presented in Table 6.3 for easier comparison. Only the results for the 3-hourly and 6-hourly measurement and intervention intervals are compared.

The performance of STAR-3D slightly increased compared to the performance of STAR-2D for both 3-hourly and 6-hourly time intervals. %BG in the different bands is higher (83.0 vs. 83.8 % for 3-hourly and 80.0 vs. 81.4 % for 6-hourly in 4.4-8.0 mmol/L and 65.0 vs. 67.5 %

for 3-hourly and 52.0 vs. 56.3 % for 6-hourly in 4.4-7.0 mmol/L). The number of patients with more than 50% BG in these bands has also slightly increased.

	STAR-2D		**STAR-3D**	
	3-hourly	**6-hourly**	**3-hourly**	**6-hourly**
# GC episodes	681	681	681	681
# GC hours	59240	60003	59209	60054
# BG measurements	28961	20272	29903	20696
# BG measurements/day	12	8	12	8
Median BG (mmol/L)	6.5 [5.9 7.3]	6.9 [6.3 7.7]	6.4 [5.8 7.2]	6.8 [6.2 7.5]
Median insulin (U/h)	3.2 [2.0 5.0]	2.5 [1.5 3.0]	3.5 [2.0 5.0]	2.5 [1.7 3.0]
Median nutrition (%GF)	100 [85 100]	90 [75 100]	100 [84 100]	85 [70 95]
% BG in 4.4-8.0 mmol/L	83	80	84	81
% BG in 4.4-7.0 mmol/L	65	52	67	56
% BG > 8.0 mmol/L	15	18	14	17
% BG < 4.4 mmol/L	1.6	1.6	1.7	1.6
% BG < 2.2 mmol/L	0.03	0.06	0.03	0.05
# patients ≥50%BG in 4.4-8.0 mmol/L (%)	589 (86%)	571 (84%)	591 (87%)	584 (86%)
# patients ≥50%BG in 4.4-7.0 mmol/L (%)	466 (68%)	372 (55%)	479 (70%)	398 (58%)
# patients min BG < 2.2 mmol/L (%)	14 (2.1%)	19 (2.8%)	12 (1.8%)	23 (3.4%)

Table 6.3: *Virtual trial results for STAR-2D and STAR-3D for 1 to 3-, and 6-hourly intervals.*

Regarding safety, the incidence of hyperglycaemia slightly increased which is directly linked with the slight increase of median [IQR] BG (6.5 [5.9 7.3] and 6.9 [6.3 7.7] mmol/L for STAR-2D vs. 6.4 [5.8 7.2] and 6.8 [6.2 7.5] mmol/L for STAR-3D). The incidence of hypoglycaemia is very similar between both protocols but the number of patients experiencing severe hypoglycaemia is higher for 3-hourly (14 vs. 12 measurements per day) and lower for 6-hourly (19 vs. 23 measurements per day) measurement and treatment intervals for STAR-2D. This indicates the 3D model improved predictions enabled to decrease hypoglycaemia compared to the 2D model for STAR 3-hourly, but this benefit is clearly affected when considering longer treatment intervals.

Both versions also provide similar workload despite slightly higher median insulin (3.2 [2.0 5.0] vs. 3.5 [2.0 5.0] U/h for 3-hourly and 2.5 [1.5 3.0] vs. 2.5 [1.7 3.0] U/h for 6-hourly) and same nutrition rates for the different intervals except for 6-hourly intervals (90.0 [75.0 100.0] vs. 85.3 [70.1 94.7] %GF).

6.4 Discussion

6.4.1 Risk and reward trade-off

The results of this trial clearly highlight the risk and reward trade-off of the extension of the time and measurement intervals already shown for STAR-2D. Indeed, extending the measurement and treatment intervals is not risk-free. Longer intervals are associated with wider 5^{th}-95^{th} percentile prediction ranges obtained for the SI predictions due to less confidence in future SI predictions. Wider predictions of SI and consequently of predicted BG induce more conservative insulin dosage with lower insulin rates to minimise hypoglycaemia.

In addition to the wider prediction ranges, longer intervals are also associated with higher risk of extreme changes in SI and thus in BG levels. BG level can thus suddenly increase or drop and ultimately leads to a hyper- or hypoglycaemic event, as seen in the increased number of patients experiencing hypoglycaemia.

Therefore, the use of longer intervals impacts performance and safety of GC. The risk associated with the extension of STAR is represented by the reduced performance (83.8 vs. 81.4 %BG within 4.4-8.0 mmol/L target band) with a general shift to higher BG levels, reduced safety with increased risk of hyperglycaemia (14.5 vs. 16.9 %BG $>$ 8.0 mmol/L) and hypoglycaemia (12 vs. 23 patients with min. BG $<$ 2.2 mmol/L) and reduced nutrition rates (99.7 vs. 85.3 %GF) to limit the increased risk of hyperglycaemia. This risk is more moderate for STAR-3D-4H and STAR-3D-5H than for STAR-3D-6H. Indeed, the performance and safety are also reduced but less than for STAR-3D-6H and more for STAR-3D-5H than STAR-3D-4H. This is also visible with the number and percentage of patients with more than 50%BG in the different bands that decreases for longer intervals.

As assumed, the reward consists in reduced workload (12.1 vs 8.3 measurements per day) and is a direct consequence of the use of longer time intervals. Here again, STAR-3D-4H and STAR-3D-5H present intermediate values with 10.3 and 9.2 measurements per day. This already represents a noteworthy decrease compared to STAR-3D-3H. An example of this risk and reward trade-off for STAR-3D-6H compared to STAR-3D-3H is shown in Figure 6.1 showing the virtual results for a patient.

By considering the results once the target band is reached, the same trade-off can be observed between reduced workload and reduced performance, safety and nutrition rates. However, they show higher performance and safety than by considering the entire GC length. Indeed, the very first hours of GC are hours where the patients are not yet stabilised. The measurement and treatment intervals are fixed to one hour. The hours to reach the target band are also hours where patients have hyperglycaemia. By discarding these hours, hours of heavy workload and high BG are not considered which explains the lower workload, the lower %BG higher than

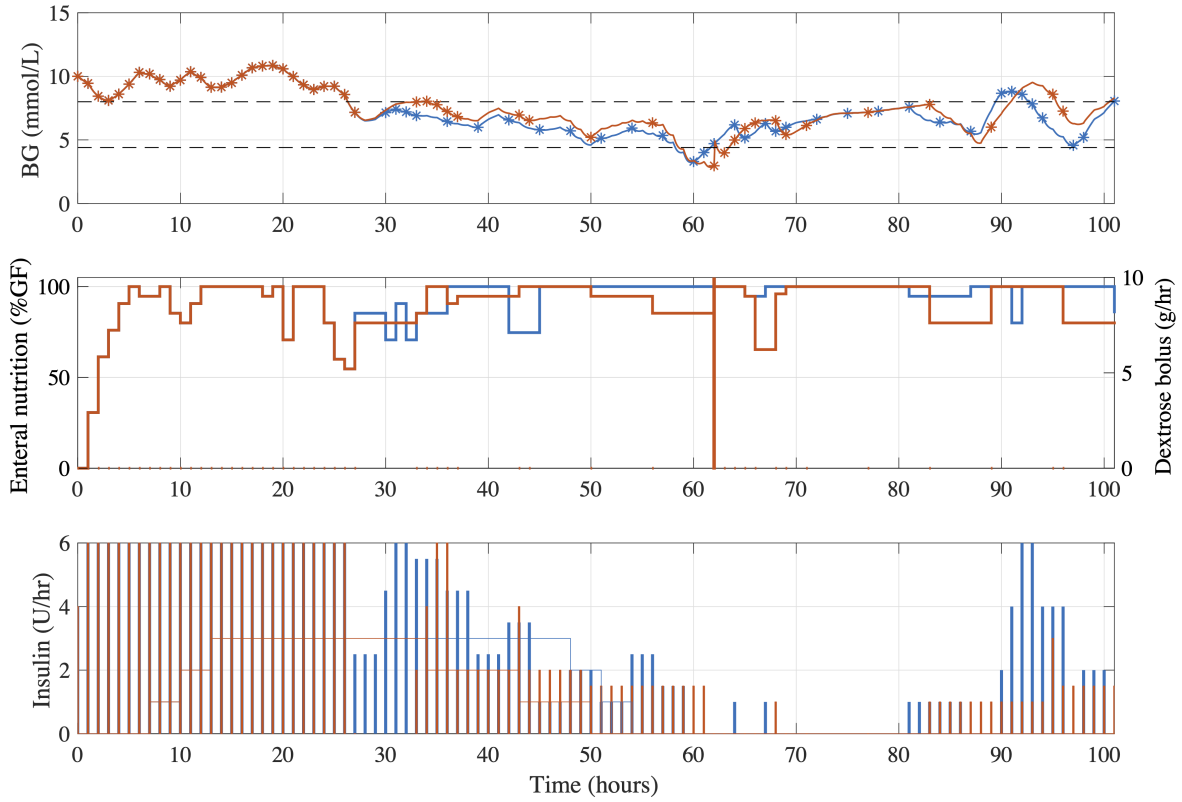


Figure 6.1: *Representation of the virtual trial results for one patient with the BG level (top), the nutrition rates and dextrose bolus (middle), the insulin bolus and infusion rates (bottom). Results are compared between STAR-3D-3H (blue) and STAR-3D-6H (red).*

8.0 mmol/L and the higher performance. These hours are common to the different time intervals. Discarding them has no influence on the changes observed by increasing the measurement and treatment interval. Most of all, this shows very high control performance once the patient reaches the target, and the ability of STAR to keep glycaemia in target.

Comparing the extension on STAR-3D with the extension of STAR-2D, both protocols present similar risk and reward trade-offs associated with the extension showing that STAR is robust when using longer measurement and treatment intervals. Performance, safety and nutrition are reduced for longer intervals but still significantly higher compared to results obtained with other protocols [34, 48, 42]. As expected while creating the 3D stochastic models, STAR-3D provides higher performances and safety than STAR-2D. Indeed, the prediction ranges obtained with the 3D models are tighter allowing more aggressive insulin dosing. In addition, the 3D models better accounts for inter- and intra-patient variability, a crucial element to consider to achieve safe GC.

While STAR-3D provides slightly safer and more effective control than STAR-2D, it shows an increased number of patients experiencing severe hypoglycaemia (19 vs. 23 patients with min BG $<$ 2.2 mmol/L) as well as the slight reduced nutrition rates (90 vs. 85.3 %GF) for STAR-3D-6H compared to STAR-2D-6H. The 3D stochastic model was shown to provide

tighter prediction ranges more than 70% of the time but it remains less than 30% where it provides wider prediction ranges for 3-hourly intervals. During these 30%, STAR-3D is then more conservative in its dosing which results in less nutrition administered and higher risk of extreme events such as severe hypoglycaemia. Despite this, there is still a reduced safety in both versions as the measurement and treatment intervals are longer. The number of patients experiencing hypoglycaemia is the highest in both STAR-3D and STAR-2D for 6-hourly interval, as expected.

Workload

As previously explained, the main reward is the reduced workload associated with longer measurement and treatment intervals. It is also interesting to look at the evolution of this workload as a function of the length of ICU stay and to compare it with the number of patients under GC.

Figure 6.2 shows the evolution of the number of measurements per every 12 hours for the different measurement intervals. This evolution is compared to the evolution of the number of patients under GC. The number of measurements per every 12 hours decreases significantly after the first 12 hours from 7.9 to 5.7 measurements for STAR-3H and from 6.6 to 4.0 measurements for STAR-6H showing that the first twelve hours clearly require the most workload. Indeed, the patients are not yet stabilised and so in most cases the measurement interval is fixed to 1-hourly. These are also the higher acute phase of illness where patients are highly resistant and variable. After the first 12 hours, the number of measurements keeps decreasing and fluctuates around 1 measurement every 3 hours for STAR-3D-4H, 1 measurement every 3.5 hours for STAR-3D-5H and 1 measurement every 4 hours for STAR-3D-6H. The difference of measurements between the different versions (more or less 2 measures/12 hours between 3-hourly and 6-hourly intervals) is constant as the time increases.

In addition, there is a significant decrease of the number of patients under GC in the first 24 hours of GC (Figure 6.3). Then, the number of patients keeps decreasing. The workload associated with GC is then the most important within the first 12 hours. Then, the numbers of measurements as well as the number of patients requiring GC decreases significantly resulting in a considerable decrease of the workload for the nurses. This trend is the same for the different versions of the protocol.

Hypoglycaemia

An important risk associated with longer measurement and treatment intervals is the higher incidence of severe hypoglycaemia. The difference is the most important between STAR-3D-3H and STAR-3D-6H (1.8% vs. 3.4%). Severe hypoglycaemia was proven to be associated with worse outcomes in GC [2, 6, 7, 20, 22]. Longer intervals are associated with higher risk of extreme changes in SI as seen in Chapter 5. SI being directly linked to BG, longer intervals

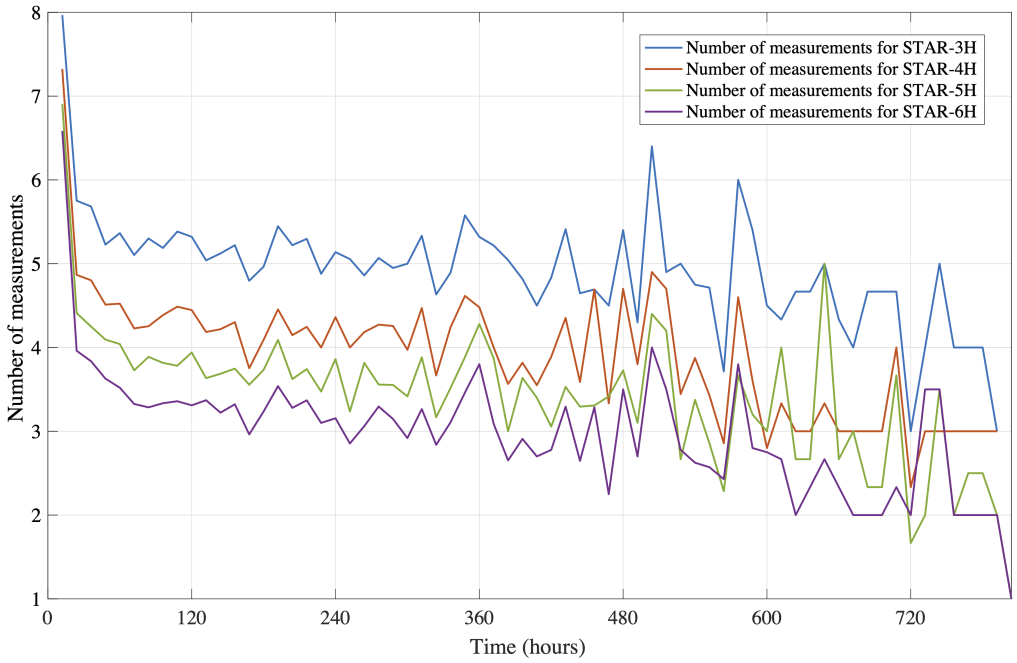


Figure 6.2: *Number of measurements per 12 hours comparison between the different measurement and treatment intervals.*

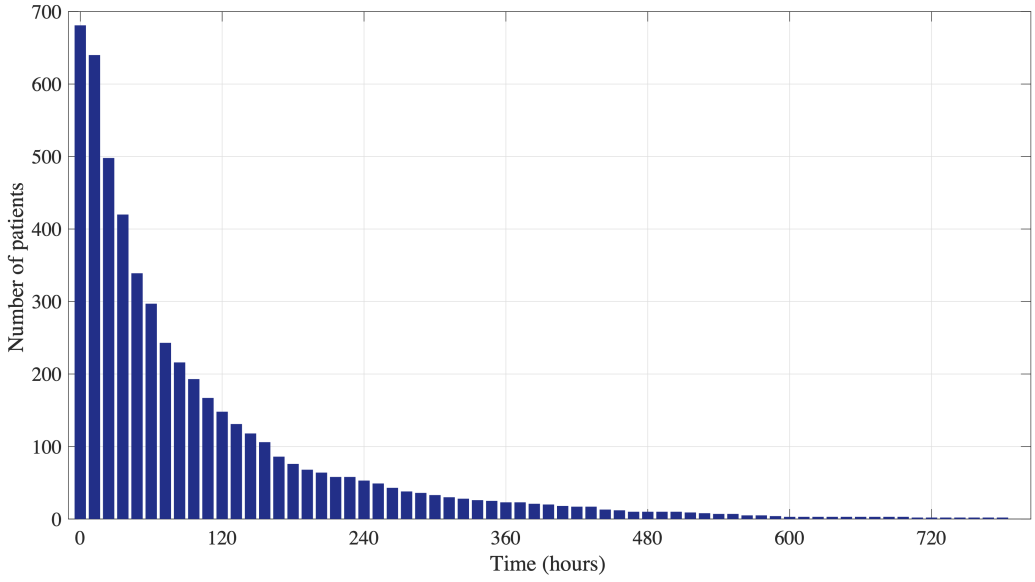


Figure 6.3: *Evolution of the number of patients under GC per 12 hours.*

are also associated with higher risk of extreme changes in BG level. For a patient that would experience a drop in BG 1 hour after the last measurement, the drop would be detected earlier for 3-hourly time interval than for 6-hourly interval leading to a severe hypoglycaemia in the second case. In the example shown in Figure 6.4, the patient is experiencing a progressive increase in SI from hour 11, which is a typical pattern characterising patient recovery. STAR-3D-3H is able to capture this increase earlier (at hour 13) and adapts its treatment while STAR-3D-6H detects this change much later, resulting in a severe hypoglycaemia event at hour 16.

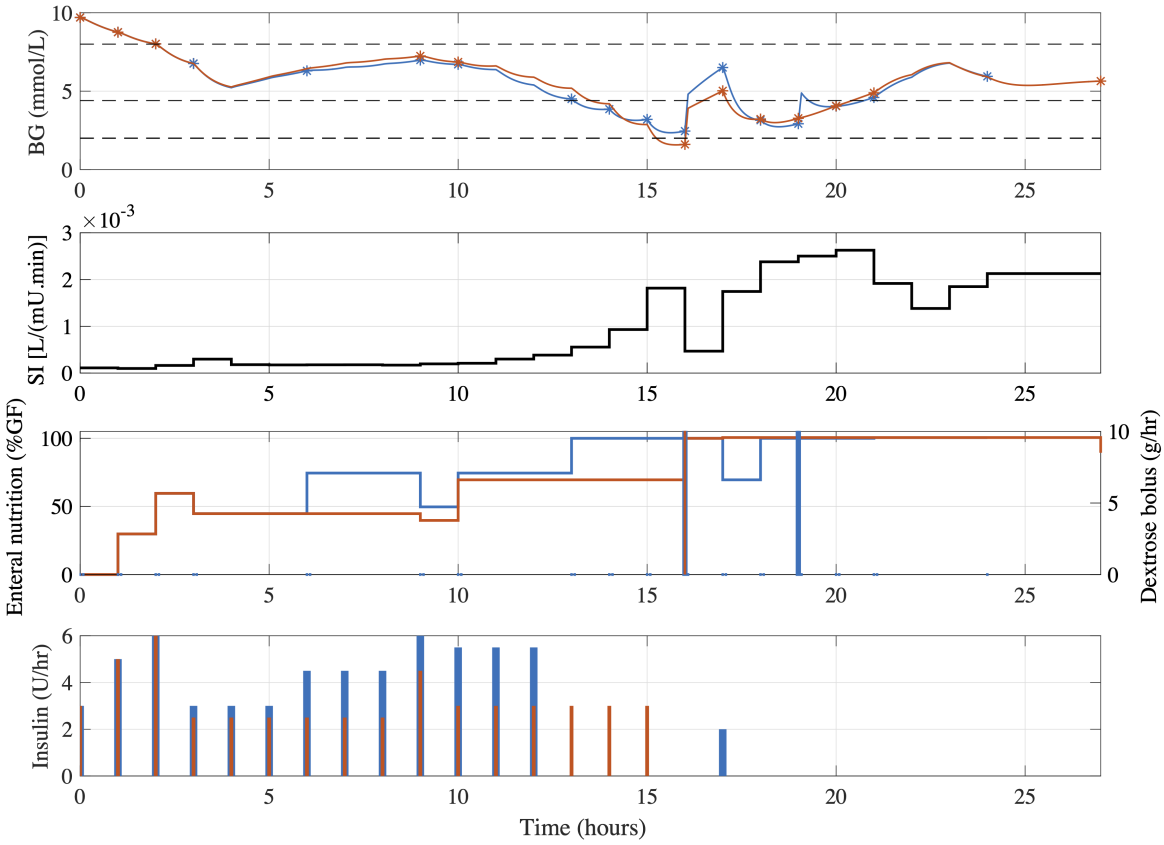


Figure 6.4: *Representation of the virtual results for one patient with severe hypoglycaemia detected at hour 16 for STAR-3D-6H. The BG level (top), the insulin sensitivity (second top), the nutrition rates and dextrose bolus (third top), the insulin bolus and infusion (bottom) are shown. Results are compared between STAR-3D-3H (blue) and STAR-3D-6H (red). Dotted lines on top panel represent the target band 4.4-8.0 mmol/L and the limit of severe hypoglycaemia 2.2 mmol/L.*

When analysing hypoglycaemic events more specifically, two observations can be made. First, some hypoglycaemic event occurs (or not) only because of measurement timing, and this can favour both the 3-hourly or 6-hourly version. However, while this generally avoids severe hypoglycaemia, patients still often reach BG values very close to the severe hypoglycaemic threshold. This situation concerns only a minority of patients and cannot really be explained. The measurements are better placed by chance.

Most interestingly, another very important observation from the 6-hourly intervals protocol is that a hypoglycaemic event may not even be detected during control, as shown in Figure 6.5.

Those hypoglycaemic events are short and may resolve without extra insulin adjustment thanks to nutrition and if SI decreases. They are due to a sudden positive peak in SI. A consequence of this peak for the same insulin and nutrition rates is a sudden negative peak in BG level leading to severe hypoglycaemia. However, the hypoglycaemic event is not detected because it occurs and resolves in less than the length of the measurement interval, i.e. 6 hours. It is very important to mention this particular case as it shows that the number of patients ex-

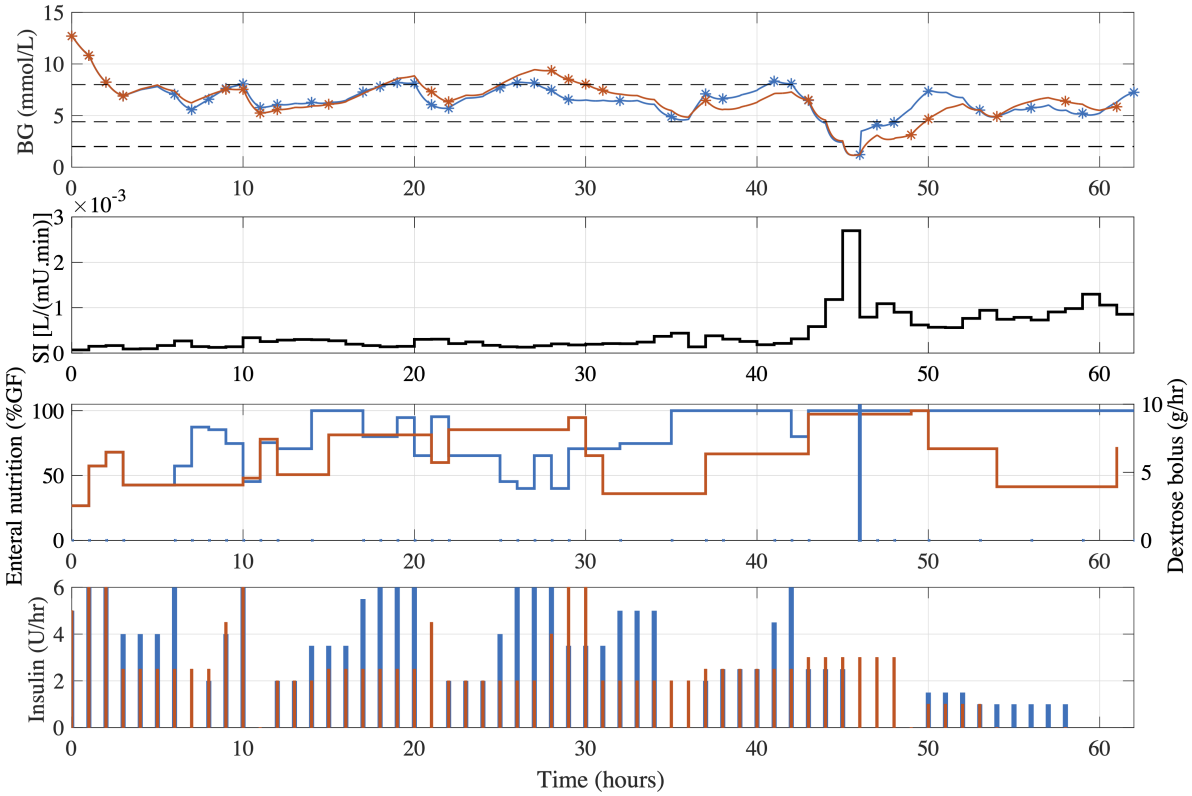


Figure 6.5: *Representation of the virtual results for one patient with severe hypoglycaemia detected at hour 46 for STAR-3D-3H. The BG level (top), the insulin sensitivity (second top), the nutrition rates and dextrose bolus (third top), the insulin bolus and infusion (bottom) are shown. Results are compared between STAR-3D-3H (blue) and STAR-3D-6H (red). Dotted lines on top panel represent the target band 4.4-8.0 mmol/L and the limit of severe hypoglycaemia 2.2 mmol/L.*

periencing severe hypoglycaemia may be underestimated in clinical practice when measuring less frequently. While measurements would suggest the patient remained stable, the patient actually experienced a severe hypoglycaemic event that would not have been measured here. An example of this situation for one patient is shown in Figure 6.5. It is clear that the patient experiences a sudden increase of SI at hour 46 leading to a severe hypoglycaemia. This event is detected by STAR-3D-3H which has its next measurement at hour 46 and can therefore administrate a dextrose bolus to increase the BG level more rapidly. The severe hypoglycaemic event goes completely unnoticed by STAR-3D-6H because the next measurement is at hour 49 and at this time, SI has returned to lower values and BG is not lower than 2.2 mmol/L anymore. This sudden rise and fall of SI could characterise a BG measurement error leading to this abnormal behaviour. However, it could also well characterise patient metabolic reactions to other factors such as drugs administration, patient handling or other.

These different configurations are a direct consequence of the different timing obtained for the different measurement and time intervals. To these different timing is associated a chance factor. For a same patient, one version can by chance detect early a hypoglycaemic event and adapt its treatment accordingly while another version may fail in detecting it. This is due to better

measurement timing. It makes it difficult to interpret the results in terms of hypoglycaemia, especially because of the very low occurrence of hypoglycaemia with STAR. This effect was already highlighted with the 2D version of STAR but it was also concluded that studying a large cohort of patients allows to balance the advantage/disadvantage induced [14].

6.4.2 Conclusions

Overall, extending the measurement and treatment intervals of STAR-3D from 3- to 6-hourly still provides safe and effective control for ICU patients. The different versions result in high %BG in target band and low incidence of hyper- and hypoglycaemia compared to other protocols. However, increasing the measurement interval shows a trade-off between reduced workload and reduced performance and safety. For longer intervals, the %BG in the different bands is reduced and the incidence of hyper- and hypoglycaemia is increased with 14 vs. 23 patients with minimum BG lower than 2.2 mmol/L in these simulations.

As for STAR-2D, the safest and most effective solution remains the use of 1-hourly intervals but this is not feasible in clinical practice and generates too much workload [14]. However, among the different interval lengths studied, STAR-3D-4H and STAR-3D-5H seems to present the best trade-off between non-negligible reduced workload and limited decrease in performance and safety.

It is also important to remember that those results were obtained from a virtual trial. It represents an ideal situation where the nurse's compliance to protocol is perfect. They are assumed to always choose the longest treatment proposed by the protocol which may not be the case in actual clinical practice. A clinical trial should be conducted to further validate the results obtained with the virtual trials on STAR-2D and STAR-3D.

6.5 Summary

To reduce the nurse's excessive workload induced by frequent measurement and treatment interventions, an extension of the measurement and treatment interval proposed by STAR from 1 to 3-hourly to 1 to 4-, 5- and 6-hourly has been developed and studied on STAR-2D and STAR-3D using virtual trials. Both versions provide robust control with high performance and safety even for longer measurement and time intervals. STAR-3D shows even higher performance and safety than STAR-2D due to the use of 3D stochastic models better accounting for inter- and intra-patient variability.

The extension showed a clear risk and reward trade-off where the risk was reduced performance and safety with lower %BG in target bands and higher incidence of hyper- and hypoglycaemia and the reward is the reduced workload (12 vs. 8 measurements per day).

Chapter 7

Virtual trials on treatment selection process optimisations

This Chapter aims at studying a new improvement of the STAR GC protocol. In addition to the extension to 1-6 hourly time intervals, the treatment selection process is modified to reduce the time and effort required from the nurses and therefore increase their compliance to the protocol. These considerations are following the high workload reported by nurses during a clinical trial undertaken at the University Hospital Center of Liège, Belgium [9].

Two modifications are implemented in this new version of STAR. One is the maximisation of the time interval between two interventions and the second one is the minimisation of the insulin variations. Their impact on the performance, safety and workload of the protocol is quantified by conducting virtual trials on the extension of STAR-3D GC framework. The modifications are tested first individually and then combined.

7.1 Introduction

The current versions of the STAR protocol developed and used here provide safe, effective GC for nearly all critically ill patients. The different clinical trials performed to validate the protocol already showed high compliance to protocol with more than 80% of unchanged interventions from the recommendations of STAR [11, 54]. However, this compliance is not perfect and different factors can negatively affect it. They are of different nature and some of them, associated with the protocol design, are the time and effort required (i.e. workload) from nurses to comply with the protocol [51].

The previous Chapter studied the impact of allowing longer measurement and treatment intervals on the performance, safety and workload of STAR-3D. This first extension significantly

reduced the workload at the cost of slightly lower performance and safety, and in particular an increase of the risk of severe hypoglycaemia. However, virtual trial simulations on virtual patients still showed very high quality control, showing potential clinical benefit from this 6-hourly extension. While workload was significantly reduced, other factors could further reduce clinical burden, especially for ICUs with low nurse per patient ratio.

The goal of this Chapter is to assess the risk and reward trade-offs of two additional extensions to optimise the treatment selection process such that it can further reduce workload in the STAR-3D GC framework. The first extension aims at allowing longer treatment intervals when BG is above the upper limit of the target, if the treatment considered results in predicted BG inside the target. The second extension aims at avoiding treatment changes as much as possible and reduce the insulin changes when possible such that less interventions are required from the clinical staff.

Virtual trials are thus conducted on the framework adapted to allow measurement and intervention intervals from 1-3 hourly to 1-6 hourly as this extension provided encouraging results virtually. Each solution is first studied individually and then, a version combining the two optimisations is considered.

7.2 Protocol extensions

7.2.1 Original treatment selection (STAR-3D)

STAR-3D current treatment selection process is only based on the 5^{th} and 95^{th} percentile predictions of BG to select the treatment maximising the nutrition and ensuring a 5% maximum risk of hypoglycaemia. The idea is to overlap the 5^{th}-95^{th} BG percentiles range as much as possible with the target band 4.4-8.0 mmol/L [41].

STAR algorithm seeks through all potential treatments to find the optimal option (Figure 7.1). Currently, it consists of two loops where, for each potential nutrition rate sorted from maximum to minimum, and for each potential insulin rate sorted also from maximum to minimum, the predicted 5^{th} and 95^{th} percentiles are calculated [41].

For each pair (nutrition, insulin), the corresponding 5^{th} BG percentile is firstly checked. If it lies in the interval between the lower bound of the target band 4.4 mmol/L and a certain tolerance (0.3 mmol/L), then the treatment is directly accepted regardless of the 95^{th} BG percentile. If the 5^{th} percentile is below the lower bound, then the treatment is rejected. The last possibility is when the 5^{th} percentile is higher than the lower band with tolerance 4.7 mmol/L. In this case, the 95^{th} BG percentile is checked. If it lies below the upper bound of the target band 8.0 mmol/L, then the treatment is kept as a solution [41].

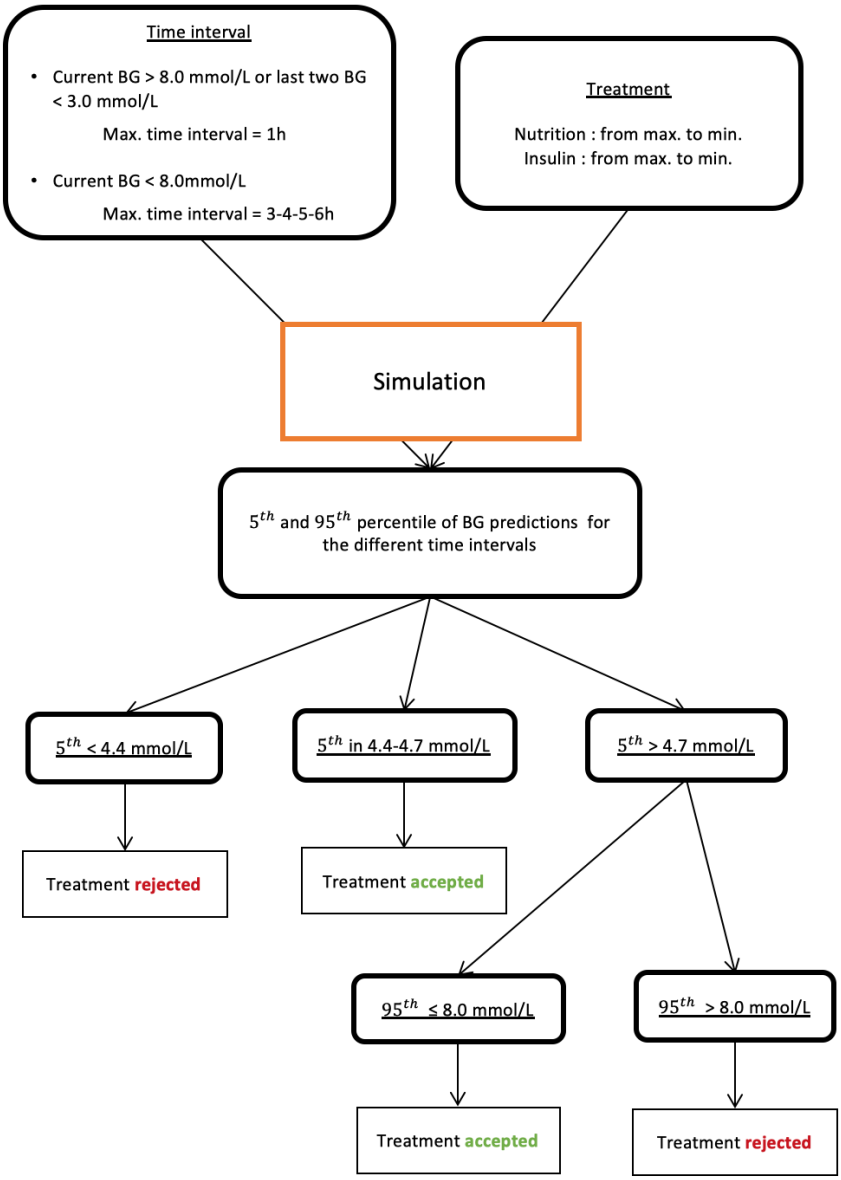


Figure 7.1: *Schematic representation of the treatment selection process of STAR-3D. For the different treatment and time intervals,* 5^{th} *and* 95^{th} *percentiles of BG are simulated and checked.*

This is done for every measurement and treatment interval allowed so from 1 hour to the longest interval allowed by the version of the protocol used. The only exceptions are when current BG level is above the upper bound 8.0 mmol/L or when the last two BG levels were below 3.0 mmol/L, then only 1 hour treatments are allowed. If no combination of insulin and nutrition gives an acceptable solution for 1 hour interval, maximum nutrition and zero insulin are chosen by default [41].

Once all the treatments have been considered, the optimal ones are recommended to the nurses who choose one between them. In virtual trials, the longest treatment is always chosen by default.

7.2.2 Time interval maximisation (STAR-TIM)

The changes performed on the treatment selection process to maximise the measurement and treatment intervals take two forms depending on the value of the current BG level. The new version is STAR Time Interval Maximised (STAR-TIM) (Figure 7.2).

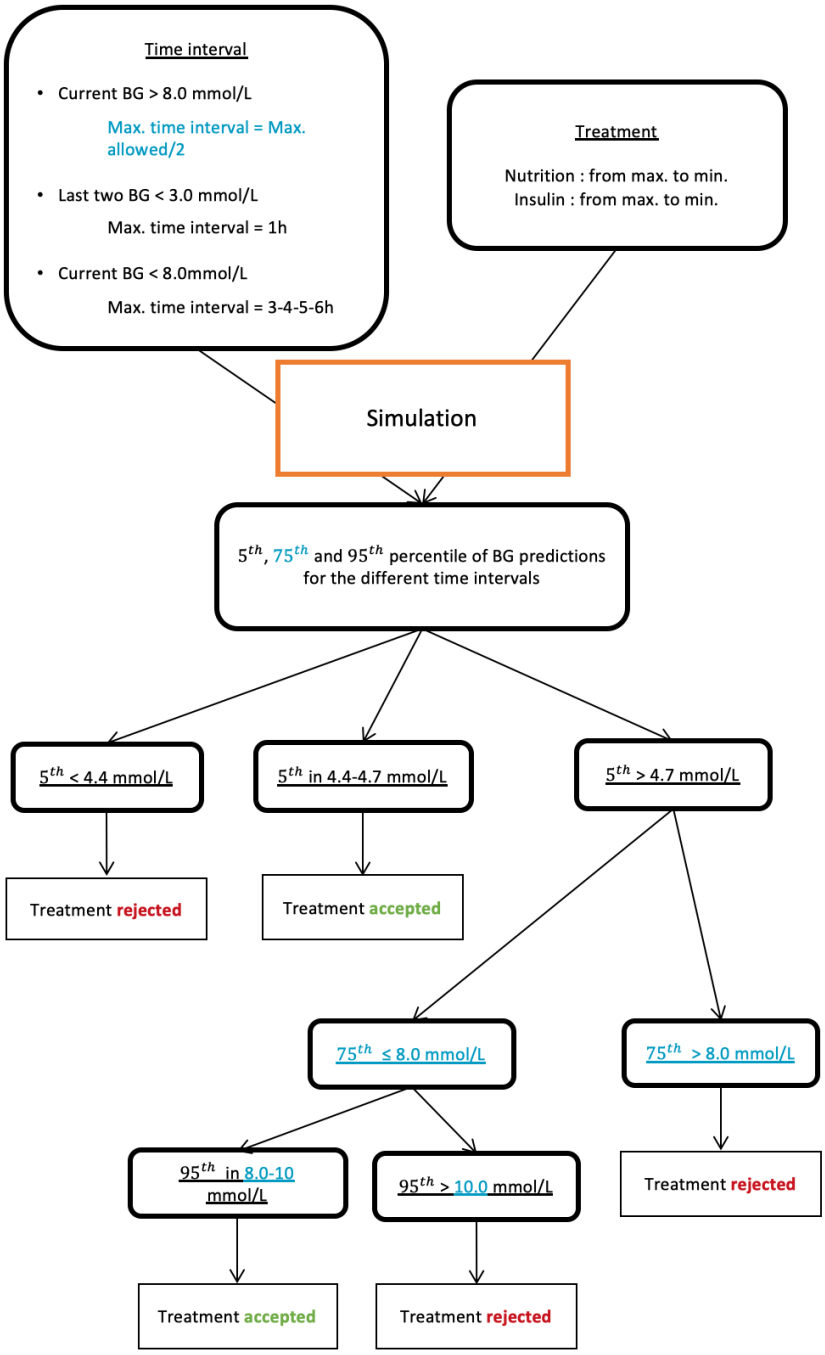


Figure 7.2: *Schematic representation of the treatment selection process of STAR-TIM. For the different treatment and time intervals,* 5^{th}, 75^{th} *and* 95^{th} *percentiles of BG are simulated and checked. Changes with respect to STAR-3D are highlighted in blue.*

The first change occurs when the current BG lies in the target band. In this case, a tolerance is added on the 95^{th} BG percentile and the 75^{th} BG is also calculated and checked. The 95^{th} percentile should be contained in 8.0-10.0 mmol/L and the 75^{th} percentile should be strictly

lower than 8.0 mmol/L to consider the treatment as acceptable (Figure 7.3). This would allow longer treatments that were not accepted in the original version to be chosen, while allowing only 20% risk of having moderate hyperglycaemia and 5% of having severe hyperglycaemia.

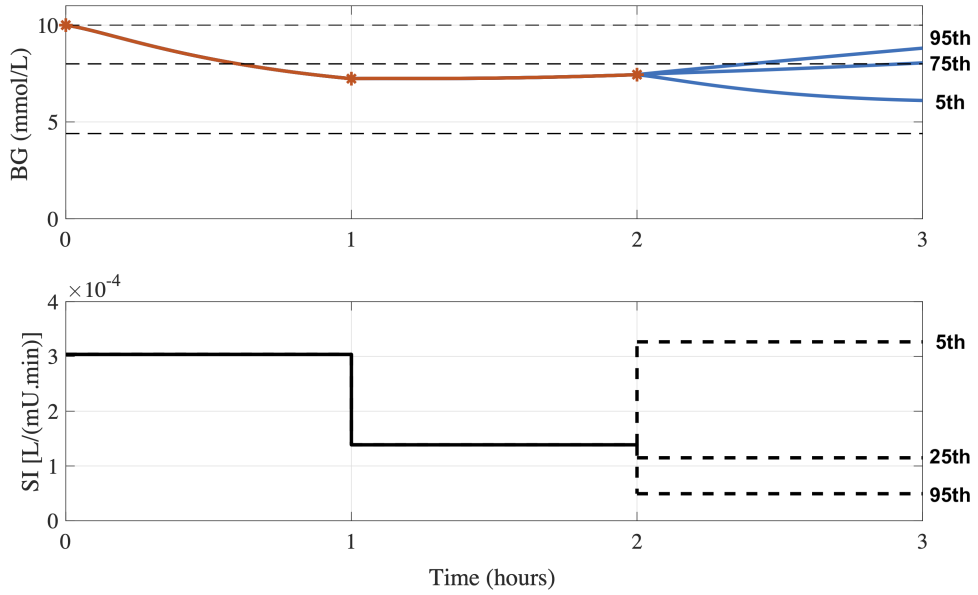


Figure 7.3: *1 hour* 5^{th}*,* 75^{th} *and* 95^{th} *percentile BG predictions (blue, top) calculated for the corresponding* 95^{th}*,* 25^{th} *and* 5^{th} *percentile SI predictions (dotted, bottom). Dotted line on top panel represent the target band 4.4-8.0 mmol/L for the* 5^{th} *and* 75^{th} *percentile predictions of BG and the limit of severe hyperglycaemia for the* 95^{th} *percentile prediction of BG.*

When the current BG is above the target band, the time interval is not limited to 1 hour anymore. The maximum time interval allowed corresponds to the half of the maximum time interval of the protocol rounded up to the next hour, i.e. 2 hours for STAR-TIM-3H and STAR-TIM-4H and 3 hours for STAR-TIM-5H and STAR-TIM-6H. The tolerances added for the first case are not used anymore and the treatments are accepted only if the 5^{th}-95^{th} percentile predictions of BG respect the same conditions as the ones of the original process.

The main reward associated with STAR-TIM is assumed to be higher median time intervals and therefore reduced workload. However, adding tolerance and allowing longer intervals when BG values are not stabilised can result in a risk of reduced performance with higher median BG and more importantly reduced safety with higher incidence of both hyper- and hypoglycaemia.

7.2.3 Insulin dosing variability minimisation (STAR-IVM)

Another factor affecting nurse's confidence and then compliance to STAR protocol is the variable insulin dosing representing a cognitive workload for the nurses. STAR uses variable insulin dosing to compensate for the possible BG variations and ensure a pre-set risk of hyper- and hypoglycaemia [6]. Nurses see this variability as a factor that can induce glycaemic variability and lead to worst GC outcomes. To reassure the nurses and increase their confidence in STAR, an idea is to decrease this variability in insulin dosing.

The changes made to minimise the variability of the insulin dosing are the following. Prior to testing all the different potential treatments, the protocol considers first the last treatment (insulin and nutrition) given to the patient during the last intervention. The 5$^{\text{th}}$ and 95$^{\text{th}}$ BG percentiles are estimated for this specific treatment and for each time interval, and checked using the same process as the one described for the original treatment. This new optimisation is denoted STAR Insulin Variability Minimised (STAR-IVM) (Figure 7.4).

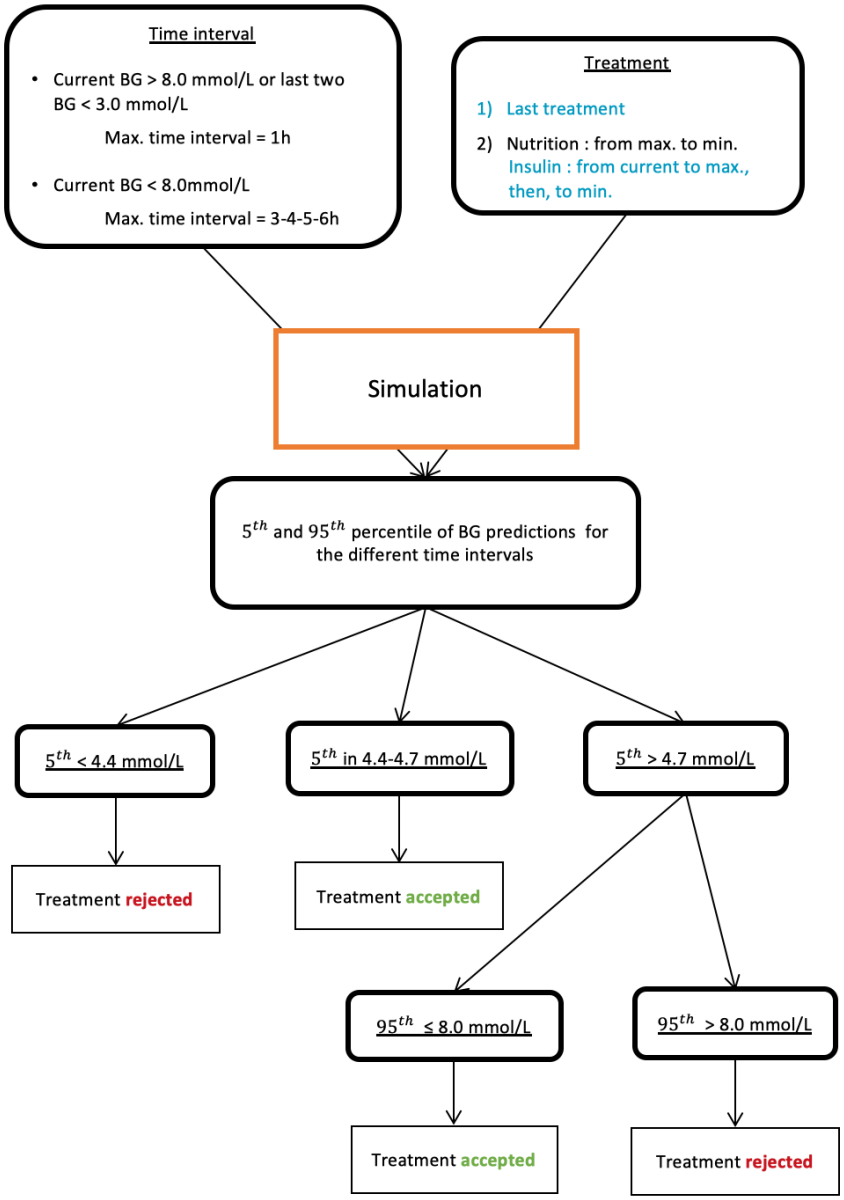


Figure 7.4: *Schematic representation of the treatment selection process of STAR-IVM. For the different treatment and time intervals,* 5$^{\text{th}}$ *and* 95$^{\text{th}}$ *percentiles of BG are simulated and checked. Changes with respect to STAR-3D are highlighted in blue.*

It is more the order into which treatments are computed and compared that is affected rather than protocol changes. The order of the potential nutrition remains from maximum to minimum. For the insulin dosing, the first value considered is not the maximum anymore but the current dose. Then, it goes to the maximum allowed before going down to the minimum

0.0 U/h. For example, if the current dose is 2.0 U/h, the protocol will explore the insulin dosing from 2.0 to 4.0 and then back to 0.0 U/h as shown in Table 7.1. Therefore, in the example below, if 2.0 U/h of insulin is acceptable, it will suggest this treatment instead of 4.0 U/h that could also be an acceptable treatment.

	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**
STAR-3D	4.0	3.5	3.0	2.5	2.0	1.5	1.0	0.0
STAR-IVM-3D	2.0	2.5	3.0	3.5	4.0	1.5	1.0	0.0

Table 7.1: *Order of allowed insulin administration comparison between STAR-3D and STAR-IVM.*

The expected improvements are reduced insulin rates (thus reduced costs related to insulin), and reduced glycaemic variability. The performance should be similar but more variable nutrition to compensate for the less variable insulin dosing.

7.2.4 Global optimisation (STAR-GO)

A last version of the protocol simulated in this Chapter is a combination of both the changes together to maximise the time interval while also minimising the insulin dosing variability. As each solution implies changes on different parts of the treatment selection process, they can be both implemented and tested also at the same time. This last version is denoted STAR Global Optimisation (STAR-GO).

The results expected from this combination are the combination of the results obtained for each optimisation, although the effect on workload and insulin dosing of each extension could be reduced when combining both. Each part of the solution is supposed to impact safety and workload differently. Combining their effect is expected to counterbalance the potential negative impacts from reduced safety against improved workload.

With respect to the original version STAR-3D, this new implementation of the treatment selection process is supposed to reduce the workload and the variability in insulin dosing. These effects will be checked by comparing the results obtained from the virtual trials with the results obtained for the extension of the original version already presented and discussed in Chapter 6.

7.3 Results

7.3.1 Time interval maximisation (STAR-TIM)

The results of the virtual trial performed on STAR-TIM are presented in Table 7.2. Efficacy is high with %BG in the band is high for both bands (82.8 %BG within the target band 4.4-

8.0 mmol/L and 64.5 %BG within 4.4-7.0 mmol/L for 3-hourly time intervals) and it surprisingly increases as the time interval increases. There is also a slight decrease of the median BG level (6.5 [5.9 7.4] mmol/L for 3-hourly vs. 6.3 [5.7 7.2] mmol/L for 6-hourly time intervals). The number of patients with more than 50%BG in the different bands is also high and slightly increases with the time interval. The glycaemic variability decreases for longer time intervals from 0.34 [0.25 0.47] mmol/L for 3-hourly to 0.24 [0.17 0.36] mmol/L for 6-hourly. There is however a slight decrease in performance for 4-hourly time interval compared to the others.

	STAR-TIM-3H	**STAR-TIM-4H**	**STAR-TIM-5H**	**STAR-TIM-6H**
# GC episodes	681	681	681	681
# GC hours	59285	59525	59773	60051
# BG measurements	27646	23484	20540	18675
# BG measurements/day	11.2	9.5	8.2	7.5
Median BG (mmol/L)	6.5 [5.9 7.4]	6.5 [5.9 7.4]	6.4 [5.8 7.3]	6.3 [5.7 7.2]
Median insulin (U/h)	3.5 [2.0 5.5]	3.5 [2.0 5.5]	3.5 [2.0 5.0]	2.5 [1.5 4.3]
Median nutrition (%GF)	100.0 [95.4 100.0]	100.0 [86.1 100.0]	88.0 [70.9 99.3]	65.2 [52.0 80.0]
% BG in 4.4-8.0 mmol/L	82.8	82.4	82.9	83.9
% BG in 4.4-7.0 mmol/L	64.5	63.7	65.0	67.8
% BG > 8.0 mmol/L	15.5	15.4	14.6	13.4
% BG < 4.4 mmol/L	1.8	2.2	2.5	2.7
% BG < 2.2 mmol/L	0.03	0.05	0.07	0.08
# patients ≥50%BG in 4.4-8.0 mmol/L (%)	590 (86.6%)	588 (86.3%)	594 (87.2%)	591 (86.8%)
# patients ≥50%BG in 4.4-7.0 mmol/L (%)	466 (68.4%)	455 (66.8%)	464 (68.1%)	475 (69.7%)
# patients min BG < 2.2 mmol/L (%)	13 (1.9%)	15 (2.2%)	25 (3.7%)	30 (4.4%)
Median BG level variations (mmol/L)	0.34 [0.25 0.47]	0.31 [0.23 0.42]	0.27 [0.20 0.38]	0.24 [0.17 0.36]
Median insulin variations (U/h)	1.0 [0.0 1.5]	1.0 [0.0 1.5]	1.0 [0.5 1.5]	1.0 [0.5 1.5]
Median time interval (min)	180 [60 180]	180 [60 240]	210 [60 300]	180 [60 360]
% unchanged nutrition interventions	62.4	51.9	30.0	22.3
% unchanged insulin interventions	31.2	31.7	31.1	32.8
% unchanged insulin and nutrition interventions	15.5	13.8	10.5	9.8

Table 7.2: *Virtual trial results for STAR-TIM for 1 to 3-, 4-, 5-, and 6-hourly intervals.*

In terms of safety, there is a difference in the evolution observed for hyper- and hypoglycaemia. There is a slight decrease of the incidence of moderate and severe hyperglycaemia as the time interval increases. This can be related to the decrease of median nutrition. On the other side, there is a significant increase in the incidence of hypoglycaemia and especially of severe hypoglycaemia with 13 (1.9%) patients experiencing severe hypoglycaemia for 3-hourly and 30 (4.4%) patients for 6-hourly time intervals. This can also be explained by the important decrease in median nutrition.

As expected, workload is significantly reduced from 11.7 measurements per day for 3-hourly intervals to 7.5 measurements for 6-hourly intervals. This is also represented by the median [IQR] time interval between interventions (180 [60 180] minutes for 3-hourly vs. 180 [60 360] minutes for 6-hourly) which is quite high.

Those results are achieved with an important decrease in median nutrition for 5-hourly and 6-hourly intervals (100.0 [95.4 100.0] %GF for 3-hourly and 4-hourly vs. 88.0 [70.9 99.3] %GF for 5-hourly and 65.2 [52.0 80.0] %GF for 6-hourly time intervals) and less unchanged nutrition interventions as the interval increases and for the nutrition, this is synonymous of higher variability in nutrition interventions. The median insulin rate is only decreased for 6-hourly time intervals which is synonymous of more conservative treatments and the percentage of unchanged insulin interventions is relatively constant. The median change in insulin rate between two interventions is 1.0 U/h. Overall, these results clearly reflect the wider SI prediction ranges for longer treatment intervals thus resulting in higher potential risk of both hyper- and hypoglycaemia, explaining both reduction in nutrition rates achieved as well as more conservative insulin dosing (lower rates).

A last worth noting observation associated with the STAR-TIM is the important transition observed between 3- and 4-hourly and 5- and 6-hourly time intervals. There is a sudden important decrease in median nutrition and increase in the incidence of severe hypoglycaemia observed for 5-hourly and 6-hourly time intervals. In the treatment selection process, the big change between these versions is the maximum interval allowed when the current BG is above the target band which is 2 hours for 3-hourly and 4-hourly and 3 hours for 5-hourly and 6-hourly.

7.3.2 Insulin dosing variability minimisation (STAR-IVM)

The results of the virtual trial performed on the optimisation STAR-IVM are gathered in Table 7.3. Performance is high with high %BG in the bands (83.3 %BG within the target band 4.4-8.0 mmol/L and 66.4 %BG within 4.4-7.0 mmol/L for 3-hourly time intervals). Performance slightly increases with longer time intervals. The number of patients with more than 50%BG within the bands increases. The increases are a bit more important for the 4.4-7.0 mmol/L band. There is a slight decrease in the glycaemic variability (0.33 [0.24 0.47] mmol/L for 3-hourly vs. 0.29 [0.21 0.41] mmol/L for 6-hourly).

	STAR-IVM-3H	STAR-IVM-4H	STAR-IVM-5H	STAR-IVM-6H
# GC episodes	681	681	681	681
# GC hours	59239	59386	59424	59501
# BG measurements	30605	27552	26270	25944
# BG measurements/day	12.4	11.1	10.6	10.5
Median BG (mmol/L)	6.5 [5.9 7.3]	6.4 [5.8 7.2]	6.3 [5.8 7.2]	6.3 [5.7 7.2]
Median insulin (U/h)	3.0 [2.0 4.5]	3.0 [2.0 4.5]	3.0 [2.0 4.5]	3.0 [2.0 4.5]
Median nutrition (%GF)	99.9 [84.7 100.0]	89.8 [74.5 100.0]	85.0 [65.8 97.3]	81.9 [64.7 95.6]
% BG in 4.4-8.0 mmol/L	83.2	83.4	83.7	83.9
% BG in 4.4-7.0 mmol/L	66.4	67.7	68.3	68.6
% BG > 8.0 mmol/L	15.1	14.5	14.1	13.9
% BG < 4.4 mmol/L	1.7	2.1	2.2	2.2
% BG < 2.2 mmol/L	0.03	0.05	0.04	0.04
# patients ≥ 50%BG in 4.4-8.0 mmol/L (%	581 (85.3%)	582 (85.5%)	587 (86.2%)	589 (86.5%)
# patients ≥ 50%BG in 4.4-7.0 mmol/L (%)	460 (67.5%)	465 (68.3%)	477 (70.0%)	478 (70.2%)
# patients min BG < 2.2 mmol/L (%)	14 (2.1%)	19 (2.8%)	18 (2.6%)	18 (2.6%)
Median BG level variations (mmol/L)	0.33 [0.24 0.47]	0.31 [0.22 0.43]	0.29 [0.21 0.41]	0.29 [0.21 0.41]
Median insulin variations (U/h)	0.5 [0.0 1.0]	0.5 [0.0 1.0]	0.5 [0.0 1.0]	0.5 [0.0 1.0]
Median time interval (min)	90 [60 180]	90 [60 180]	90 [60 180]	120 [60 180]
% unchanged nutrition interventions	48.2	35.8	33.0	32.4
% unchanged insulin interventions	35.0	34.1	33.0	33.2
% unchanged insulin and nutrition interventions	16.6	14.4	13.3	13.3

Table 7.3: *Virtual trial results for STAR-IVM for 1 to 3-, 4-, 5-, and 6-hourly intervals.*

Concerning safety, there is a slightly decreased incidence of hyperglycaemia for longer time intervals. For the hypoglycaemia, a slightly increased incidence of moderate hypoglycaemia is observed and related to the slight decrease in median BG level (from 6.5 [5.9 7.3] mmol/L for 3-hourly to 6.3 [5.7 7.2] mmol/L for 6-hourly time intervals). However, the incidence of severe hypoglycaemia shows an increase for 4-hourly and then a slight decrease for 5- and 6-hourly intervals.

The workload decreases but remains high as the time interval increases (12.1 measurements for 3-hourly vs. 10.5 for 6-hourly intervals). This high workload is also represented by the low median [IQR] time interval (90 [60 180] minutes for 3-hourly intervals and 120 [60 180] minutes for 6-hourly intervals).

In this version, the results are obtained with a constant median [IQR] insulin rate and a low median insulin variation of 0.5 U/h between two interventions. The percentage of unchanged insulin interventions decreases slightly as the time interval increases. In addition, the mean [IQR] nutrition achieved is quite high and decreases with the time interval but less than for the maximisation of the time interval (from 99.9 [84.7 100.0] %GF for 3-hourly to 81.9 [64.7 95.6] %GF for 6-hourly time intervals). The percentage of unchanged nutrition interventions also decreases.

7.3.3 Global optimisation (STAR-GO)

The last trial was performed using the combination of both optimisations and the results are presented in Table 7.4. As for the two other trials, the performance is high and slightly increases with the time interval. This is represented by the increased %BG in the different bands between 3-hourly and 6-hourly time intervals (82.7 vs. 83.4 %BG within 4.4-8.0 mmol/L target band and 64.7 vs. 66.4 %BG within 4.4-7.0 mmol/L). The number of patients with more than 50%BG in the bands evolves differently for each band. A slight decrease of this number is observed for the wider 4.4-8.0 mmol/L target band while it increases for the tighter and safer 4.4-7.0 mmol/L band. The glycaemic variability decreases with 0.34 [0.25 0.46] mmol/L for 3-hourly vs. 0.24 [0.17 0.36] mmol/L for 6-hourly time intervals.

Overall, the performance obtained for STAR-GO is lower than the performance observed for each optimisation implemented individually. There is also a slight decrease in performance observed for 4-hourly time intervals already noted for STAR-TIM.

Concerning safety, interesting observations can also be made. The incidence of hyperglycaemia increases as the time interval increases and is slightly higher than for the two optimisations separately. The incidence of both moderate and severe hypoglycaemia increases (1.7 %BG $<$ 4.4 mmol/L for 3-hourly vs. 2.7 %BG $<$ 4.4 mmol/L for 6-hourly tome intervals), this increase being linked to the decrease of median nutrition, but the number of patients experiencing severe hypoglycaemia is the highest for 5-hourly with 27 patients and the lowest for 4-hourly intervals with 13 patients. Those numbers are more similar to the ones obtained with the time interval maximisation rather than for the insulin rate variability minimisation.

The workload is similar to the one obtained for STAR-TIM and evolves the same way by decreasing from 11.2 measurements per day to 7.5 measurements. The median [IQR] time interval is also similar to one of STAR-TIM.

	STAR-GO-3H	STAR-GO-4H	STAR-GO-5H	STAR-GO-6H
# GC episodes	681	681	681	681
# GC hours	59312	59536	59790	60068
# BG measurements	27608	23413	20614	18799
# BG measurements/day	11.2	9.4	8.3	7.5
Median BG (mmol/L)	6.5 [5.9 7.4]	6.5 [5.9 7.4]	6.4 [5.8 7.3]	6.3 [5.7 7.2]
Median insulin (U/h)	3.5 [2.0 5.0]	3.5 [2.0 5.0]	3.0 [2.0 4.5]	2.5 [2.0 4.0]
Median nutrition (%GF)	100.0 [92.0 100.0]	100.0 [85.3 100.0]	89.4 [72.0 99.7]	65.3 [52.0 80.0]
% BG in 4.4-8.0 mmol/L	82.7	82.4	82.5	83.4
% BG in 4.4-7.0 mmol/L	64.7	64.1	65.2	66.4
% BG > 8.0 mmol/L	15.6	15.4	14.9	13.9
% BG < 4.4 mmol/L	1.7	2.2	2.5	2.7
% BG < 2.2 mmol/L	0.03	0.04	0.08	0.08
# patients ≥50%BG in 4.4-8.0 mmol/L (%)	588 (86.3%)	586 (86.0%)	588 (86.3%)	583 (85.6%)
# patients ≥50%BG in 4.4-7.0 mmol/L (%)	460 (67.5%)	458 (67.2%)	453 (66.5%)	473 (69.5%)
# patients min BG < 2.2 mmol/L (%)	14 (2.1%)	13 (1.9%)	27 (4.0%)	25 (3.7%)
Median BG level variations (mmol/L)	0.34 [0.25 0.46]	0.30 [0.23 0.42]	0.27 [0.19 0.38]	0.24 [0.17 0.36]
Median insulin variations (U/h)	0.75 [0.5 1.0]	1.0 [0.5 1.5]	1.0 [0.5 1.5]	0.75 [0.5 1.0]
Median time interval (min)	180 [60 180]	180 [60 240]	210 [60 300]	180 [60 360]
% unchanged nutrition interventions	59.5	49.6	28.0	20.4
% unchanged insulin interventions	32.2	30.6	30.2	33.2
% unchanged insulin and nutrition interventions	16.7	13.0	10.1	9.1

Table 7.4: *Virtual trial results for STAR-GO for 1 to 3-, 4-, 5-, and 6-hourly intervals.*

Those results are achieved with a high but decreasing nutrition from 100 [92.0 100.0] %GF for 3-hourly to 65.3 [52.0 80.0] %GF for 6-hourly time intervals which is lower but still high for ICU patients compared to most ICU settings [48]. There is also an important decrease in the percentage of unchanged nutrition interventions which is initially quite high and decreases importantly. This is linked to the higher variability of the nutrition interventions observed. The median insulin rate decreases as the time interval increases and is comprised between the results obtained for the two optimisations as well as the median insulin variations and the percentage of unchanged insulin interventions.

As for the trial performed on STAR-TIM, there is a strong difference in terms of nutrition and incidence of hypoglycaemia between the 3- and 4- hourly vs. the 5- and 6- hourly versions of STAR-GO.

7.4 Discussion

7.4.1 Transition in time interval maximisation

For STAR-TIM, a transition was observed between the results obtained for 3-, 4-hourly and for 5-, 6-hourly time intervals. This difference was marked by an increase in the incidence of severe hypoglycaemia and a strong decrease in nutrition administration.

In the implementation of the treatment selection process, the main difference observed by changing the time interval is the maximum time interval allowed when the current BG is above the target band. For the 3- and 4-hourly versions of STAR-TIM, this interval is limited to 2 hours and for the 5- and 6-hourly versions, it is limited to 3 hours. As a consequence, longer intervals may be more frequently allowed, increasing the risk of extreme changes in BG levels and therefore of severe hypoglycaemia (or hyperglycaemia). This change in intervals results also in a different measurement timing which can unluckily lead to severe hypoglycaemia.

The other effect of allowing longer intervals even for non-stabilised patients is the strong decrease in nutrition administration. Treatment recommendations with lower nutrition will be favoured with respect to others if they allow longer treatment intervals. An example of this situation is visible in Figure 7.5. At hour 3, the treatment chosen by STAR-TIM-6H provides less nutrition but a longer time interval than the one by STAR-TIM-3H. There are also cases where the treatment chosen administers less nutrition and higher insulin rates than the previous one because it allowed longer treatment intervals. This was already the case in STAR-3D but occurs more frequently here as longer treatment intervals can be considered more often because of the higher tolerance on the 95^{th}. This is encountered, for example, at hours 30 and 93 in Figure 7.5.

A solution to reduce the risks associated with STAR-TIM and the significant decrease in nutrition rates achieved can be to limit the maximum time interval allowed to 2 hours when the current BG is above the target band regardless of the maximum time intervals considered. Indeed, the 3- and 4-hourly versions allowing a maximum interval of 2 hours were shown to provide similar performance while reaching much higher nutrition administered and lower incidence of hypoglycaemia than the 5- and 6-hourly versions of STAR-TIM allowing 3 hours measurement intervals. However, by looking more in detail to the results, this might not be the main reason for the important decrease. Longer treatment intervals are almost never chosen when BG is above the target band.

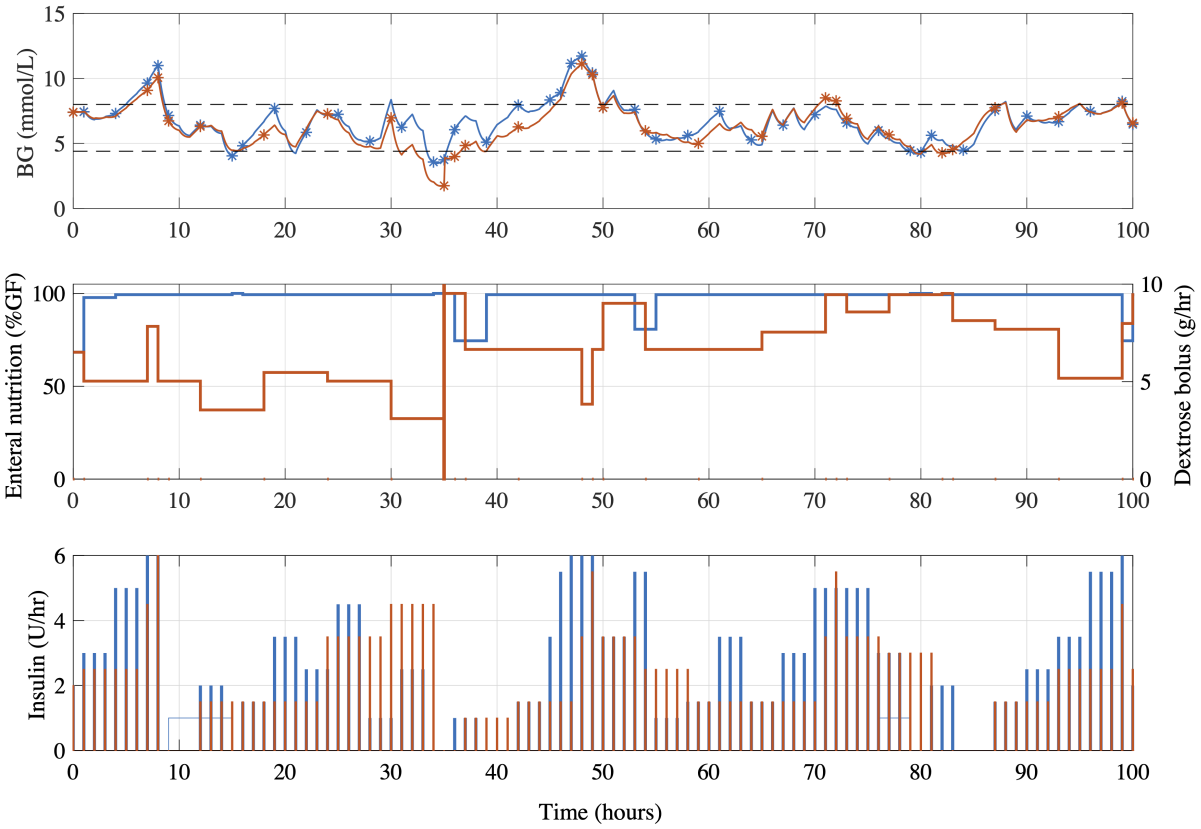


Figure 7.5: *Excerpt of the virtual results for one patient with time interval maximisation. The BG level (top), the nutrition rates and dextrose bolus (middle), the insulin bolus and infusion (bottom) are shown. Results are compared between 3-hourly (blue) and 6-hourly (red). Dotted lines on top panel represent the target band 4.4-8.0 mmol/L.*

Another solution would be to adapt the tolerance on the 95$^{\text{th}}$ percentile. The decrease in nutrition and higher risk of hypoglycaemia might also be a consequence of the higher tolerance on the 95$^{\text{th}}$ percentile which can have more impact when longer treatment intervals can be considered.

To be able to conclude on the influence of each modification and therefore on the solution to adopt, they should be analysed separately. This will be further analysed in future work.

7.4.2 Balance of effects in global optimisation

During its development, STAR-GO was defined as a combination of both time interval maximisation and insulin variations minimisation. In addition to the implementation, the combination of both optimisations is also noted in the results obtained.

The different positive and negative effects of each optimisation can be observed in the results obtained for the global optimisation. Some effects also counterbalance such as the median insulin variation and the number of patients experiencing severe hypoglycaemia. The results obtained for each of these variables are between the ones obtained for STAR-TIM and

STAR-IVM. Globally, the effects of the time interval maximisation prevail, the same transition between 3- and 4- hourly intervals and 5- and 6- hourly intervals is noted.

Figure 7.6 shows an example of a patient illustrating the differences between the three optimisations. First, the severe hypoglycaemia occurring at hour 26 for the two others is avoided with STAR-IVM. Then, the important reduction in nutrition observed for STAR-TIM and STAR-GO is also marked as well as the increase in median insulin rate for STAR-IVM. Finally, there seems to be more or less the same number of changes in the interventions. However, when these changes are related to the number of interventions and measures, the ratio reduces and there are more unchanged interventions for STAR-IVM.

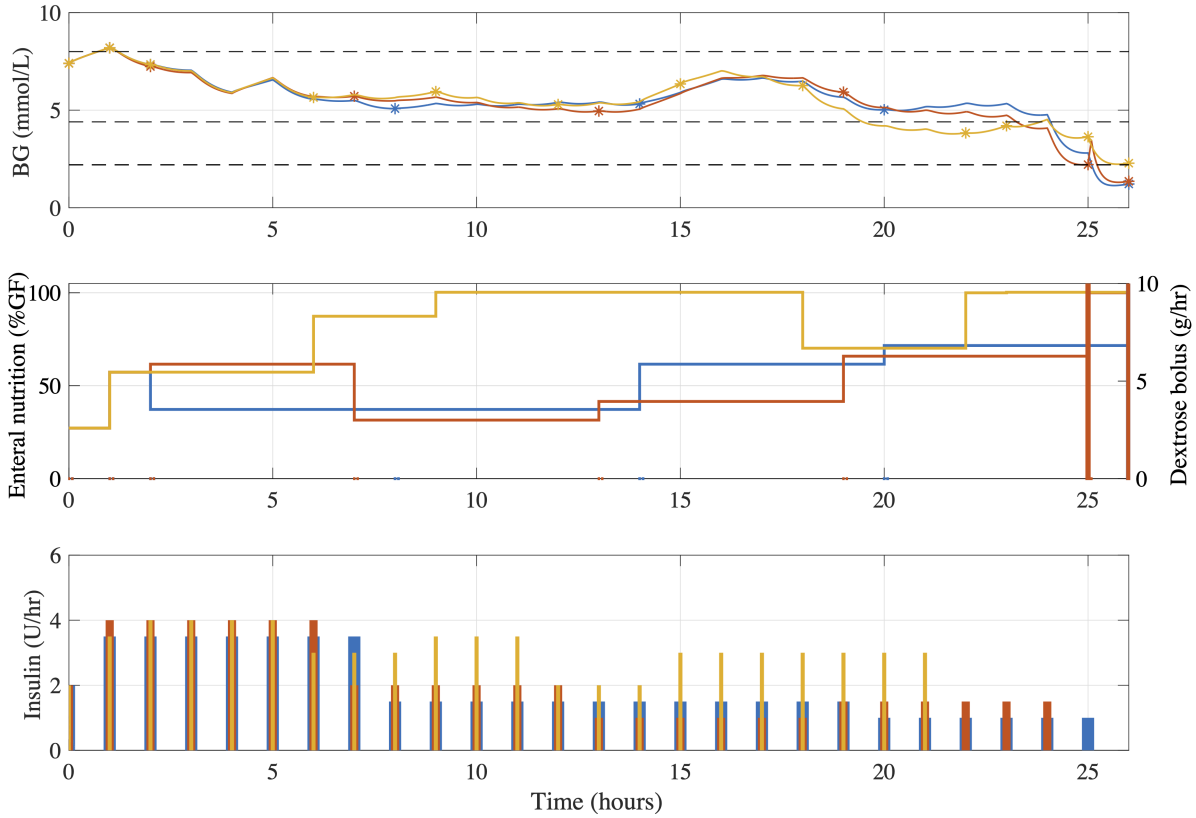


Figure 7.6: *Representation of the virtual results for one patient. The BG level (top), the nutrition rates and dextrose bolus (middle), the insulin bolus and infusion (bottom) are shown. Results are compared for 6-hourly time intervals between STAR-TIM (red), STAR-IVM (yellow) and STAR-GO (blue). Dotted lines on top panel represent the target band 4.4-8.0 mmol/L and the limit of severe hypoglycaemia 2.2 mmol/L.*

7.4.3 Risk and reward trade-offs

During their development, the different versions of the treatment selection process were associated with potential risks and rewards. To quantify the risk and reward trade-off associated with each version, the results obtained for the three optimisations considered in this Chapter are compared with the results obtained for STAR-3D for 3-hourly (Table 7.5) and 6-hourly (Table 7.6) time intervals.

STAR-TIM

The reward associated with the STAR-TIM is as expected a reduction of the number of measurements per day compared to STAR-3D (11.2 vs. 12.1 measurements/day for 3-hourly and 7.5 vs 8.3 measurements/day for 6-hourly). There is also an improved percentage of unchanged interventions and particularly of unchanged nutrition interventions for both 3-hourly and 6-hourly time intervals. This reward is achieved with an increased risk of hypoglycaemia especially for 6-hourly with 30 patients experiencing severe hypoglycaemia for STAR-TIM against 23 observed for STAR-3D. The other important risk is the relatively much lower median nutrition for 6-hourly time intervals. The median nutrition administered is reduced by 20% compared to STAR-3D for the 6-hourly interval (85.3 %GF for STAR-3D vs. 65.2 %GF for STAR-TIM) which is an important difference.

As already mentioned, two solutions to reduce the risks associated with the time interval maximisation would be to limit the time interval allowed to 2 hours when the current BG is above the target band and not 3 hours as it is in this version and to adapt the tolerance on the 95^{th} percentile. This should reduce the risk of severe hypoglycaemia and reduce nutrition at the cost of a slight increase of the workload.

Unlike the initial assumptions made by implementing STAR-TIM, the performance is not really impacted by the higher tolerance placed on the 95^{th} percentile. Indeed, the %BG in the different bands is a bit lower for STAR-TIM with 3-hourly intervals but higher for 6-hourly and particularly for the 4.4-7.0 mmol/L band. This is linked to the lower median BG level obtained for 6-hourly time intervals.

Overall, this design successfully managed to further reduce workload, at the cost of a significantly decreased nutrition rates achieved and increased incidence of severe hypoglycaemia.

STAR-IVM

The main reward associated with STAR-IVM is the reduced median insulin variation (0.5 U/h for STAR-IVM vs. 1.0 U/h for STAR-3D) and the increased percentage of unchanged insulin and nutrition interventions for the different time intervals. It also induces a decrease of the incidence of severe hypoglycaemia for 6-hourly time intervals with only 18 patients experiencing severe hypoglycaemia compared to the 23 patients for STAR-3D.

However, it results in a decreased median time interval and therefore, an increased workload. This negative effect is particularly visible for 6-hourly time intervals (10.5 measurements/day for STAR-IVM and 8.5 measurements/day for STAR-3D). By considering the current treatment administered, the protocol can choose treatment with insulin dosing leading to higher risk of extreme BG levels in the next hours. To compensate for this effect, the time interval is reduced

resulting in lower incidence of both hyper- and hypoglycaemia with an increased workload and insulin dosing.

The same observation as with the time interval maximisation can be made for the performance. The lower median BG level obtained for 6-hourly time intervals reflects the increased %BG in the different bands.

Contrary to initial assumptions, the use of insulin is a bit reduced for 3-hourly but not for 6-hourly. Limiting the insulin dosing variations is then not associated with reduced costs for all the time intervals. In addition, lower insulin dosing variability induces higher glycaemic variability for 4-,5-, 6-hourly time intervals and consequently worse GC outcomes.

Here again, the design successfully reduced the insulin dosing variability and the interventions required from the nurses at the cost of an increased workload in terms of measurements and an unexpected increased glycaemic variability.

	3-hourly			
	STAR-3D	**STAR-TIM**	**STAR-IVM**	**STAR-GO**
# GC episodes	681	681	681	681
# GC hours	59209	59285	59239	59312
# BG measurements	29903	27646	30605	27608
# BG measurements/day	12.1	11.2	12.4	11.2
Median BG (mmol/L)	6.4 [5.8 7.2]	6.5 [5.9 7.4]	6.5 [5.9 7.3]	6.5 [5.9 7.4]
Median insulin (U/h)	3.5 [2.0 5.0]	3.5 [2.0 5.5]	3.0 [2.0 4.5]	3.5 [2.0 5.0]
Median nutrition (%GF)	99.7 [84.5 100.0]	100.0 [95.4 100.0]	99.9 [84.7 100.0]	100.0 [92.0 100.0]
% BG in 4.4-8.0 mmol/L	83.8	82.8	83.2	82.7
% BG in 4.4-7.0 mmol/L	67.5	64.5	66.4	64.7
% BG > 8.0 mmol/L	14.5	15.5	15.1	15.6
% BG < 4.4 mmol/L	1.7	1.8	1.7	1.7
% BG < 2.2 mmol/L	0.03	0.03	0.03	0.03
# patients ≥50%BG in 4.4-8.0 mmol/L (%)	591 (86.8%)	590 (86.6%)	581 (85.3%)	588 (86.3%)
# patients ≥50%BG in 4.4-7.0 mmol/L (%)	479 (70.3%)	466 (68.4%)	460 (67.5%)	460 (67.5%)
# patients min BG < 2.2 mmol/L (%)	12 (1.8%)	13 (1.9%)	14 (2.1%)	14 (2.1%)
Median BG level variations (mmol/L)	0.35 [0.25 0.49]	0.34 [0.25 0.47]	0.33 [0.24 0.47]	0.34 [0.25 0.46]
Median insulin variations (U/h)	1.0 [0.5 1.5]	1.0 [0.0 1.5]	0.5 [0.0 1.0]	0.75 [0.5 1.0]
Median time interval (min)	120 [60 180]	180 [60 180]	90 [60 180]	180 [60 180]
% unchanged nutrition interventions	41.0	62.4	48.2	59.5
% unchanged insulin interventions	29.9	31.2	35.0	32.2
% unchanged insulin and nutrition interventions	11.0	15.5	16.6	16.7

Table 7.5: *Virtual trial results summary for 3-hourly time intervals. Comparison between STAR-3D, STAR-TIM, STAR-IVM and STAR-GO.*

	6-hourly			
	STAR-3D	**STAR-TIM**	**STAR-IVM**	**STAR-GO**
# GC episodes	681	681	681	681
# GC hours	60054	60051	59501	60068
# BG measurements	20696	18675	25944	18799
# BG measurements/day	8.3	7.5	10.5	7.5
Median BG (mmol/L)	6.8 [6.2 7.5]	6.3 [5.7 7.2]	6.3 [5.7 7.2]	6.3 [5.7 7.2]
Median insulin (U/h)	2.5 [1.7 3.0]	2.5 [1.5 4.3]	3.0 [2.0 4.5]	2.5 [2.0 4.0]
Median nutrition (%GF)	85.3 [70.1 94.7]	65.2 [52.0 80.0]	81.9 [64.7 95.6]	65.3 [52.0 80.0]
% BG in 4.4-8.0 mmol/L	81.4	83.9	83.9	83.4
% BG in 4.4-7.0 mmol/L	56.3	67.8	68.6	66.4
% BG > 8.0 mmol/L	16.9	13.4	13.9	13.9
% BG < 4.4 mmol/L	1.6	2.7	2.2	2.7
% BG < 2.2 mmol/L	0.05	0.08	0.04	0.08
# patients ≥50%BG in 4.4-8.0 mmol/L (%)	584 (85.7%)	591 (86.8%)	589 (86.5%)	583 (85.6%)
# patients ≥50%BG in 4.4-7.0 mmol/L (%)	398 (58.4%)	475 (69.7%)	478 (70.2%)	473 (69.5%)
# patients min BG < 2.2 mmol/L (%)	23 (3.4%)	30 (4.4%)	18 (2.6%)	25 (3.7%)
Median BG level variations (mmol/L)	0.22 [0.15 0.32]	0.24 [0.17 0.36]	0.29 [0.21 0.41]	0.24 [0.17 0.36]
Median insulin variations (U/h)	1.0 [0.5 1.5]	1.0 [0.5 1.5]	0.5 [0.0 1.0]	0.75 [0.5 1.0]
Median time interval (min)	60 [60 360]	180 [60 360]	120 [60 180]	180 [60 360]
% unchanged nutrition interventions	19.9	22.3	32.4	20.4
% unchanged insulin interventions	33.9	32.8	33.2	33.2
% unchanged insulin and nutrition interventions	8.4	9.8	13.3	9.1

Table 7.6: *Virtual trial results summary for 6-hourly time intervals. Comparison between STAR-3D, STAR-TIM, STAR-IVM and STAR-GO.*

STAR-GO

The different risk and reward trade-offs highlighted for STAR-TIM and STAR-IVM are combined in STAR-GO. The reward associated with the combination is a reduced workload of approximately one measurement per day compared to the original version and higher percentages of unchanged interventions. Performance is similar but higher for 6-hourly time intervals.

The risks are higher incidence of hypoglycaemia and significantly reduced nutrition for 6-hourly. The nutrition is similar to the one obtained for the time interval maximisation but the increased incidence of severe hypoglycaemia is lower because it was counterbalanced by the reduced incidence obtained for the insulin dosing variability minimisation. There is also an increased glycaemic variability.

However, the risk and reward trade-off highlighted here for STAR-GO and more globally for each optimisation studied evolve with the time interval. Indeed, this is noted by the opposite evolution of performance and incidence of hyperglycaemia between STAR-3D and STAR-GO.

Figure 7.7 allows to better visualise this evolution by showing a summary of the main risks and rewards associated with STAR-GO for the different time intervals. The results obtained for 4-hourly and 5-hourly time intervals are also visible in this Figure even though they are not shown in the Tables 7.5 and 7.6. Only STAR-GO is compared as it combines well the results of each optimisation.

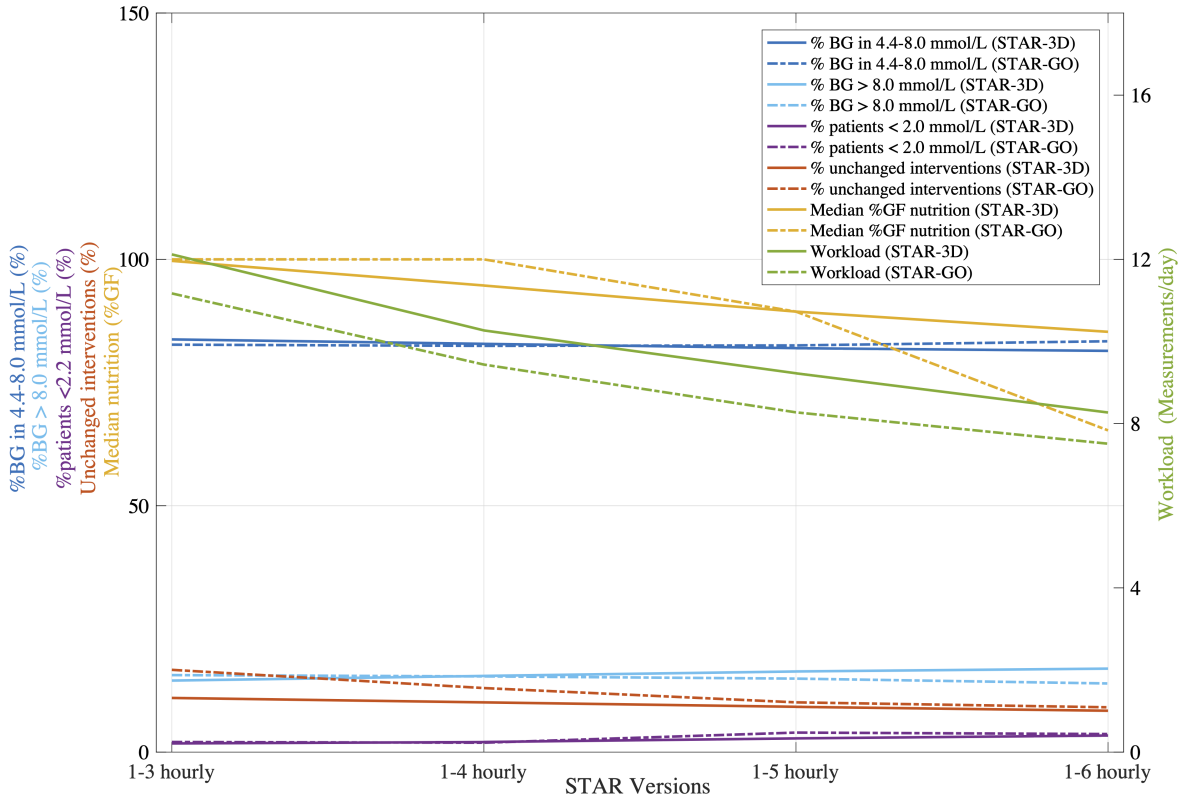


Figure 7.7: *Comparison of performance, safety and workload between STAR-3D (solid line) and STAR-GO combining time interval maximisation and insulin variations minimisation (dotted line) as a function of the time intervals.*

For 3-hourly time intervals, the reward associated with each optimisation of the treatment selection process (lower workload and higher percentage of unchanged interventions) is clearly visible. The risks are however limited as the nutrition and the incidence of hyper- and hypoglycaemia are barely impacted. These observations together with the previous ones allow

to conclude that the new treatment process implemented in STAR-GO is well suited to be used with 3-hourly time intervals as the risks associated are limited compared to the rewards obtained.

For 4-hourly, the situation is similar. The reward is still clear with only a bit less unchanged interventions and in this case increased nutrition. On the other side, the risks associated are not increased so the global optimisation is also appropriate to be used with 4-hourly time intervals.

From 5-hourly time intervals, the situation is a bit different. First, for 5-hourly, one main reward, the reduced workload is obtained. Except the slight increased incidence of severe hypoglycaemia, the rest of the results seems similar between the two protocols suggesting that STAR-GO has no significant impacts on GC using 5-hourly time intervals.

Then, for 6-hourly, the reward associated with STAR-IVM is not so noticeable. The incidence of hyperglycaemia is slightly lower than for the different time intervals. However, the risk expressed by much lower nutrition administration may exceed the main reward of one measurement less per day but a solution has been proposed to reduce that risk.

7.4.4 Conclusions

Globally, the new treatment selection processes implemented here fulfill their functions. The changes implemented to maximise the time interval reduce the workload and those to minimise the insulin dosing variability reduce the number of interventions required of the nurses. STAR-GO also combines well the different effects.

In addition, the number of patients with more than 50% BG in the different bands is high for the different protocols and time intervals tested. This shows that an effective control was achieved for nearly all patients.

Those improvements are not risk-free. Each one is associated with different risks. The nutrition is reduced, the incidence of hypoglycaemia is increased for longer time intervals and the workload and glycaemic variability are increased for less insulin variations. Those risks also add and/or counterbalance in the protocol combining the improvements. However, they remain limited except for 6-hourly time intervals which encourages their use in clinical practice.

Solutions were also proposed to reduce the important decrease in nutrition administration and the increased incidence of hypoglycaemia induced by STAR-TIM for 6-hourly time intervals, by fixing interval to a maximum of 2 hours when above target and by adapting the tolerance on the 95^{th} percentile when in the target. These solutions should be tested to see if they actually increase nutrition, thus positively impacting the results.

Once again, it is important to mention that those results were obtained using virtual trials. They assume a full compliance of the nurse which is not representative of the reality. As encouraging results were already obtained with these virtual trials, clinical trials should be conducted on STAR-GO to further validate its use.

7.5 Summary

To further reduce the workload associated with GC and to increase the nurse's confidence in STAR, two changes were implemented in the treatment selection process of STAR-3D. Their goal is to reduce the number of measurements and interventions required and to reduce the variability in insulin dosing.

To check the validity of these improvements, virtual trials were conducted on each change implemented individually and then, on a global optimisation combining the two changes. The trials were performed on the extension of STAR-3D developed in Chapter 3 as it provided positive results.

The trials performed showed encouraging results confirming the assumed effects of each change and highlighting the risk and reward trade-offs associated with each optimisation. By maximising the time interval and minimising the insulin dosing variability, the workload was reduced in terms of number of measurements per day and insulin and nutrition interventions. The risks associated with these rewards were mainly reduced safety and nutrition for 6-hourly intervals.

Those results are positive for a future use of this new protocol in clinical practice and particularly in ICUs where the nurse's compliance and confidence in the protocol is not optimal. However, some adjustments still need to be made and a clinical trial should confirm the results obtained virtually.

Chapter 8

Conclusions

8.1 General conclusions

Stress-induced hyperglycaemia is a common glucose complication occurring in critically ill patients. It is part of the stress response of the body following a severe trauma. Stress-induced hyperglycaemia is associated with worse outcomes for critically ill patients and glycaemic control has been introduced to reduce and stabilise BG levels. This control is achieved through protocols modulating insulin and in some cases nutrition. One of such GC protocols is the Stochastic TARgeted (STAR) GC protocol. Two versions of the stochastic models used in STAR have previously been developed, providing two versions of STAR, and the most recent one STAR-3D was shown to provide tighter predictions with a more patient-specific control and therefore expected improved clinical outcomes.

New versions of STAR-3D are studied in this master thesis. Their aim is to reduce the workload and the treatment variability associated with the protocol perceived as a clinical burden for the nurses and impeding the adoption of the protocol in some intensive care units. The different versions are investigated by assessing the risk and reward trade-off of each of them. This is done by conducting virtual trials on virtual patients. Using virtual trials allows to optimise and validate the protocol prior to its clinical implementation saving time, money and preventing avoidable risks on real patients.

The different in silico trials are performed on a same cohort of 681 virtual patients characterised by unique insulin sensitivity profiles. These patients are used to create the 3D stochastic models. These models are created for the six different time intervals considered using five-fold cross-validation. They show larger prediction width as the time interval increases possibly associated with reduced safety for the patients. The five-fold cross-validation also allows to conclude that the models are generalisable to other cohorts and protocols.

The first trial is an extension of the measurement and treatment interval of STAR-3D from 1-3 hourly to 1-6 hourly. This extension has previously been studied on STAR-2D and the protocol was shown to provide robust control even for longer intervals. Results obtained with STAR-3D also clearly highlight a risk and reward trade-off with reduced workload at the cost of lower %BG in the target band and higher incidence of both hyper- and hypoglycaemia as the measurement and intervention interval increases. Overall, 4- and 5-hourly intervals appear to offer the best risk and reward trade-off with non negligible reduced workload at the cost of limited decrease in performance and safety of STAR-3D. Compared to STAR-2D, performance and safety are improved thanks to tighter predictions obtained with the stochastic models better accounting for inter- and intra-patient variability.

The second set of trials tests different optimisations of the treatment selection process of STAR-3D. The optimisations are tested on the extension of the time intervals because of the encouraging results obtained with the first virtual trial. The proposed solutions are first studied separately and then together in a global optimisation process. The results obtained from the trials show that each version fulfills the functions it is implemented for and the effects of each add up or counterbalance in the global optimisation.
A first solution, STAR-TIM is implemented to further reduce the workload associated with STAR by maximising the time interval between measurements and interventions. The workload is effectively reduced for STAR-TIM with high performance at the cost of much lower nutrition rates and lower safety.
The second solution is implemented in STAR-IVM and consists in reducing the insulin dosing variability. Here again, STAR-IVM successfully reduces the insulin variability and the need to change the treatment administered at the expense of increased workload.
The combination of both solutions in STAR-GO provides a safe and efficient control for nearly all patients. Despite some further optimisations of the treatment selection process to limit the risks mentioned, results are encouraging for a future use of this new version of STAR-3D in clinical practice.

8.2 Perspectives and Future work

This work investigated the risk and reward trade-offs associated with different versions of the STAR-3D protocol. These studies were made in silico using virtual trials providing results in an ideal situation of full nurse's compliance. However, this does not completely reflect the reality as nurses are free to choose the recommendations given by the protocol. To be able to conclude on the validity of a protocol, clinical trials have to be performed.

The conduction of a clinical trial is thus the next step to validate the extension of STAR to longer treatment and measurement intervals. The encouraging results obtained virtually for STAR-2D in a previous study and for STAR-3D in this work need to be confirmed clinically

before actually implementing the protocol in intensive care units.

On the other side, future work also needs to be carried out on the optimisations of the treatment selection process prior to their clinical testing. For STAR-TIM, two modifications have been implemented in the treatment selection process and it was not possible to detect the influence of each of them by simply looking at the results. Further virtual trials should be conducted on each modification implemented separately to study their impact and be able to test the solutions proposed to limit the reduction in nutrition rates administration and the increased incidence of hypoglycaemia observed for longer time intervals in STAR-TIM and STAR-GO. If these trials validate these versions, clinical trials could than be conducted on STAR-GO.

Appendices

Appendix A

Parameters of the ICING model

Parameter	**Signification**	**Value**	**Units**
α_G	Saturation of insulin-mediated glucose uptake	0.0154	$[L/mU]$
α_I	Saturation of hepatic insulin clearance	17×10^{-3}	$[L/mU]$
CNS	Glucose uptake by central nervous system	0.3	$[mmol/min]$
d_1	Glucose transfer rate from stomach to gut	0.0347	$[min^{-1}]$
d_2	Glucose transfer clearance rate from gut	0.0069	$[min^{-1}]$
EGP	Endogenous glucose production (hepatic)	1.16	$[mmol/min]$
k_1	Insulin secretion model parameter	14.9	$[(mU \cdot L)/mmol/min]$
k_2	Insulin secretion model parameter	-49.9	$[mU/min]$
n_C	Rate parameter: cellular degradation of internalised insulin	0.006	$[min-1]$
n_I	Rate parameter: diffusion of insulin between plasma and interstitium	0.006	$[min^{-1}]$
n_K	Rate parameter: kidney clearance of insulin	0.0542	$[min^{-1}]$

n_L	Rate parameter: general hepatic insulin clearance	0.1578	$[min^{-1}]$
p_G	Other non-insulin mediated glucose clearance	0.006	$[min^{-1}]$
P_{max}	Maximum glucose flux out of the gut	6.11	$[mmol/min]$
u_{max}	Maximum insulin secretion	266.7	$[mU/min]$
u_{min}	Minimum insulin secretion	16.7	$[mU/min]$
V_G	Glucose distribution volume	13.3	$[L]$
V_I	Insulin distribution volume	4	$[L]$
x_L	Fractional first pass hepatics insulin clearance from portal vein	0.67	$[-]$

Table A.1: *Parameters values and definitions of the ICING model [7, 44].*

Variable	**Signification**	**Units**
$D(t)$	Oral glucose input rate (enteral nutrition)	$[mmol/min]$
$PN(t)$	Intravenous glucose input rate (parenteral nutrition)	$[mmol/min]$
$u_{ex}(t)$	Intravenous insulin input rate	$[mU/min]$

Table A.2: *Exogenous variables description of the ICING model [7, 44].*

References

[1] Deepanjali Vedantam et al. "Stress-Induced Hyperglycemia: Consequences and Management". In: *Cureus* 14.7 (2022), e26714.

[2] Chien-Wei Hsu. "Glycemic control in critically ill patients". In: *World Journal of Critical Care Medicine* 1.1 (2012), pp. 31–39.

[3] J Geoffrey Chase et al. "Organ failure and tight glycemic control in the SPRINT study". In: *Critical Care* 14.R154 (2010).

[4] Vincent Uyttendaele et al. "Untangling glycaemia and mortality in critical care". In: *Critical Care* 21.152 (2017).

[5] Vincent Uyttendaele et al. "Is intensive insulin therapy the scapegoat for or cause of hypoglycaemia and poor outcome?" In: *IFAC Journal of Systems and Control* 9.100063 (2019).

[6] Alicia Evans et al. "Stochastic Targeted (STAR) Glycemic Control: Design, Safety, and Performance". In: *Journal of Diabetes Science and Technology* 6.1 (2012), pp. 102–115.

[7] Vincent Uyttendaele. "Patient-Specific Metabolic Variability and Precision Glycaemic Control in Critical Care". PhD University of Liège, University of Canterbury, 2020.

[8] Kent W. Stewart et al. "Safety, efficacy and clinical generalization of the STAR protocol: a retrospective analysis". In: *Annals of Intensive Care* 6.24 (2016).

[9] Vincent Uyttendaele et al. "STAR-3D clinical trial results: Improved performance and safety". In: *IFAC-PapersOnLine* 54.15 (2021), pp. 490–495.

[10] Vincent Uyttendaele et al. "3D kernel-density stochastic model for more personalized glycaemic control: Development and in-silico validation". In: *BioMedical Engineering Online* 18.102 (2019).

[11] Vincent Uyttendaele et al. "Preliminary results from the STAR-Liège clinical trial: Virtual trials, safety, performance, and compliance analysis". In: *IFAC-PapersOnLine* 51.27 (2018), pp. 355–360.

[12] Vincent Uyttendaele et al. "Translating A Risk-Based Glycaemic Control Framework for Critically Ill Patients: STAR-Liège". In: *IFAC-PapersOnLine* (2020).

[13] Pascale Carayon and Ayşe P. Gürses. "A human factors engineering conceptual framework of nursing workload and patient safety in intensive care units". In: *Intensive and Critical Care Nursing* 21.5 (2005), pp. 284–301.

[14] Vincent Uyttendaele et al. "Risk and reward: Extending stochastic glycaemic control intervals to reduce workload". In: *BioMedical Engineering Online* 19.26 (2020).

[15] Jane Reece et al. *Campbell Biologie*. 4th ed. ERPI Sciences, 2004. (French translation).

[16] Arthur C. Guyton and John E. Hall. *Textbook of Medical Physiology*. 12th ed. Saunders, 2011.

[17] J.R. Tortora and S. R. Grabowski. *Principes d'anatomie et de physiologie*. Ed. by De Boeck Université. Deuxième édition française. 1994.

[18] Sophie Van Cromphaut. "Hyperglycaemia as part of the stress response: the underlying mechanisms". In: *Best Practice and Research: Clinical Anaesthesiology* 23.4 (2009), pp. 375–386.

[19] Pia V. Röder et al. "Pancreatic regulation of glucose homeostasis". In: *Experimental molecular medicine* 48 (2016), e219.

[20] Sophie Penning. "Tight Glycaemic Control : Model-based methods to answer critical questions about this controversial therapy". PhD University of Liège, 2014.

[21] Stephen L Aronoff et al. "Glucose Metabolism and Regulation: Beyond Insulin and Glucagon". In: *Diabetes Spectrum* 17.3 (2004), pp. 183–190.

[22] Jean-Claude Lacherade, Sophie Jacqueminet, and Jean-Charles Preiser. "An Overview of Hypoglycemia in the Critically Ill". In: *Journal of Diabetes Science and Technology* 3.6 (2009), pp. 1242–1249.

[23] M. G. Annetta et al. "Diabetic and nondiabetic hyperglycemia in the ICU". In: *Current Anaesthesia and Critical Care* 17.6 (2006), pp. 385–390.

[24] Shamim I. Ahmad. *Diabetes : an old disease, a new insight*. Ed. by Shamim I. Ahmad. Vol. 771. Springer Science+ Business Media, LLC, 2012, p. 485.

[25] Cambridge Dictionary. *Hypermetabolism*. URL: https://dictionary.cambridge.org/dictionary/english/hypermetabolism. (accessed: 24.03.2023).

[26] Kathleen M. Dungan, Susan S. Braithwaite, and Jean-Charles Preiser. "Stress hyperglycaemia". In: *The Lancet* 373.9677 (2009), pp. 1798–1807.

[27] Amina Godinjak et al. "Hyperglycemia in Critically Ill Patients: Management and Prognosis". In: *Medical archives* 69.3 (2015), pp. 157–160.

[28] Henry Paw and Rob Shulman. *Handbook of Drugs in Intensive Care: An A-Z Guide*. 6th ed. Cambridge University Press, 2019.

[29] Sean M. Bagshaw et al. "The impact of early hypoglycemia and blood glucose variability on outcome in critical illness". In: *Critical Care* 13.3 (2009), R91.

[30] James S. Krinsley. "Glycemic variability: A strong independent predictor of mortality in critically ill patients". In: *Critical Care Medicine* 36.11 (2008), pp. 3008–3013.

[31] J. Geoffrey Chase et al. "Overview of Glycemic Control in Critical Care: Relating Performance and Clinical Results". In: *Journal of Diabetes Science and Technology* 1.1 (2007), pp. 82–91.

[32] J. Geoffrey Chase et al. "Tight glycemic control in critical care - The leading role of insulin sensitivity and patient variability: A review and model-based analysis". In: *Computer Methods and Programs in Biomedicine* 102.2 (2011), pp. 156–171.

[33] Fatanah Suhaimi et al. "What Makes Tight Glycemic Control Tight? The Impact of Variability and Nutrition in Two Clinical Studies". In: *Journal of Diabetes Science and Technology* 4.2 (2010), pp. 284–298.

[34] Simon Finfer et al. "Intensive versus Conventional Glucose Control in Critically Ill Patients". In: *The New England Journal of Medicine* 360.13 (2009), pp. 1283–1297.

[35] Simon Finfer et al. "Hypoglycemia and Risk of Death in Critically Ill Patients". In: *The New England Journal of Medecine* 667.12 (2012), pp. 1108–1118.

[36] Jessica Lin et al. "Stochastic modelling of insulin sensitivity and adaptive glycemic control for critical care". In: *Computer Methods and Programs in Biomedicine* 89.2 (2008), pp. 141–152.

[37] Geoffrey J. Chase et al. "Model-based Glycaemic Control in Critical Care - A review of the state of the possible". In: *Biomedical Signal Processing and Control* 1.1 (2006), pp. 3–21.

[38] Mathijs Vogelzang et al. "Computer-assisted glucose control in critically ill patients". In: *Intensive Care Medicine* 34.8 (2008), pp. 1421–1427.

[39] Timothy Lonergan et al. "A Simple Insulin-Nutrition Protocol for Tight Glycemic Control in Critical Illness: Development and Protocol Comparison". In: *Diabetes Technology Therapeutics* 8.2 (2006), pp. 191–206.

[40] Nurhamim Ahamad et al. "Efficacy and Safety of SPRINT and STAR Protocol on Malaysian Critically-Ill Patients". In: *IEEE EMBS Conference on Biomedical Engineering and Sciences* (2016), pp. 370–375.

[41] Liam M. Fisk et al. "STAR Development and Protocol Comparison". In: *IEEE Transactions on Biomedical Engineering* 59.12 (2012), pp. 3357–3364.

[42] J. Geoffrey Chase et al. "Validation of a model-based virtual trials method for tight glycemic control in intensive care". In: *BioMedical Engineering Online* 9.84 (2010).

[43] Kent W. Stewart et al. “Nutrition delivery, workload and performance in a model-based ICU glycaemic control system”. In: *Computer Methods and Programs in Biomedicine* 166 (2018), pp. 9–18.

[44] Jessica Lin et al. “A physiological Intensive Control Insulin-Nutrition-Glucose (ICING) model validated in critically ill patients”. In: *Computer Methods and Programs in Biomedicine* 102.2 (2011), pp. 192–205.

[45] Jessica Lin et al. “Stochastic modelling of insulin sensitivity variability in critical care”. In: *Biomedical Signal Processing and Control* 1.3 (2006), pp. 229–242.

[46] Vincent Uyttendaele et al. “A 3D insulin sensitivity prediction model enables more patient-specific prediction and model-based glycaemic control”. In: *Biomedical Signal Processing and Control* 46 (2018), pp. 192–200.

[47] Wai-Ki Ching et al. *Markov Chains : Models, Algorithms and Applicationq*. 2nd ed. Vol. 189. Springer New York, NY, 2013.

[48] Kent W. Stewart et al. “Nutrition delivery of a model-based ICU glycaemic control system”. In: *Annals of Intensive Care* 8.4 (2018).

[49] Christopher G. Pretty et al. “Impact of sensor and measurement timing errors on model-based insulin sensitivity”. In: *Computer Methods and Programs in Biomedicine* 114.3 (2014), e79–e86.

[50] Jennifer L. Dickson et al. “Generalisability of a Virtual Trials Method for Glycaemic Control in Intensive Care”. In: *IEEE Transactions on Biomedical Engineering* 65.7 (2018), pp. 1543–1553.

[51] J. Geoffrey Chase et al. “Impact of Human Factors on Clinical Protocol Performance: A Proposed Assessment Framework and Case Examples”. In: *Journal of Diabetes Science and Technology* 2.3 (2008), pp. 409–416.

[52] Matthew Signal et al. “Glycemic Levels in Critically Ill Patients: Are Normoglycemia and Low Variability Associated with Improved Outcomes?” In: *Journal of Diabetes Science and Technology* 6.5 (2012), pp. 1030–1037.

[53] Payam Refaeilzadeh, Lei Tang, and Liu Huan. “Cross-validation”. In: *Encyclopedia of Database Systems*. Ed. by Ling Liu and M. Tamer Özsu. 1st ed. Springer New-York, NY, 2009, pp. 532–538.

[54] Athirah Abdul Razak et al. “Assessment of glycemic control protocol (STAR) through compliance analysis amongst malaysian ICU patients”. In: *Medical Devices: Evidence and Research* 13 (2020), pp. 139–149.