Analysis, classification and management of insulin sensitivity variability in a glucose-insulin system model for critical illness

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A thesis submitted for the degree of

Doctor of Philosophy

in

Mechanical Engineering

at the

University of Canterbury,

Christchurch, New Zealand

24 January 2012

Acknowledgements

I would like to thank a number of people who have made my time working on this research for the past few years a rewarding experience.

To my supervisors, Prof. Geoff Chase and Dr. Geoff Shaw, for their enthusiasm, optimism, inspiration and guidance.

To Jessica Lin and Aaron Le Compte for their guidance, patience, knowledge and friendship.

To Fatanah, Matt, Ummu, Ash, Normy and Paul in the Centre for BioEngineering, for your friendship and making the work environment enjoyable and productive.

Finally, to Mum, Dad and Mike for their unconditional support and encouragement.

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Abstract

Hyperglycaemia in critical care is common and has been linked to increased mortality and morbidity. Tight control of blood glucose concentrations to more normal levels can significantly reduce the negative outcomes associated with hyperglycaemia. However, hypoglycaemia and glycaemic variability have also been independently shown to increase mortality in critically ill patients. Further complicating the matter, critically ill patients exhibit high inter- and intra patient metabolic variability and thus consistent, safe control of glycaemia has proved very difficult.

Model-based and model-derived tight glycaemic control methods have shown significant ability to provide very tight control with little or no hypoglycaemia in the intensive care unit (ICU). The model-based control practised in the Christchurch Hospital ICU uses a physiological model that relies on a single, time-varying parameter, SI, to capture the patient-specific glycaemic response to insulin. As an identified parameter, SI is prone to also capturing other, unintended, dynamics that add variability on multiple timescales. The objective of this research was to enable enhanced glycaemic control by addressing this variability of the SI parameter through better modelling and implementation.

An improved model of insulin secretion as a function of blood glucose concentration was developed using data collected from a recent study at the Christchurch Hospital ICU. Separate models were identified for non-diabetic patients and diagnosed, or suspected type II diabetic patients, with $R^2 = 0.61$ and 0.69, respectively. The gradients of the functions identified were comparable to data published in a number of other studies on healthy and diabetic subjects.

The transcapilliary diffusion (n_I) and cellular clearance (n_C) rate parameters were optimised using data from published microdialysis studies. Interactions between these key parameters determine maximum interstitial insulin concentrations available for glucose disposal, and thus directly influence SI. The optimal values of these parameters were determined to be $n_I = n_C = 0.0060$ min^{-1}.

Models of endogenous glucose production (EGP), as functions of blood glucose concentration and time, were assessed. These models proved unsatisfactory due to difficulties in identifying reliable functions with the available data set. Thus, it was determined that EGP should continue to be treated as a population constant, except during real-time glycaemic control, where the value may be adjusted temporarily to ensure valid *SI* values.

The first 24 hours of ICU stay proved to be a period of significantly increased *SI* variability, both in terms of hour-to-hour changes and longer-term evolution of level. This behaviour was evident for the entire study cohort as a whole and was particularly pronounced during the first 12-18 hours. The subgroup of cardiovascular surgery patients, in which there was sufficient data for analysis, mirrored the results of the whole cohort, but was found to have even lower and more variable *SI*. Glucocorticoid steroids were also found to be associated with clinically significant reductions in overall level and increases in hour-to-hour variability of *SI.*

To manage variability caused by factors external to the physiological model, the use of several stochastic models was proposed. Using different models for the early part of ICU stay and for different diagnostic subgroups as well as when patients were receiving certain drug therapies would permit control algorithms to reduce the impact of the *SI* variability on outcome glycaemia.

The impact of measurement timing and BG concentration errors on the variability of *SI* was assessed. Results indicated that the impact of both sources of errors on *SI* level was unlikely to be clinically significant. The impact of BG sensor errors on hour-to-hour *SI* variability was more pronounced. Understanding the effect of sensor and timing errors on *SI* allows their impact to be reduced by using the 5-95 percentile forecast range of stochastic models during glycaemic control.

The performance of the model incorporating the proposed insulin kinetic parameters and secretion enhancements was validated for clinical glycaemic

control and virtual trial purposes. This validation was conducted by self- and cross validation on a cohort independent to that with which the model was developed. The use of multiple stochastic models to reduce the impact of this extrinsic variability during glycaemic control was validated using virtual trials.

Chapter 1. Introduction

Stress-induced hyperglycaemia is prevalent in critical care and can occur in patients with no history of diabetes [Capes et al. 2000; Krinsley 2004; Van den Berghe et al. 2001]. Hyperglycaemia used to be seen as a positive adaptive response in the critically ill [Mesotten & Van den Berghe 2009]. However, two landmark studies, by Van den Berghe et al. [2001] and Krinsley [2004] showed that actively controlling blood glucose (BG) concentrations to more normal levels with insulin, significantly reduced mortality in critical care patients. These papers signalled a new era of research into hyperglycaemia and its prevention in the ICU.

Hyperglycaemia was found not only to be associated with mortality [Chase et al. 2008; Krinsley 2003,2004; Van den Berghe et al. 2001; Van den Berghe et al. 2003], but also with increases in other negative clinical outcomes. These other outcomes include severe infection [Bistrian 2001], sepsis and septic shock [Branco et al. 2005; Das 2003; Marik & Raghavan 2004; Oddo et al. 2004], myocardial infarction [Capes et al. 2000], and polyneuropathy and multiple-organ failure [Langouche et al. 2005; Van den Berghe et al. 2001]. In each of these cases or patient subgroups, lower blood glucose levels were associated with reduced mortality and/or complications.

Further, there was also evidence of significant reductions in the need for dialysis, bacteraemia testing and the number of blood transfusions with aggressive blood glucose control using intensive insulin therapy [Krinsley 2004; Van den Berghe et al. 2001; Van den Berghe et al. 2003]. All these results pointed towards the conclusion that the control of blood glucose to normal levels in critical care had a significant clinical impact. Equally, they create a very strong case that links elevated glycaemia and glycaemic variability to poor outcomes. Thus, conversely, lower glycaemic levels, regardless of how obtained, yield better outcomes.

1.1   Aetiology of hyperglycaemia in critical care

Hyperglycaemia in critically ill patients is generally considered a result of the stress response [Weissman 1990]. The counter-regulatory hormones: cortisol, glucagon, the catecholamines, as well as growth hormone, are significantly elevated almost immediately post critical-insult, but decline rapidly over the first 12-48 hours [Chernow et al. 1987; Frayn 1986; Jaattela et al. 1975; Weissman 1990]. These hormones are known to cause increased hepatic glucose production, inhibition of insulin secretion and peripheral insulin resistance [Weissman 1990], all of which cause elevated blood glucose concentrations during the acute phase of critical illness.

This acute phase evolves into the 'flow' phase of injury, which can last days or weeks and is characterised by hypermetabolism and muscle catabolism. Hyperglycaemia often persists into the flow phase, but the causes are not as well understood, as the time-course of the counter-regulatory hormones does not match that of the metabolic changes [Frayn 1986].

In addition to these injury-related causes, pre-existing glucose intolerance and the administration of some medications in the ICU may play a role in hyperglycaemia. In particular, glucocorticoid steroids [Bradley 2002; Pretty et al. 2010], the catecholamines, and β-blockers [Luna & Feinglos 2001; Sarafidis & Nilsson 2006] are commonly used drugs that have been recognized to increase hyperglycaemia. The situation is exacerbated by exogenous nutritional support regimes with high glucose content [Krishnan et al. 2003; Woolfson 1980].

Currently, the exact reasons for the benefits derived from tight glycaemic control (TGC) are not fully known, but have been extensively analysed in the literature [Bellomo & Egi 2005; Diringer 2005; Finney et al. 2003; Krinsley 2004; Langouche et al. 2005; Mesotten et al. 2004; Van den Berghe 2004; Van den Berghe et al. 2005]. However, recent studies by Weekers et al. [2003] and Langouche et al. [2005] indicated some major causes. Specifically, tight glycaemic control reduces glucotoxicity due to high blood glucose, which in turn reduces oxidative stress and superoxides, stress hormone responses, damage to

the endothelium and vascular walls. Hyperglycaemia was also shown to reduce immune response and bactericidal activity.

Thus, tight control of blood glucose concentrations in critical care can be beneficial. However, there is little consensus on what constitutes desirable glycaemic performance, or how to achieve it [Gale & Gracias 2006; Mackenzie et al. 2005; Schultz et al. 2006; Suhaimi et al. 2010].

1.2   Glycaemic control in critical care

Van den Berghe et al. [Van den Berghe et al. 2001] showed that tight blood glucose control to less than 6.1 mmol/L reduced cardiac surgical ICU patient mortality by 18-45% in a randomised controlled trial. Krinsley [2004] reported a 17–29% total reduction in mortality over a wider, more critically ill, ICU population with a higher glucose limit of 7.75 mmol/L in a retrospective study. However, repeating these results that reduced mortality and other outcomes has been difficult [Griesdale et al. 2009].

Several large trials [Brunkhorst et al. 2008; Finfer et al. 2009; Preiser et al. 2009] were unable to repeat the early results of Van den Berghe et al. [2001] or other successes by Krinsley [2004] and Chase et al. [2008]. For example, the VISEP study by Brunkhorst et al. [2008] was stopped for safety due to unacceptable rates of hypoglycaemia, while the Glucontrol trial of Preiser et al. [2009] had numerous unintended protocol violations. Thus, the role of TGC during critical illness and suitable glycaemic ranges have been under scrutiny in recent years [Chase & Shaw 2007; Kalfon & Preiser 2008; Moghissi et al. 2009; Preiser et al. 2009; Schultz et al. 2008; Van den Berghe et al. 2006b].

Overall, conclusions are varied with both success [Chase et al. 2008; Krinsley 2004; Van den Berghe et al. 2001], failure, [Finfer et al. 2009] and, primarily, no clear outcome [Brunkhorst et al. 2008; Chase & Shaw 2007; De la Rosa et al. 2008; Preiser et al. 2009; Schultz et al. 2008; Treggiari et al. 2008; Van den Berghe et al. 2006a; Vanhorebeek et al. 2007; Wiener et al. 2008], as summarised

by Griesdale et al. [2009]. These conflicting results, coupled with safety concerns arising from increased incidences of hypoglycaemia during some trials have shrouded TGC with controversy [Chase et al. 2011b; Griesdale et al. 2009].

The review by Chase et al. [2011b] suggests that the controversy surrounding the efficacy of TGC and its application are primarily due to lack of understanding of both the control problem and patient-specific dynamics. Specifically, while the overall cohort control statistics may appear good, the individual patients may not have received adequate tight control. The paper goes on to suggest that as mortality and morbidity are highly patient-specific outcomes, they will depend on how well each patient was controlled, rather than the overall cohort results. Hence, TGC is effective at reducing mortality and improving outcomes for a whole cohort, if and only if it is equally effective for every patient in that cohort.

Further complicating the control problem are the issues of hypoglycaemia and glycaemic variability. These factors have both been independently linked to mortality in critically ill patients [Egi et al. 2006; Egi et al. 2010; Hermanides et al. 2010; Krinsley 2008]. More specifically, Bagshaw [2009] showed that hypoglycaemia and variability within the first 24 hours of ICU stay are each associated with increased mortality. In vitro, high glycaemic variability was shown to increase oxidative stress [Piconi et al. 2006] and apoptosis [Risso et al. 2001], thereby suggesting a rationale to explain the clinical association with poor outcome.

The glycaemic control problem is thus defined by the simultaneous constraints of maintaining blood glucose concentrations within a relatively tight band for each individual patient, while avoiding excess variability. The 'actuators' available in exercising control are insulin and glucose inputs. Blood glucose concentration is the only state that is observable in clinical real-time. These conditions present a situation in which only model-based approaches may currently provide the robust, adaptive and patient-specific solution required to manage highly dynamic ICU patient metabolism.

1.3   Model-based glycaemic control

Model-based and model-derived TGC methods have shown significant ability to provide very tight control with little or no hypoglycaemia in the ICU [Chase et al. 2006; Chase et al. 2008; Chase & Shaw 2007; Cordingley et al. 2009; Evans et al. 2011; Hovorka et al. 2007; Le Compte et al. 2009]. Model-based control relies on a physiological model that captures the glucose-insulin system dynamics and allows blood glucose concentrations to be accurately predicted, knowing the insulin and glucose inputs. A control algorithm can use these predictions to select optimal insulin and carbohydrate-nutrition interventions for forthcoming periods.

A common aspect of the models that have successfully been used for TGC is one or more identified parameters capturing the glycaemic response to insulin, often termed insulin sensitivity [Chase et al. 2008; Cordingley et al. 2009; Evans et al. 2011; Hovorka et al. 2007; Le Compte et al. 2009]. The insulin sensitivity parameter(s) varies over time and between patients, allowing the models to adapt and provide safe, effective control for each individual. The specific form of the parameter(s) is dependent upon the model that defines it. In the model used throughout this thesis (detailed in Chapter 2), insulin sensitivity is represented by a single parameter, *SI*, that captures the whole-body glycaemic response to exogenous insulin. Regardless of the specific definition of the insulin sensitivity parameter(s), for effective prediction and thus model-based control, it must be relatively free from unwanted variability.

SI naturally varies between critically ill patients and over time within the individual patient as the stress response progresses. The pharmacokinetic-pharmacodynamic (PK-PD) model must capture these changes to enable accurate BG prediction. However, being a parameter identified from limited clinical measurements, *SI* is prone to also capturing other, unwanted, dynamics that are not strictly related to insulin sensitivity, but have nowhere else to go within the model. These unintended artefacts influence the *SI* parameter on multiple timescales and thus, analysis of variability must address longer-term

changes in level, in addition to hour-to-hour changes. This unwanted variability in *SI* can be lumped into two broad categories:

1. Unmodelled variability of other parameters within the physiological model (**Intrinsic Variability**).
2. Physiological changes external to the specific PK-PD model that are not explicitly modelled (**Extrinsic Variability**).

Unwanted variability in *SI* degrades the quality of control that can be achieved with model-based TGC. Hence, this variability must be minimised. The objective of this thesis is thus to understand and manage unwanted variability by improved modelling, where possible, and better application of the model to the control problem where the cause is extrinsic.

1.4   Preface

This thesis presents the analysis and management of several important causes of intrinsic and extrinsic *SI* variability in the ICING (Intensive Control Insulin-Nutrition-Glucose) model, used for tight glycaemic control and analysis [Evans et al. 2011; Lin et al. 2011]. Where possible, for intrinsic variability, the modelling is enhanced through the analysis and application of improved data and concepts. The impact of extrinsic variability is assessed, quantified, and where necessary, means are proposed to mitigate the impact of these sources of variability on the outcome of model-based TGC. The proposed measures are validated with self- and cross validation analyses and virtual trials using the recently developed STAR protocol [Evans et al. 2011].

The specific components of the PK-PD model that this thesis addresses are: Insulin secretion, insulin transport kinetics, and endogenous glucose production. These components have a direct and substantial impact on the *SI* parameter, as it represents the metabolic balance between glucose appearance and insulin-mediated glucose uptake. New data and concepts have become available to apply to these areas, providing the opportunity to reduce unwanted intrinsic *SI* variability.

Sources of extrinsic variability examined in this thesis are: Patient type and condition, drug therapies and measurement errors. These factors are thought to result in significant variability that is not explicitly modelled and thus cannot be reduced by improved modelling. Hence, the impact of these elements must be mitigated through understanding, and smarter use of *SI* in the control application.

Chapter 2 reviews the model of the glucose-insulin regulatory system and the methodology that is used in Christchurch for glycaemic control in critical care.

Intrinsic variability

Chapter 3 develops a model for pancreatic insulin secretion as a function of blood glucose concentration, based on data collected during a prospective trial at the Christchurch Hospital ICU. This improved treatment of endogenous insulin results in a more accurate insulin sensitivity parameter.

Chapter 4 improves the modelling of interstitial insulin kinetics, primarily through the refinement of population constant kinetic parameters, based on published data. More accurate transport kinetics reduce unmodelled artefacts in identified values of *SI*.

Chapter 5 investigates EGP and how its treatment within the model may be improved. Modelling EGP as functions of time and blood glucose concentration are explored.

Chapter 6 presents the enhanced ICING-2 model, incorporating the changes proposed in Chapters 3-5.

Extrinsic variability

Chapter 7 assesses the impact of patient type and condition on the variability of *SI*. This analysis formalises the anecdotal experience that certain periods of

patient stay and diagnostic categories are more variable, and thus harder to control.

Chapter 8 examines the effects of two common drug therapies, glucocorticoid steroids and Metoprolol, thought to reduce insulin sensitivity. Knowledge of the way drug therapies impact *SI* can lead to improved application of the model during control.

Chapter 9 quantifies and analyses the influence of measurement errors, in the form of measurement timing and BG sensor errors, on the identified *SI* parameter.

Validation

Chapter 10 presents the validation of ICING-2 model, using self- and cross validation analyses on a critically ill cohort, independent to that on which the model was developed.

Chapter 11 presents simulated control trials on 'virtual patients' as a tool to validate the measures proposed to reduce the impact of extrinsic *SI* variability on outcome glycaemia.

Chapters 12 and 13 summarise the key aspects of the thesis and present possible future improvements and applications for this research.

Chapter 2. Background

2.1   Modelling and physiology

A physiological model that captures the glucose-insulin system dynamics and allows accurate blood glucose prediction is the basis for model-based glycaemic control. Metabolic modelling of the glucose-insulin system has a very deep history in the published literature. The vast majority of these models have their roots in basic compartment modelling with differential equations [Carson & Cobelli 2001]. These models and, in particular, those from which the model in this thesis is derived, have been extensively reviewed by Razak [2011], Le Compte [2009] and Lin et al. [2011]. This section provides a summary of the basic requirements for a compartment model that can be used in clinical real-time and introduces the ICING model used throughout the rest of this thesis.

A compartment model consists of five basic elements:
1. Compartments in which substances exist at varying concentrations.
2. Kinetics describing the transport of substances between compartments.
3. Dynamics that describe the interaction of substances with each other or the environment.
4. Appearance of substances into the compartment system from the external environment.
5. Clearance of substances back to the external environment.

In addition to these five basic elements, a successful model for clinical control should also be physiologically valid, clinically applicable and mathematically identifiable [Chase et al. 2011a]. These additional factors ensure that the output of the model provides useful information about the physiology of a patient and can be identified in clinical real-time using the limited data available.

The model used throughout the first part of this thesis, investigating intrinsic *SI* variability, is the ICING model described by Lin et al. [2011]. This model was developed to be more physiologically comprehensive than its predecessors [Lin et al. 2011; Razak 2011], primarily by incorporating more detailed insulin kinetics. The current ICING model definition is presented in Equations 2.1 - 2.7.

The current associated parameter values and descriptions are listed in Table 2.1. Table 2.2 shows the exogenous input variables to the model.

$$\dot{G}(t) = -p_G G(t) - S_I G(t) \frac{Q(t)}{1 + \alpha_G Q(t)} + \frac{P(t) + EGP - CNS}{V_G} \qquad 2.1$$

$$\dot{Q}(t) = n_I \big(I(t) - Q(t)\big) - n_C \frac{Q(t)}{1 + \alpha_G Q(t)} \qquad 2.2$$

$$\dot{I}(t) = n_K I(t) - n_L \frac{I(t)}{1 + \alpha_I I(t)} - n_I \big(I(t) - Q(t)\big) + \frac{u_{ex}(t)}{V_I} + (1 - x_L) \frac{u_{en}(I)}{V_I} \qquad 2.3$$

$$P(t) = \min(d_2 P2, \ P_{\max}) + PN(t) \qquad 2.4$$

$$\dot{P1}(t) = -d_1 P1 + D(t) \qquad 2.5$$

$$\dot{P2}(t) = -\min(d_2 P2, \ P_{\max}) + d_1 P1 \qquad 2.6$$

$$u_{en}(I) = k_1 e^{\frac{I(t)^{k_2}}{k_3}} \qquad 2.7$$

Table 2.1 Parameter values and descriptions for the ICING model.

Parameter	Value	Unit	Description
p_G	0.006	min^{-1}	Non-insulin mediated glucose removal
EGP	1.16	mmol/min	Endogenous glucose production rate
CNS	0.3	mmol/min	Central nervous system glucose uptake
V_G	13.3	L	Plasma glucose distribution volume
V_I	3.15	L	Plasma and interstitial insulin distribution volume
α_G	0.0154	L/mU	Insulin binding saturation parameter
α_I	0.0017	L/mU	Hepatic insulin clearance saturation parameter
n_I	0.003	min^{-1}	Trans-endothelial diffusion rate
n_C	0.003	min^{-1}	Interstitial insulin degradation rate
n_K	0.0542	min^{-1}	Renal insulin clearance rate
n_L	0.1578	min^{-1}	Hepatic insulin clearance rate
x_L	0.67		Fractional first-pass hepatic insulin extraction
d_1	0.0347	min^{-1}	Glucose transport rate from stomach to gut
d_2	0.0069	min^{-1}	Glucose transport rate from gut to plasma
$P_{\max}$	6.11	mmol/min	Maximum glucose flux from gut to plasma
k_1	45.7	mU/min	Maximum endogenous insulin secretion rate
k_2	1.5		Insulin secretion suppression factor 1
k_3	1000		Insulin secretion suppression factor 2

Table 2.2 Exogenous input variables to the ICING model.

Variable	Unit	Description
PN(t)	mmol/min	Intravenous glucose input rate (parenteral nutrition)
D(t)	mmol/min	Oral glucose input rate (enteral nutrition)
u_{ex}(t)	mU/min	intravenous insulin input rate

Figure 2.1 shows a schematic diagram of the ICING model. This diagram includes both the glucose-insulin system and the gastric component, which models the movement of glucose from nutrition through the stomach to the gut and subsequent absorption into the glucose compartment. The glucose, plasma insulin and interstitial insulin compartments of the glucose-insulin system are shown as circles, denoted G(t), I(t) and Q(t), respectively. The kinetics, appearance and clearance of insulin and glucose are indicated with solid arrows. The dynamic interaction between interstitial insulin and insulin-mediated glucose uptake, governed by the *SI* model parameter, is indicated with a dashed arrow.
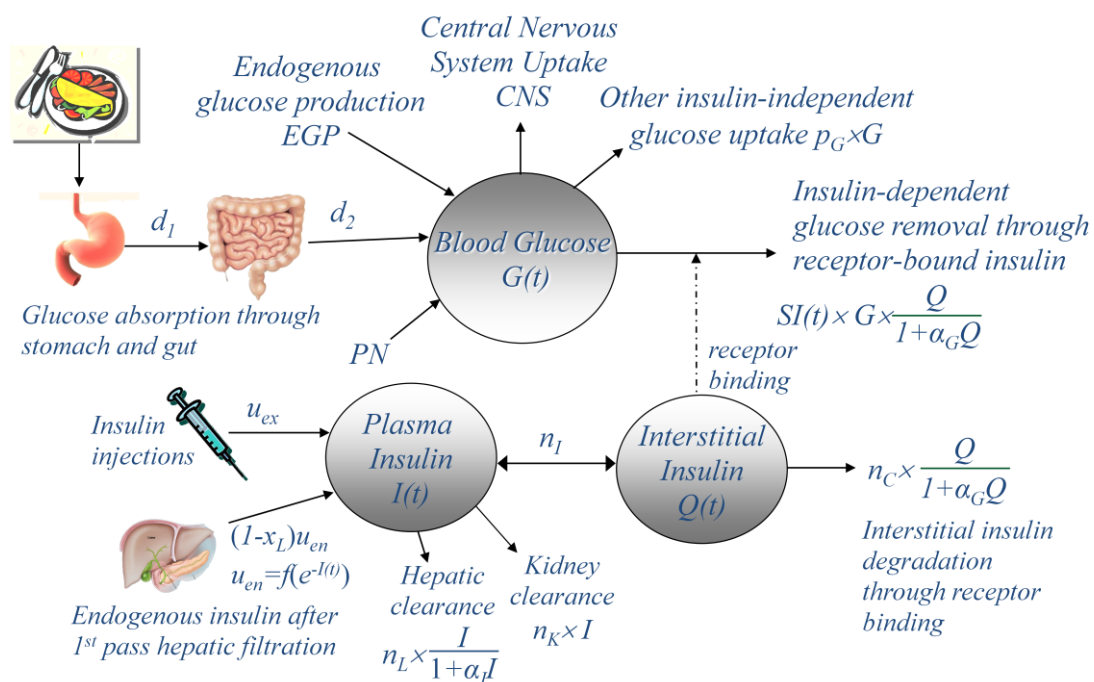
Figure 2.1. Schematic diagram of the ICING compartment model showing the compartments, kinetics and dynamics, appearance and clearance.

In the ICING model, insulin sensitivity, SI, is the critical patient-specific parameter that is fitted hourly to clinical blood glucose measurements using an integral-based fitting method [Hann et al. 2005]. The identification of SI relies not only on measured BG concentrations, but also the interstitial insulin concentration and total glucose flux through the compartment, both of which cannot be measured directly in clinical real-time. These other factors are primarily influenced by insulin kinetics, defined by n_I and n_C, and the modelled endogenous insulin (U_{en}) and glucose (EGP) appearance rates. However, with limited clinical data available, only one model parameter, SI can be uniquely identified [Docherty et al. 2011]. Hence, these other parameters must be treated as population constants or modelled independently.

Thus, the task of reducing intrinsic SI variability boils down to using the best data available to determine or model these particular parameters as accurately as possible for a fairly broad, critically ill population. A major goal of this thesis is to explore the impact of several specific model parameters and incorporate new physiological data to improve clinical performance and physiological relevance:

Chapter 3 uses recently obtained clinical data to develop a more accurate model of endogenous insulin secretion for critically ill patients. This sub-model is of particular importance as endogenous insulin can make up a large part of the total insulin appearance rate and consequently has a significant impact on SI.

Chapter 4 investigates the kinetic parameters n_I and n_C, which define the diffusion of insulin between the plasma and interstitium and cell-receptor binding and clearance. The interactions between these two parameters determine the maximum interstitial insulin concentrations and thus insulin-mediated glucose disposal.

Chapter 5 investigates modelling EGP as functions of blood glucose concentration and time, to better capture the enhanced glucose appearance rate characteristic of the acute stress response [Weissman 1990]. Endogenous glucose production can constitute a large part, if not all, of the glucose

appearance, particularly during the early part of a patient's ICU stay. Thus, as with insulin secretion, EGP can have a significant impact on *SI*.

2.2   Role of *SI* in model-based control

The model-based glycaemic control approach used in this thesis is known as STAR (Stochastic, TARgeted) [Evans et al. 2012; Evans et al. 2011]. The STAR approach relies on the physiological model (Equations 2.1- 2.7) and one or more stochastic models of *SI* that describe the probability density of *SI* for the forthcoming hour, given the value identified over the previous hour. These stochastic models of *SI* enable BG concentrations to be forecast one or more hours ahead with associated confidence levels, given known or proposed insulin and nutritional inputs. This process is illustrated schematically in Figure 2.2.
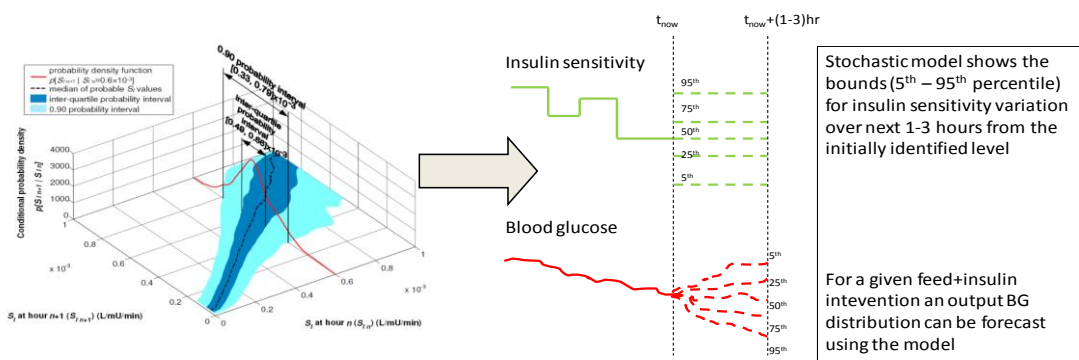
Figure 2.2. BG forecasting based on a stochastic model of *SI*.

The generation and validation of these stochastic models are described in detail by Lin [2007]. Briefly, existing data from critically ill patients are used to identify *SI* profiles with the ICING model. The *SI* profiles are broken down into paired (SI_n, SI_{n+1}) data points and kernel density estimation methods used to create a smooth, continuous model surface that reflects the sample data pattern. Specifically, $SI_{n+1} \sim F(SI_n)$ and thus, for any identified value of SI_n, the stochastic model provides a continuous, empirical estimate of the probability function of SI_{n+1}, for the subsequent hour. Experience has shown that a minimum of approximately 1300 hours of data is required to generate reliable stochastic models.

The ability to forecast BG concentrations with associated confidence levels enables the STAR control algorithm to optimise insulin and nutrition inputs, while keeping the risk of hypoglycaemia below a clinically specified limit (typically 5%). The STAR approach explicitly targets the 5th and 95th percentile forecast BG outcomes (Figure 2.2.) to the clinically selected target BG range. Hence, STAR aims to maximise the likelihood that the next BG measurement will be in the desired target range, given constraints on the risk of hypoglycaemia and nutrition and insulin administration.

The stochastic method captures behaviours of the cohort used to generate the models. However any particular patient is not guaranteed to follow cohort-defined behaviour, and can be influenced by external factors such as individual disease state and therapy. The task of reducing the impact of extrinsic *SI* variability on outcome glycaemia thus becomes one of selecting appropriate additional stochastic models to use with the STAR protocol. However, to maintain reliability over broad cohorts, particularly for managing risk of hypoglycaemia, the models must derive from large numbers of data points and thus be relatively few in number given the finite data set. Therefore, additional stochastic models should only be considered for conditions where there is a clear need for them, justified by significant differences in *SI* variability associated with clear, defined causes, as investigated in Chapters 7 and 8.

Chapter 3.   Endogenous Insulin Secretion Model

This section investigates intrinsic *SI* variability, resulting from the unmodelled variability of other parameters within the physiological model. The endogenous insulin secretion model is of particular importance as endogenous insulin can make up a large part of the total insulin appearance rate. Thus, endogenous insulin has a significant impact on identified values of *SI* and consequently, intrinsic *SI* variability.

3.1   Introduction

Correctly modelling endogenous (pancreatic) insulin secretion is important to the overall accuracy of any glucose-insulin system model. In the absence of exogenous insulin or with low-doses, endogenous secretion is responsible for a significant percentage of insulin-mediated glucose disposal. Therefore, it has a significant impact on the identified *SI* parameter, particularly in these situations. Hence, reducing error in the insulin secretion model can reduce intrinsic *SI* variability and thus increase the accuracy and utility of the parameter for glycaemic control.

A number of studies have established models of endogenous insulin secretion as a function of blood glucose level and its derivative, almost exclusively in healthy and diabetic individuals [Camastra et al. 2005; Ferrannini et al. 2005; Mari et al. 2002a; Mari et al. 2002b]. These models primarily focus on the endogenous response to glycaemic change resulting from meals. However, during critical illness, endogenous secretion may be enhanced, [Black et al. 1982; Watters et al. 1997] possibly due to stress hyperglycaemia. Equally, it may be suppressed by counter-regulatory hormones such as adrenaline, cortisol and glucagon [Bessey & Lowe 1993; Deibert & DeFronzo 1980; Gelfand et al. 1984]. Hence, healthy and diabetic insulin secretion models may not be appropriate to critically ill patients.

Importantly, a thorough search of the literature has not located any studies in which endogenous secretion was determined for critically ill patients. During a

clinical trial studying sepsis in the Christchurch Hospital ICU, 19 patients had blood samples taken to determine pre-hepatic endogenous insulin secretion. From this data, a model of insulin secretion as a function blood glucose could be identified.

3.2 Subjects and Methods

3.2.1 Patients and samples

19 patients from the Christchurch Hospital ICU enrolled in a prospective clinical trial studying sepsis each had an additional two sets of blood samples assayed for insulin and C-peptide. Patients were included in the study if they met all of the following criteria:

- Age ≥ 16 years.
- Expected survival ≥ 72 hours.
- Expected ICU length of stay ≥ 48 hours.
- Entry to the SPRINT TGC protocol (2 sequential BG measurements ≥ 8 mmol/l).
- Suspected sepsis or SIRS score ≥ 3.

Patients with suspected sepsis received treatment for sepsis with antibiotics. No diagnosed Type I diabetic patients were included. This study was approved by the Upper South Regional Ethics Committee, New Zealand.

Table 3.1 Summary of patient characteristics. Data are shown as median [IQR] where appropriate.

N	19
Age (years)	68 [57-75]
Gender (M/F)	10/9
APACHE II score	22.0 [18.3-26.8]
Confirmed sepsis	79%
Hospital mortality (L/D)	13/6
Diagnosed T2DM	3

One additional patient admitted to the ICU after pancreatoduodenectomy (Whipple procedure) was excluded from this analysis as this procedure involved removing a section of the pancreas and may thus have affected insulin secretion.

Two further patients each only had one set of blood samples assayed as one was discharged from the ICU within 48 hours and the other did not meet the criteria for the second set to be taken.

Table 3.2 Summary of patient diagnoses.

APACHE III diagnoses		Number
Non-operative	Respiratory	9
	Gastrointestinal	1
	Neurological	2
	Sepsis	4
Operative	Gastrointestinal	2
	Trauma	1

Each patient had two sets of blood samples taken, where each set consisted of 4 separate samples. The first set of samples was taken at the commencement of the SPRINT TGC protocol. The second set was taken when the patient consistently met less than 2 of the SIRS criteria (Systemic Inflammatory Response Syndrome) [1992].

The first sample of each set was taken immediately prior to bolus delivery of insulin as required by SPRINT (t = -1 min). The remaining three samples were taken at t = 10, 40 and 60 min. Plasma was separated from the blood samples and frozen for subsequent analysis. The testing laboratory reported that one sample (out of 143) was extremely haemolysed, to the extent that it may have lowered the measured C-peptide concentration and was thus excluded from the analysis.

Plasma glucose levels were not sampled at the same time points as insulin and C-peptide. As per normal clinical practise with the SPRINT protocol, blood glucose measurements were taken 1-2 hourly. Blood glucose levels corresponding to the insulin and C-peptide samples were linearly interpolated from these clinical measurements.

Insulin and C-peptide concentrations were determined using immunometric assays (Elecsys 2010, Roche Diagnostics, Germany). Blood glucose levels were measured with a bedside glucometer (Super-Glucocard II, Arkray Inc., Japan). The reported coefficients of variation (CV_A) for the insulin and C-peptide assays were 3.8% and 4.5% respectively [Roche 2004,2005]. Measurement error for the BG sensors was typically around 10% [Arkray 2007] (Chapter 9).

3.2.2 Analysis methods

Endogenous insulin secretion (Uen) can be determined from a series of plasma C-peptide measurements. C-peptide is produced by the pancreatic β-cells as a by-product of splitting insulin from its precursor, proinsulin, and is secreted in equimolar ratio with insulin [Rubenstein et al. 1969]. Unlike insulin, C-peptide is cleared almost entirely by the kidneys, making it a much more reliable marker of endogenous secretion than plasma insulin concentrations. Therefore, models independently linking C-peptide kinetics and insulin kinetics can be used to determine and capture pre-hepatic insulin secretion [Polonsky et al. 1986; Van Cauter et al. 1992].

The pharmacokinetic model and population kinetic parameters reported by Van Cauter et al. [1992] were used to deconvolve insulin secretion rates from measured C-peptide data. Age-based kinetic parameters were used for non-diabetic patients, while the population parameters reported for T2DM subjects were used for patient with diagnosed or suspected type II diabetes.

The resulting secretion rates were taken only from the approximately steady-state regions of the profile (-1, 40 and 60 mins) as the bolus insulin prescribed by SPRINT at 0 mins may have reduced pancreatic secretion for some period. Insulin infusions over 2 U/hr have been shown to suppress endogenous insulin secretion in healthy subjects 30-45% [Argoud et al. 1987]. Measured concentrations suggest that plasma insulin had returned to pre-bolus levels by 40 mins. The data density from this study was not high enough to reliably capture any suppression effects resulting from the bolus insulin.

Model fitting was performed by minimising the sum of the geometric means of the squared deviations in each dimension. This method allows for uncertainty in both the dependent and independent variables, while maintaining scale invariance [Draper & Yang 1997; Tofallis 2002]. Goodness of fit was assessed using the coefficient of determination, R^2, calculated for the constrained model.

3.3   Results and Discussion

3.3.1   Calculated endogenous secretion rates

Figure 3.1 shows calculated pre-hepatic insulin secretion plotted against blood glucose, its derivative and plasma insulin. The distinct group at the lower right of the left panel of Figure 3.1 (shown in red) consists of the three diagnosed type II diabetic patients and two others with a significantly impaired insulin response to hyperglycaemia. The clear separation between these patients and the remainder of the cohort suggests two separate models for insulin secretion; one for non-diabetic patients and one for diagnosed or suspected type II diabetic patients.
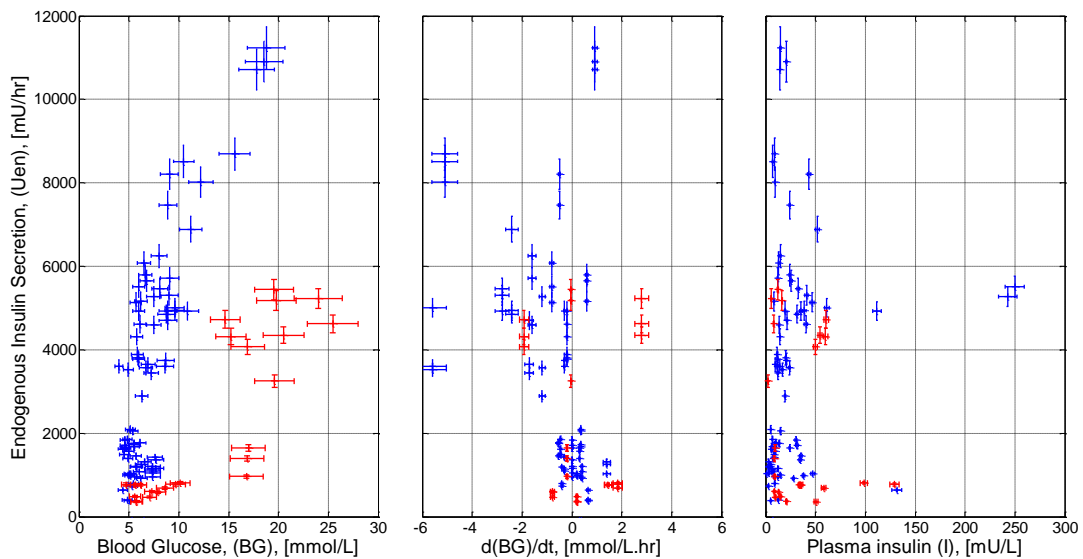
Figure 3.1 Pre-hepatic insulin secretion plotted against each of the measured variables. Data indicating patients with an impaired insulin response to hyperglycaemia are shown in red.

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3.3.2 Secretion rate bounds

It is likely that there is a physiological upper limit on pancreatic secretion rate. A non-zero minimum secretion rate is also required by the ICING model to prevent large insulin sensitivity changes when exogenous insulin is started or stopped. With little or no exogenous insulin and low pancreatic secretion rates (<500 mU/hr) the concentration of the remote insulin compartment (Q) approaches zero. Hence, mathematically, *SI* must be very large to maintain the observed glucose flux.

In a study of the potentiating effects of glucagon-like-peptide-1 (GLP-1) on insulin secretion, Kjems et al. [2003] achieved some very secretion high rates that suggest a reasonable physiological upper bound. The study involved stepped glucose infusions at 4 rates of GLP-1 infusion (0, 0.5, 1.0 & 2.0 pmol/kg.min) given to type II diabetic patients and healthy controls. Insulin secretion rates were deconvolved using the method and population parameters of Van Cauter et al [1992]. Figure 3.2, reproduced from Kjems et al. [2003], shows the calculated insulin secretion rates (ISR) as a function of BG for healthy subjects receiving the maximum GLP-1 infusion, when insulin secretion is maximally stimulated. Estimating the maximum achieved at 20 pmol/kg.min corresponds to 16000 mU/hr for an 80kg subject.
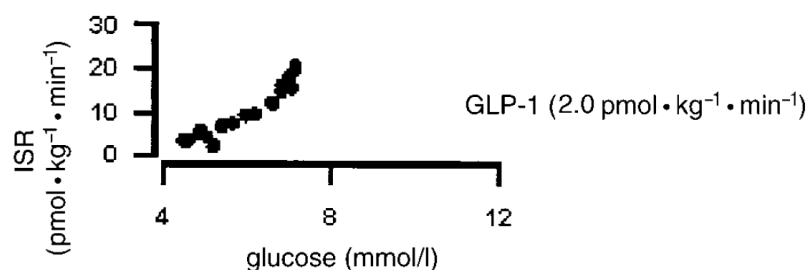
Figure 3.2 Mean dose-response relationship between plasma glucose and pre-hepatic insulin secretion rates of healthy subjects during graded glucose infusion with a GLP-1 dose of 2.0 pmol/kg.min. [Kjems et al. 2003].

Kjems et al. [2003] reported mean baseline, fasted secretion rates for diabetic and healthy patients of 1.9 and 1.8 pmol/kg.min, corresponding to 1500 mU/hr for an 80kg person. Ferrannini et al. [2005] reported a median fasting secretion

rate of 53 pmol/min.m^2 for lean, non-diabetic subjects. Assuming a body surface area (BSA) of 1.8m^2, this value corresponds to a rate of 954 mU/hr. The values reported by Kjems et al. [2003] and Ferrannini et al. [2005] suggest that upper and lower bounds on pre-hepatic insulin secretion rates of 16000 mU/hr and 1000 mU/hr would be appropriate.

3.3.3   Model fitting

As in previous studies [Camastra et al. 2005; Ferrannini et al. 2005; Mari et al. 2002a; Mari et al. 2002b], models of the form shown in Equation 3.1 were fitted to the data. Where x_j denotes the independent variables (BG, dBG/dt, plasma insulin) and c is a bias constant.

$$f(x) = \sum_j a_j x_j + c \qquad\qquad 3.1$$

Model fitting was performed by minimising the sum of the geometric means of the squared deviations in each dimension [Tofallis 2002]. Endogenous secretion was constrained between upper and lower bounds of 16000 mU/hr and 1000 mU/hr. The resulting model coefficients (a_j) and goodness of fit values are shown in Table 3.3.

Table 3.3 Coefficients for endogenous insulin secretion models fitted with 1, 2 and 3 independent variables (dimensions).

	Model	Coefficients				Goodness of fit (R^2)
		Constant c [mU/hr]	Blood glucose a_1 [mU.l/mmol.hr]	BG derivative a_2 [mU.l/mmol]	Plasma insulin a_3 [l/hr]	
Non-diabetic	1-dim.	-2996	893			0.61
	2-dim.	-2573	760	-773		0.59
	3-dim.	-2811	848	-931	-23	0.41
T2DM	1-dim.	-1644	296			0.69
	2-dim.	-1466	302	-586		0.69
	3-dim.	-691	286	-563	-17	0.57

The best model for insulin secretion, in terms of both fit to data and simplicity is the 1-dimensional model based on blood glucose level alone. Figure 3.3 shows the data and both non-diabetic (blue) and T2DM models (red). Equations 3.2 and 3.3 describe the non-diabetic and T2DM models, respectively.

ND $\quad Uen = 893 \times BG - 2996 \quad$ constrained to [1000 – 16000] mU/hr $\quad$ 3.2

T2DM $\quad Uen = 296 \times BG - 1644 \quad$ constrained to [1000 – 16000] mU/hr $\quad$ 3.3
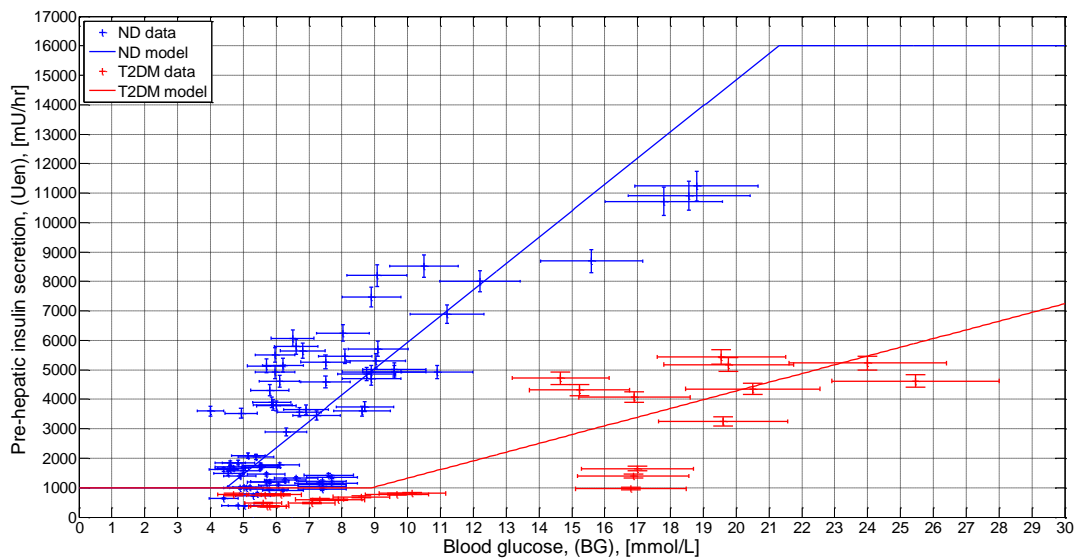
Figure 3.3 Pre-hepatic insulin secretion data and 1-dimensional model fits. Non-diabetic data and model shown in blue (R^2 = 0.61); T2DM data and model shown in red (R^2 = 0.69).

Two points of particular note regarding the model fit are the variability in secretion rate and the number of points below the lower bound. There is considerable variability in secretion rates for any given blood glucose level, particularly in the range 6-10mmol/l. For example, blood glucose measurements in the range 6.5-7.0 mmol/l are associated with secretion rates between 1319-6076 mU/hr, a 4.5-fold range. In addition, individual patients show a range of secretion rates spanning up to 2385 mU/hr within a 60-minute period. There are numerous data points (23%) below the minimum secretion level of 1000 mU/hr including one identified at –52.5 mU/hr (not shown).

Both the inter- and intra patient variability and the number of points below the lower bound are likely a result of using population kinetic parameters for the C-peptide model. The study by Van Cauter et al. [1992] shows considerable variation between patients. Coefficients of variation for the kinetic parameters of normal and T2DM subjects were reported in the range 16-36% and the linear regression of long half-life against age had a correlation coefficient, r=0.28. Thus, there was significant variation around the best-fit population parameters.

Physiologically, the cause of the secretion rates below the lower bound could also be due to diminished secretion capacity. Of the 24 data points (23%) below 1000 mU/hr, 13 were from the five type II diabetic individuals or suspected, undiagnosed individuals.

3.3.4   Model validation

To validate the secretion model, comparisons were made to published data. There is very little data available in the literature concerning insulin secretion rates in critically ill patients. Most studies tend to focus on healthy subjects and those with diabetes. Table 3.4 presents the results of a number of published studies in which insulin secretion profiles have been related to blood glucose levels. All these studies used the method and kinetic parameters of Van Cauter et al. [1992] to calculate insulin secretion rates from plasma C-peptide concentrations.

Table 3.4 shows reported results for the glucose coefficient in the range 432-2754 mU.l/mmol.hr for healthy subjects and 160-1113 mU.l/mmol.hr for diabetic subjects. The glucose coefficients of 893 and 296 mU.l/mmol.hr identified in this study for non-diabetic and diabetic critically ill patients are comparable with this widely spread published data. It is interesting to note that the glucose coefficients reported by studies involving Ferrannini [Camastra et al. 2005; Ferrannini et al. 2005; Mari et al. 2002a; Mari et al. 2002b] tend to be considerably higher than those reported by others, or those resulting from this study, possibly reflecting an unreported difference in methods or approach.

Table 3.4 Glucose coefficient data from the literature. Results have been converted to the units of measurement used in this study where necessary. Assumptions used for these conversions were: w = 80 kg; BSA_{lean} = 1.8 m^2; $BSA_{obese/T2DM}$ = 2.1 m^2.

Study	Cohort	Glucose coefficient a_1 [mU.l /mmol.hr]
Ferrannini et al. [2005]	Lean normal glucose tolerance	2646
	Obese normal glucose tolerance	1932
	Impaired glucose tolerance	1155
	T2DM	294
Mari et al. [2002b]	Control	2664
	T2DM	1113
Mari et al. [2002a]	Healthy 24 hr meal test (5-7 mmol/l)	2196
	Healthy 2 hr protocol (5-7 mmol/l)	2592
	Healthy OGTT (5-7 mmol/l)	2754
Camastra et al. [2005]	Healthy controls	1290
	20 Obese Non-Diabetic	1860
Kjems et al. [2003]	Healthy saline infusion	480
	T2DM saline infusion	160
	Healthy GLP-1 max. infusion rate	5360
	T2DM GLP-1 max. infusion rate	1040
Jones et al. [1997]	Non-diabetic insulin sensitive	485
	Non-diabetic insulin resistant	664
Byrne et al. [1995]	No MODY1 mutation baseline	761
	No MODY1 mutation glucose-primed	1400
Chang et al. [2003]	T2DM with NN2211 (GLP-1 derivative)	1008
	T2DM with Placebo	432
	Controls	1152

3.3.5   Limitations

The two major limitations of this study were the blood glucose measurements and the population C-peptide parameters. Blood glucose measurements were not taken simultaneously with insulin and C-peptide samples and the measurements that were taken used bedside glucometers. The normal, clinical BG measurements that were available 1-2 hourly necessitated linear interpolation to estimate levels associated with the insulin and C-peptide measurements. Additionally the clinical measurements had an estimated coefficient of variation of 10% compared with 2-3% for laboratory results.

Linear interpolation of BG values resulted in a single value for dBG/dt for each set of measurements, possibly compromising the utility of this specific parameter as an independent variable in the model. However, the utility of dBG/dt is questionable in a critical care model where BG is kept relatively constant with a glycaemic control protocol and patients are fed by constant infusion (enterally or parenterally). This term has more relevance in secretion models in response to a bolus meal or glucose challenge as seen in studies on type II diabetic subjects [Ferrannini et al. 2005; Mari et al. 2002a; Mari et al. 2002b], where the dBG/dt term is only used when the change in BG is positive.

Insulin secretion rates calculated in this study relied on the population kinetic parameters reported by Van Cauter et al. [1992] for healthy and diabetic subjects. Use of these values assumed that renal uptake of C-peptide in critically ill patients was not significantly different to healthy subjects. No published studies were found reporting renal C-peptide metabolism in critically ill patients. Hence, short of repeating the work of Van Cauter in a critically ill population, the values used provided the best available estimates of the transport parameters, and have been used by others in this setting [Hovorka et al. 2008].

In the ICU, renal dysfunction is relatively common. Changes to the renal metabolism of C-peptide resulting from kidney dysfunction would cause errors in the calculated insulin secretion rates from this study as the deconvolution depends upon population estimates of the renal C-peptide clearance rate. In this study one patient was diagnosed with renal failure, however their circulating C-peptide levels and resulting insulin secretion rates were not substantially different from the other patients, so they were not excluded from the analysis.

3.3.6 Impact on *SI*

The endogenous insulin secretion functions proposed in this study result in a much wider range of secretion levels than previously used with this glucose-insulin system model [Lin et al. 2011]. The previous secretion model provided a relatively constant pancreatic output of approximately 2800 mU/hr for physiological plasma insulin concentrations. For non-diabetic patients with BG in

the range 4.0-7.0 mmol/L, the model developed in this analysis would result in secretion rates of 1000-3300 mU/hr, which are comparable to 2800 mU/hr and thus unlikely to have a significant impact on *SI*. At higher BG levels, the secretion rates could be significantly higher and thus, the identified value of *SI* would be lower. Hence, the impact of the proposed models on *SI* is dependent upon the specific BG concentration and diabetic status of the patient.

The models proposed in this study better capture the variability of insulin secretion, evident in Figure 3.3, than the current, relatively constant, secretion model. However, considerably variability in secretion rate, not accounted for by BG concentration, still remains. Thus, while these new models represent a significant improvement over the current model, and will reduce unwanted intrinsic variability from *SI*, some variability will persist and affect the identified values of *SI*.

3.4   Summary

The results of this study show that a simple constrained linear function of blood glucose provided the best model of pre-hepatic insulin secretion in critically ill patients. Separate models were identified for non-diabetic patients and diagnosed or suspected type II diabetic patients with R^2 = 0.61 and 0.69 respectively. The glucose coefficients of 893 and 296 mU.l/mmol.hr identified for non-diabetic and diabetic patients were comparable to data published in a number of other studies.

The proposed model of endogenous insulin secretion based on physiological measurements should reduce unwanted intrinsic variability from *SI* and therefore increase the accuracy and utility of the parameter in control and analysis applications.

Chapter 4. Interstitial Insulin Kinetics

Like endogenous insulin secretion, insulin kinetics are a potential source of unwanted variability in model-based estimations of *SI*. The parameters describing insulin clearance and transport vary between individuals and over time. However, unlike insulin secretion, identifying the transport parameter values directly is difficult, if not impossible, and there are as yet no models relating them to readily measurable clinical variables. Population constants based on data from healthy individuals are therefore the best available estimates, for example [Sherwin et al. 1974; Van Cauter et al. 1992]. Nonetheless, these constant parameters need to be optimised to the target population to ensure maximum accuracy and utility of the insulin sensitivity parameter.

4.1   Introduction

Insulin-mediated glucose uptake primarily occurs from the interstitial fluid. Insulin from plasma is transported to the interstitial fluid surrounding tissue cells where it binds to cell-wall receptors, activating glucose uptake [Jefferson & Cherrington 2001]. Hence, correctly modelling interstitial insulin kinetics is important to reducing unwanted intrinsic variability in model-based *SI*.

In general, insulin kinetics models developed for healthy or diabetic subjects are used quite successfully and without modification for critically ill patients [Chase et al. 2006; Hovorka et al. 2008; Lin et al. 2011; Van Herpe et al. 2006]. The insulin kinetics of the ICING model were derived from the model developed by Lotz et al. [2008] primarily for impaired glucose tolerance and type II diabetic subjects. The study by Lin et al. [2011] showed that the ICING model worked well in critically ill patients, with parameter values remaining largely unchanged. However, interstitial insulin kinetic parameters, transcapilliary diffusion (n_I) and cellular clearance (n_C) rate, were identified as being 16-times smaller than those by Lotz et al. [2008] for healthy and diabetic subjects, leading to a significantly longer 'effective' insulin half-life.

The parameter identification conducted by Lin et al. [2011] utilised a grid-search to minimise the fitting and prediction errors of the model over 42941 hours of data from 173 critically ill patients. Although providing the mathematically optimal parameter values for that particular cohort, the grid-search method did not necessarily enhance the physiological foundations of the model. In particular, the optimal parameters were centred in parameter spaces with consistently low errors so that a wide range of parameter values was admissible for very limited difference in model performance.

This study extended the fitting and prediction error grid-search identification of the interstitial insulin kinetic parameters of Lin et al. [2011] to two further, independent, critically ill cohorts. Additionally, data from published microdialysis studies was used to directly determine the kinetic parameters from physiological measurements. These better data are used to more accurately justify and validate the parameters chosen.

4.2   Subjects and Methods

This investigation of interstitial insulin kinetic parameters was conducted in two stages. Initially, the grid-search of Lin et al. [2011] was repeated on two independent cohorts to confirm a suitable domain of values consistent with acceptable model performance. This step was followed by the analysis of data from 6 published studies (12 data sets) that used microdialysis to assay interstitial insulin levels simultaneously with plasma insulin levels, enabling direct determination of the kinetic parameters.

4.2.1   Patients

Two separate cohorts, independent from those used by Lin et al. [2011] and independent from each other were used to determine suitable domains for n_I and n_C by grid-search. The two cohorts consisted of 9 patients from the STAR-Liege pilot trial [Penning et al. 2011] and 20 patients from the Christchurch Hospital ICU sepsis study. Details of these cohorts are shown in Table 4.1.

The two cohorts spanned a range of ICU patient types. The STAR-Liege patients were from a clinical pilot trial of a tight glycaemic control protocol conducted at the Centre Hospitalier Universitaire (CHU) in Liège, Belgium in July 2010. The pilot trial was 24 hours long and included 9 primarily cardiovascular or cardiac surgery (7) patients from the hospital's intensive care units. The Christchurch ICU sepsis cohort consisted of 20 patients enrolled in a prospective clinical trial studying sepsis during 2009-10. These patients were predominantly non-surgical (16) and diagnosed with sepsis (79%).

Table 4.1 Summary of patient characteristics. Data are shown as median [IQR] where appropriate.

	STAR-Liege	Sepsis Christchurch
N	9	20
Age (years)	74 [69-79]	66 [57-75]
Gender (M/F)	6/3	10/10
APACHE II score	N/A	22.5 [18.8-27.3]
Hospital mortality (L/D)	6/9	14/6
Operative/Non-operative	9/0	4/16
Diagnosed T2DM	4	3

Blood glucose levels in Christchurch were measured with Super-Glucocard II glucometers (Arkray Inc., Japan). BG levels in Liege were measured with Accu-Chek Inform (Roche Diagnostics, Mannheim, Germany) glucometers. Measurement errors associated with these devices are approximately 10% and 3%, respectively [Arkray 2007; Roche 2008].

Ethical consent was granted by the Comité d'éthique hospitalo-facultaire de l'Universitaire de Liège (B70720108843) for the performance of STAR-Liege trial and the audit, analysis and publication of the data. The Upper South Regional Ethics Committee, New Zealand, approved the Christchurch ICU sepsis study.

4.2.2 Fitting and prediction grid search analysis

A grid search evaluating both model fitting and prediction error was performed over a wide domain for both n_I and γ. The parameter γ is the steady-state ratio of

interstitial insulin (Q) to plasma insulin (I) concentrations and defines n_C through Equation 4.1 provided the steady state concentration Q is low so that saturation effects are limited. It is defined:

$$\gamma = \frac{n_I}{n_I + n_C}$$

<div align="right">4.1</div>

Studies indicated that the steady state interstitial to plasma insulin ratio is between 0.4 and 0.6 [Gudbjornsdottir et al. 2003; Sjostrand et al. 1999; Sjostrand et al. 2000]. Lotz et al. [2008] use a population value of 0.5 for this ratio. Hence the range of values of γ evaluated in the grid-search spanned 0.3-0.7. Values of n_I were evaluated in the range 0.001-0.05 min^{-1}, covering those proposed by Lin et al. [2011] and Lotz et al.

At each coordinate pair of the grid-search (n_I, γ), cohort and per-patient median BG fitting and prediction errors were evaluated, as per the study of Lin et al. [2011]. One-hour-ahead BG prediction values were calculated with the identified *SI* held constant from the previous hour to assess prediction performance. In cases where BG measurements were greater than 1 hour apart, errors were calculated to a linearly interpolated value. Errors were assessed as percentages of measured (or interpolated) BG values to enable fair comparison across a wide range of glycaemic levels.

4.2.3 Microdialysis analysis

To identify n_I and γ in a more direct, physiological manner, data was used from 6 published studies (12 data sets). These studies used microdialysis to directly sample interstitial insulin concentrations. Plasma insulin levels concentrations sampled simultaneously. The 6 independent studies were conducted using infused and endogenous insulin at varying physiological and supra-physiological levels. Data used in this analysis was taken from the studies listed in Table 4.2.

Using reported arterial insulin concentrations (I) as input, interstitial concentrations (Q) were simulated with the ICING interstitial insulin kinetics

sub-model described in Equation 4.2, repeated from Equation 2.2. These simulated results were then compared to the reported interstitial measurements. The beauty of this method was in the simplicity of the interstitial insulin sub-model. There are only two parameters that affect the kinetics at physiological insulin levels; n_I and γ. Thus, only one equation is required, and the desired variables are separated from any other equations, data, or parameter values, eliminating any other potential biases

$$\dot{Q} = n_I(I - Q) - \frac{n_C Q}{1 + \alpha_G Q} \qquad\qquad 4.2$$

Table 4.2 Published microdialysis studies used to investigate interstitial insulin kinetic parameters

Study	Study Method	Study Population	N	Interstitial sampling location
Jansson et al. [1993]	Euglycaemic-hyperinsulinaemic clamp	Healthy non-obese	5	Abdominal subcutaneous fat
Castillo et al. [1994]	Euglycaemic-hyperinsulinaemic clamp	Healthy: Body fat <=12%	3	Subcutaneous lymph vessel; lower leg
	Euglycaemic-hyperinsulinaemic clamp	Healthy: Body fat 13-21%	5	Subcutaneous lymph vessel; lower leg
	Euglycaemic-hyperinsulinaemic clamp	Healthy: Body fat 22-35%	3	Subcutaneous lymph vessel; lower leg
	Euglycaemic-hyperinsulinaemic clamp	Healthy: Body fat >=36%	2	Subcutaneous lymph vessel; lower leg
Sjostrand et al. [2002]	Euglycaemic-hyperinsulinaemic clamp	Healthy lean	10	Forearm muscle
	Euglycaemic-hyperinsulinaemic clamp	Healthy obese	10	Forearm muscle
Gudbjornsdottir et al. [2003]	Euglycaemic-hyperinsulinaemic clamp	Healthy lean	10	Forearm muscle
Herkner et al. [2003]	Oral glucose tolerance test	Healthy lean	8	Mid thigh muscle
	Euglycaemic-hyperinsulinaemic clamp	Healthy lean	8	Mid thigh muscle
Sjostrand et al. [2005a]	Oral glucose tolerance test	Healthy lean	10	Forearm muscle
	Oral glucose tolerance test	Healthy obese	10	Forearm muscle

A grid-search was performed over a range of n_I and γ values to find the region of minimum error between simulated and measured interstitial insulin concentrations. The error value was defined as the sum of absolute differences between the simulated and measured concentrations at the experimental sampling points, divided by the average interstitial insulin level during the experiment. Errors across all data sets were evaluated by two methods to ensure a robust minimum that was not skewed by data from a single study. Specifically:

1. Each error value was weighted equally, by summing absolute error values at each (n_I, γ) pair across all 12 data sets.
2. Each study was weighted equally by scaling the calculated errors into the range 0-1 prior to summing across all data sets.

4.3 Results and Discussion

4.3.1 Fitting and prediction grid-search results

Figure 4.1 and Figure 4.2 show the results of the grid-search over n_I and γ for the two independent cohorts (STAR-Liege and Christchurch ICU sepsis). Cohort median fitting error (%) is shown on the top panel and cohort median 1-hour-ahead prediction error (%) on the bottom.
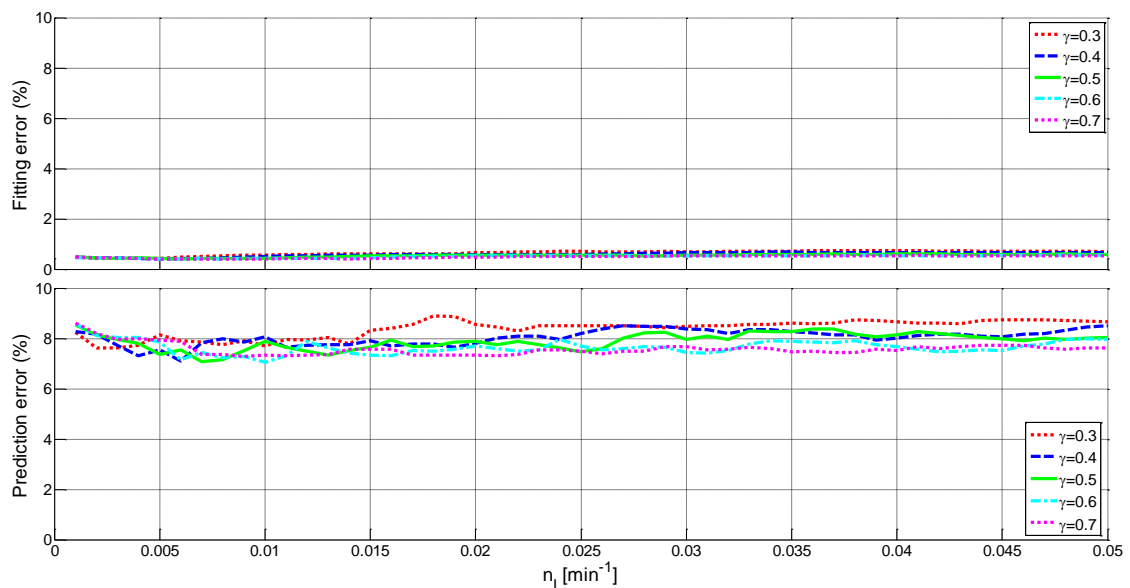
Figure 4.1 Fitting (top) and 1-hour-ahead prediction (bottom) errors (%) for the STAR-Liege cohort across a range of n_I and γ values.

Figure 4.1 and Figure 4.2 shed little light on optimal parameter values. The profiles for STAR-Liege in Figure 4.1 are quite flat across the domain of parameter values and show no obvious minima. The profiles for the Christchurch ICU sepsis cohort in Figure 4.2 indicate that the optimal value of n_I would be in the range 0.003-0.01 min^{-1}, depending on the choice of γ. For $\gamma = 0.5$ assumed by Lin et al. [2011] and Lotz et al. [2008], prediction error was minimised for $n_I = 0.007$ min^{-1}. However, fitting and prediction errors in this region were well below the BG measurement error of 10% for all values of γ tested. Hence, no significant performance improvement would be gained by selection of any particular parameter set within this restricted domain.
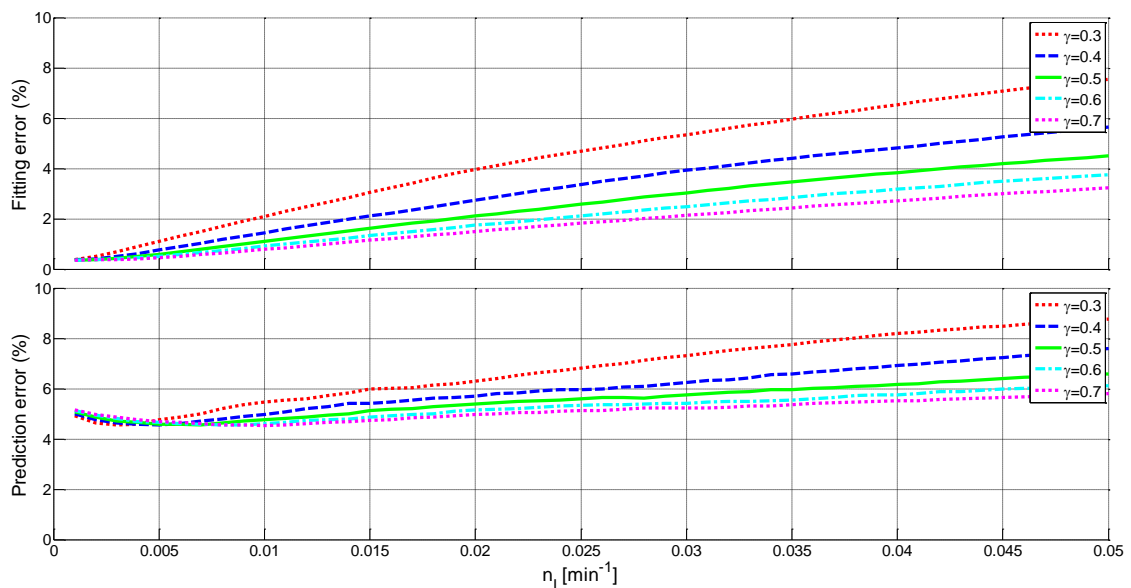
Figure 4.2 Fitting (top) and 1-hour-ahead prediction (bottom) errors (%) for the Christchurch ICU sepsis cohort across a range of n_I and γ values.

4.3.2 Microdialysis results

Grid-search results for the parameter optimisation using published microdialysis data are shown in Figure 4.3. The left panel shows the results from method 1 where each error value was weighted equally. The right panel shows the results from method 2 where each study was weighted equally. Data from the Herkner et al. [2003] clamp study have been omitted as the minimum error was located at $n_I = 0$, which does not make sense, physiologically.

Figure 4.3 shows the regions around the minimum error points, where the contours indicate errors 1% and 5% greater than the minimum values. The parameter set, n_I =0.0060 min^{-1}, γ = 0.5 (n_I = n_C) is enclosed within both these regions and provides a good compromise between the two identified minima. This set is also consistent with the results from the fitting and prediction error grid-search on the Christchurch ICU sepsis cohort. However, unlike the fitting and prediction error grid-search, this method used direct physiological measurements to identify well-defined error minima. Hence, the optimal parameter values identified are more physiologically relevant than those derived from 'external' assessments using blood glucose fitting and prediction errors.
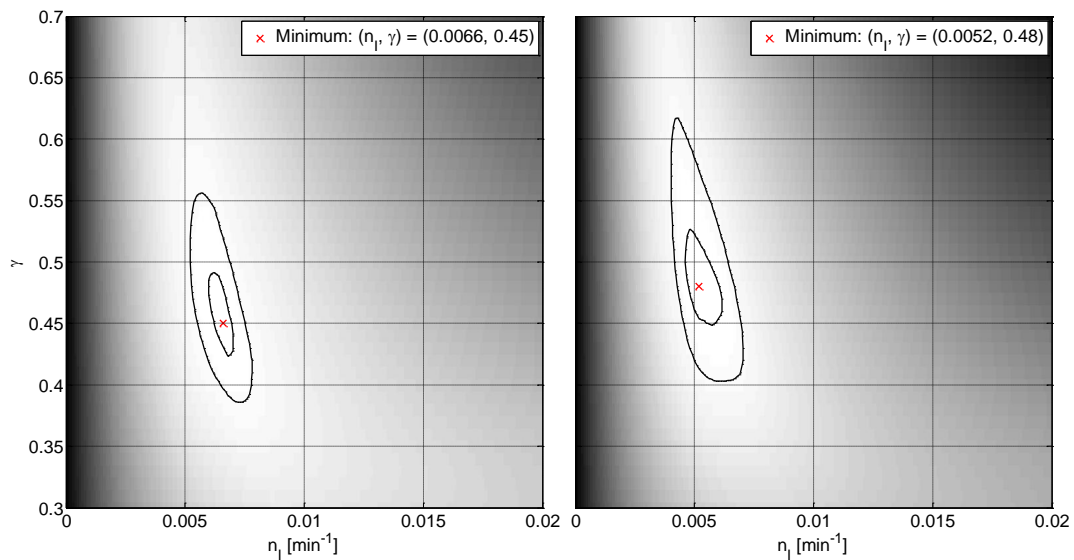
Figure 4.3 Grid-search error results from microdialysis analysis showing optimal parameter values. The left panel shows the results where each error value was weighted equally, and the right panel shows the results where each study was weighted equally. Contours are at error 1% and 5% greater than the minimum. Lighter areas represent lower error and darker areas, greater.

Table 4.3 shows the individual optimal parameter values for each data set. The associated errors are shown along with the error obtained using the selected parameter set, n_I =0.0060 min^{-1}, γ = 0.5.

Table 4.3 Individual results from published microdialysis studies. Study minimum error is associated with the study optimal n_I and γ. Overall error is associated with the selected parameter set, n_I =0.0060 min^{-1}, γ = 0.5. The errors are unitless and represent mean absolute fractional error at each measurement point.

Study	Study Method	Study Population	Study optimal n_I [min^{-1}]	Study optimal γ	Study minimum error	Overall error
Jansson et al. [1993]	Clamp	Healthy non-obese	0.0054	0.30	0.142	0.233
Castillo et al. [1994]	Clamp	Healthy: Body fat <=12%	0.0031	0.53	0.103	0.305
	Clamp	Healthy: Body fat 13-21%	0.0048	0.62	0.038	0.090
	Clamp	Healthy: Body fat 22-35%	0.0041	0.61	0.029	0.101
	Clamp	Healthy: Body fat >=36%	0.0040	0.44	0.044	0.204
Sjostrand et al. [2002]	Clamp	Healthy lean	0.0128	0.48	0.060	0.191
	Clamp	Healthy obese	0.0054	0.70	0.057	0.072
Gudbjornsdottir et al. [2003]	Clamp	Healthy lean	0.0061	0.67	0.143	0.180
Herkner et al. [2003]	OGTT	Healthy lean	0.0116	0.31	0.300	0.458
	Clamp	Healthy lean	0	0	0.137	1.546
Sjostrand et al. [2005a]	OGTT	Healthy lean	0.0600	0.57	0.101	0.610
	OGTT	Healthy obese	0.0400	0.46	0.058	0.516

Figure 4.4 shows two contrasting examples of the simulated and measured interstitial insulin concentrations using the selected parameter values. Panels A and B show data from the Castillo study [1994] for subjects with body fat in the range of 13-21%. Panels C and D show data from the oral glucose tolerance test (OGTT) study by Herkner et al. [2003]. Measured arterial insulin is presented in the top panels (A and C), with measured and modelled interstitial insulin in the bottom (B and D) along with the absolute error between them. These two studies had similar insulin concentrations and thus make a good comparison.

The model fit to data is very good for the Castillo study [1994] in the left panel and not so good for the Herkner study [2003] in the right panel. The interstitial insulin peak at 15 mins in the Herkner study does not correspond to any feature in the plasma insulin profile. The plasma insulin-sampling scheme may have missed a peak, the interstitial insulin peak may be spurious, or insulin may have been delivered to the interstitium independent of plasma as the authors' propose. This study was conducted using oral glucose (75 grams) to stimulate insulin secretion. Therefore, a sharp plasma insulin peak would not be expected [Caumo & Luzi 2004], particularly within 15 minutes of glucose ingestion. The ICING model assumes passive diffusion of insulin across the endothelium. Hence, with no plasma insulin peak to create a sharp concentration gradient, the model could not reproduce the reported peak in interstitial insulin, resulting in the poor fit.
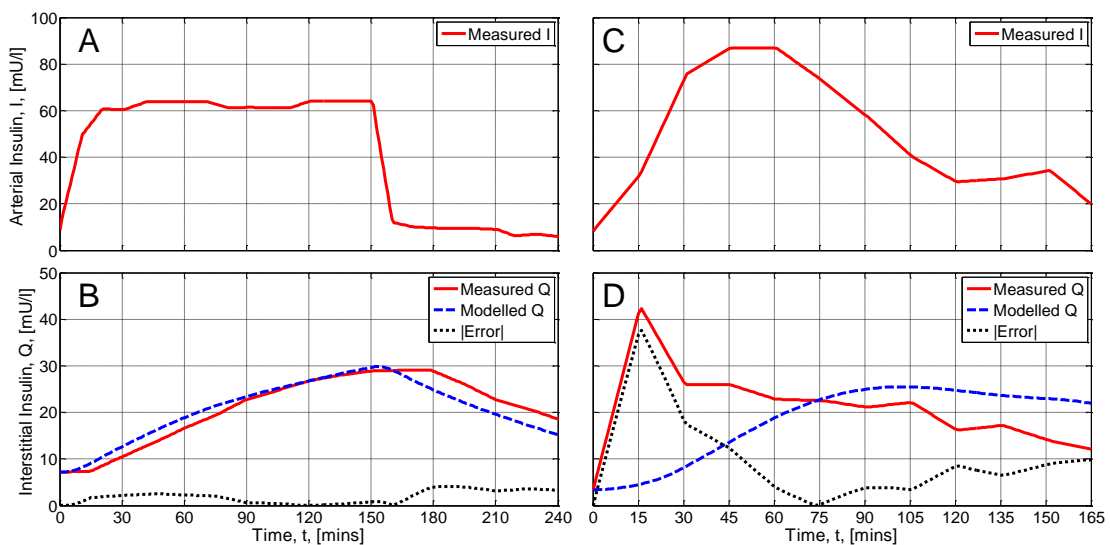
Figure 4.4 Two contrasting examples from the simulation of microdialysis data using the selected parameter set, n_I =0.0060 min^{-1}, γ = 0.5. The panels on the left show a good model fit to measured data from Castillo et al. [1994] (body fat 13-21%). The panels on the right show a poor fit from Herkner et al. [2003] (OGTT). The upper panels present plasma insulin concentrations and the lower panels measured and modelled interstitial insulin concentrations.

Modelled interstitial insulin profiles did not fit either data set from the Herkner et al. [2003] study very well. The OGTT example from this study is shown in the right panel of Figure 4.4. The other data set from Herkner involved a

euglycaemic-hyperinsulinaemic clamp procedure, in which the interstitial insulin levels were lower than during the OGTT study (<10 mU/l), despite sustained higher plasma levels (>65 mU/l for 60 mins).

There are no obvious reasons for these poor fits and they may be due to the complicated and difficult nature of microdialysis sampling of interstitial fluid. Data from the Herkner et al. [2003] clamp study were omitted as the minimum error was located at n_I = 0 min^{-1}, which does not make sense, physiologically.

The remaining studies had mean absolute error values at their individual optimal parameter values of less than 15% of their average interstitial insulin concentration. At the selected parameter set, the errors were less than 30%, except for the OGTT study by Sjostrand et al. [2005a]. The optimal n_I values for these two data sets were very high (n_I = 0.060 and 0.040 min^{-1}), though similar to those used by Lotz et al. [2008]. Hence, the errors for this study were large with the much smaller value of n_I = 0.0060 min^{-1} selected.

It should be noted that the data from the Sjostrand et al. study [2005a] was corrected prior to use in this analysis for the error present in the original article, as per their retraction [Sjostrand et al. 2005b].

4.3.3   Comparison of results

Using direct physiological measurements from 6 published microdialysis studies, the optimal parameter values n_I = 0.0060 min^{-1}, γ = 0.5 were identified. These values were optimal in terms of minimising the sum of absolute errors between simulated and measured interstitial insulin concentrations. γ = 0.5 ($n_I = n_C$) is unchanged from the values reported by Lin et al. [2011] and Lotz et al. [2008]. However, n_I = 0.0060 min^{-1} is between the values reported in those two studies; n_I = 0.003 min^{-1} and n_I = 0.0486 min^{-1}.

The value of n_I identified for the ICING model by Lin et al. [2011] was approximately 16-times smaller than that used by Lotz et al. [2008] for healthy and diabetic subjects. The result of this reduction in transcapillary diffusion (n_I)

and cellular insulin clearance (n_C, through γ) rates, was that insulin persisted much longer in the interstitial compartment, reflecting the insulin pooling and delayed utilization effects observed in critically ill patients by Doran et al. [2005].

The parameter n_I used by Lotz et al. [2008] was the transcapilliary diffusion rate for C-peptide identified by Van Cauter et al. [1992]. This choice was justified on the grounds that insulin and C-peptide have similar molecular weights (5800 Da and 3600 Da respectively) and passive properties. Parameter values were identified for each individual based on age, gender, body surface area and diabetic or obese status, as proposed by Van Cauter et al. The mean value identified across the study cohort was n_I = 0.0486 min^{-1} [Lotz et al. 2008].

A possible reason for the discrepancy between the values identified in this study and those of Lotz et al. [2008] is that trans-endothelial insulin diffusion is a saturable process [Lin et al. 2011]. The experimental diffusion rates adopted from Van Cauter et al. [1992] are determined by using C-peptide measurements. Although C-peptide has very similar molecular properties to insulin, it does not go through a high and variable degree of first pass extraction in the portal vein [Van Cauter et al. 1992]. Therefore, its concentration is several folds higher than insulin in plasma. If the diffusion process is to any level saturable [Thorsteinsson 1990], the rates determined using C-peptide measurements would not be reflective of insulin.

The 'effective' or interstitial half-life of insulin is defined by the interstitial kinetic parameters in Equation 4.3 [Lin et al. 2011]. This half-life characterizes the clearance rate of insulin from the interstitium where it effects the uptake of glucose into tissue cells. Previously published reports suggest values in the range 25-130 mins [Mari & Valerio 1997; Natali et al. 2000; Turnheim & Waldhausl 1988].

$$ t_{1/2} = \frac{log_e(2)}{n_I + n_C} \qquad\qquad 4.3 $$

The effective half-life associated with the kinetic parameters identified by Lin et al. [2011] was $t_{1/2}$ = 116 mins. This value better matched data from previous studies than the short $t_{1/2}$ = 7 mins used by Lotz et al. [2008]. The effective half-life insulin determined from the values of n_I and n_C identified in this study is $t_{1/2}$ = 58 mins, is also within the range reported by previous studies.

4.3.4 Impact on *SI*

The overall impact on *SI* of the proposed increase in transport and clearance is limited. For a given blood glucose level, *SI* is proportional to the area under the interstitial insulin concentration curve (AUC_Q). Hence, the impact on *SI* is proportional to the impact on AUC_Q.

During steady-state conditions, when no boluses or large changes to infusions have occurred, *SI* is unaffected as γ was unchanged. For non-steady-state conditions, the specific effect on *SI* resulting from changes to n_I and n_C depends on the delivery method of exogenous insulin.

Bolus insulin delivery creates a large, short duration (10-15 mins) concentration gradient from the plasma to the interstitium. This large gradient, coupled with faster diffusion from an increased n_I initially dominates the increased clearance rate and results in higher peak interstitial concentrations. However, the higher diffusion and clearance rates also serve to pull the interstitial concentration back towards the steady-state plasma level faster, once the transient peak has decayed. Thus, increases to AUC_Q and concomitant reductions in *SI* are limited, provided the interstitial half-life of insulin is much greater than the plasma half-life (3-7 mins).

For infused insulin, *SI* is only affected when the infusion rate is altered. Faster diffusion and clearance result in decreases to *SI* when the infusion rate is increased and increases to *SI* when the infusion rate is reduced, for a given glucose level and all other effects presumed unchanged. The magnitude of the impact on AUC_Q and *SI* is a function of the transport and clearance parameters, the length of time since the rate was altered and the size of the change relative to

the previous level. With large, regular (1-2 hourly) changes to the infusion rate, the impact on *SI* could be in the order of 20-30%, but this behaviour is not typical with infusions in the ICU. Equally, alterations in patient state will also play a role over these time periods. Hence, the likely changes to *SI* in clinical situations would be limited.

4.4   Summary

The results of this investigation suggest that optimal values for the interstitial insulin kinetic parameters are $n_I = n_C = 0.0060$ min^{-1}. These parameter values are associated with an effective interstitial insulin half-life t$_{\frac{1}{2}}$ = 58 mins, within the range of 25-130 mins reported by others.

This study used two independent, critically ill cohorts and data from six published microdialysis studies to determine the optimal parameter values. The external clinical data and model performance metrics were unable to provide significant resolution in determining optimal values. However, using direct physiological measurement data from microdialysis studies provided a sound physiological foundation for the kinetic parameter values.

The impact on *SI* of these parameter alterations from the original ICING model are likely to be limited in normal, clinical situations. In particular, as the parameters are population constants, they are unlikely to alter the overall variability of *SI*.

Chapter 5. Endogenous Glucose Production

Endogenous glucose production can constitute a large part, if not all, of the glucose appearance, particularly during the early part of a patient's ICU stay. Thus, as with insulin secretion and interstitial insulin kinetic parameters, EGP can have a significant impact on intrinsic *SI* variability.

5.1   Introduction

In the context of this metabolic system model, EGP represents net glucose produced by the body, primarily by the liver, and released into the blood. EGP can represent a significant proportion of the glucose appearance in plasma, particularly when patients are fasted or receiving little exogenous nutrition. Hence, EGP impacts on model-based insulin sensitivity by directly contributing to the net glucose flux that must be balanced by insulin-mediated glucose uptake.

The current ICING model assumes constant EGP at a level that optimises model performance over the entire cohort [Lin et al. 2011]. However, instances where *SI* is forced to take non-negative, physiological values, particularly during the first 48 hours of SPRINT, indicate that the current assumption is inadequate for some patients, and potentially introduces unintended variability into the model-based *SI* parameter. This study attempts to assess the impact and improve the handling of EGP in the ICING model using existing, fundamental clinical data.

EGP can be directly measured *in vivo* by balance (arterial-venous difference) or tracer methods [Radziuk & Pye 2001]. Many studies have been carried out on critically ill populations to determine EGP in various disease and injury states [Black et al. 1982; Chiolero et al. 2000; Lattermann et al. 2003; Revelly et al. 2005; Shaw & Wolfe 1989; Tappy et al. 1999; Thorell et al. 2004; Watters et al. 1997; Wilmore et al. 1980; Wolfe et al. 1979], or simulated critical illness with stress hormone infusions [Bessey et al. 1984; Gelfand et al. 1984]. This study investigates glycaemic level as a surrogate marker for stress in critical illness that drives EGP. Additionally, EGP as a function of time is investigated,

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particularly in the early, acute phase of critical illness, where these stress drivers are generally greatest.

5.1.1 Background

EGP includes glucose released into the blood from both stored glycogen (glycogenolysis) or *de novo* glucose production from non-carbohydrate substrates (gluconeogenesis). EGP in humans primarily occurs in the liver and to a lesser extent the kidneys [Cherrington 1999]. The rate of production is a function of both stimulus and availability of substrates.

Both insulin and hyperglycaemia inhibit EGP. Hypoglycaemia and the counter-regulatory hormones (glucagon, cortisol, the catecholamines and growth hormone) stimulate EGP [Cherrington 1999]. In healthy individuals, the fine balance between these mediators maintains relatively constant plasma glucose levels throughout life. However, in critical illness, counter-regulatory hormones are significantly elevated almost immediately post critical-insult, but decline rapidly over the first 12-48 hours [Chernow et al. 1987; Frayn 1986; Jaattela et al. 1975; Weissman 1990]. These hormones can stimulate excess hepatic glucose production resulting in or exacerbating, stress-induced hyperglycaemia [Gelfand et al. 1984; Weissman 1990; Wilmore 1981].

A number of published glucose dynamics models developed for healthy and diabetic subjects incorporate explicit glucose appearance from EGP. EGP rates have been modelled as functions of plasma insulin concentration [Hovorka et al. 2002], blood glucose and insulin concentrations [Andreassen et al. 1994; Arleth et al. 2000; Lehmann & Deutsch 1992; Lotz et al. 2006], and glucose, insulin and glucagon concentrations [Cobelli et al. 1982; Parker et al. 2000]. The four published critical care specific models incorporate EGP as a function of insulin [Hovorka et al. 2008], BG and insulin [Pielmeier et al. 2010], a constant [Lin et al. 2011], or not explicitly specified [Van Herpe et al. 2006]. In reality, EGP is modulated by the interaction of many hormones that are elevated in critical illness [Gelfand et al. 1984; Mizock 1995]. These interactions are too complicated to be accurately captured by relatively simple, clinically relevant models.

Additionally, the interactions are likely to have patient-specific and therapy-specific variation that also cannot be readily captured.

Specific to clinical use in the critical care setting, modelling EGP as a function of insulin and glucagon concentrations may be unnecessarily complicated. Without explicitly measuring these hormone concentrations, modelling errors are potentially added to what is already a complicated system with substantial inter- and intra patient variability. Equally, there are no current methods to assay these hormones in real-time at the bedside. Hence, a model for clinical use cannot rely on these physiologically critical hormones to provide and patient specificity or real-time insight to reduce variability in this model element.

5.2   Subjects and Methods

5.2.1   Patients and samples

Two cohorts were used in this study. A cohort of 200 patients from the Christchurch Hospital ICU was used to investigate modelling EGP as a function of BG. A sub-cohort of 10 patients with fitting errors greater than 20% for short periods during the first 48 hours of SPRINT was used to investigate EGP as a function of time. All of these patients were on the SPRINT protocol for at least 48 hours. Table 5.1 presents a summary of the two cohorts.

Table 5.1 Summary of patient characteristics. Data are shown as median [IQR] where appropriate.

Cohort	SPRINT > 48hrs	Poor fit
N	200	10
Age (years)	65 [49-73]	72 [66-75]
Gender (M/F)	126/74	3/7
APACHE II score	19.0 [16.0-25.0]	25.0 [18.3-26.5]
Hospital mortality	27%	20%
Operative/Non-operative	70/130	3/7
Diabetic T1DM/T2DM	7/24	1/2
Maximum fitting error (%)	5 [2-11]	28 [24-36]

The Upper South Regional Ethics Committee, New Zealand granted approval for the audit, analysis and publication of this data.

5.2.2 Analysis methods

In the absence of tracer or balance data, fitting error and *SI* level can provide information about the performance of the glucose dynamics model. For example, negative values of *SI* are not physiologically possible and are prevented during parameter identification by a non-negative constraint. This non-negative constraint can cause BG fitting errors when the glucose rate of appearance from nutrition and the modelled EGP is not high enough to balance glucose utilisation.

5.2.2.1 EGP as a function of BG

The basic form of the EGP(G) function was reasoned to be approximately 'U'-shaped, based on fundamental physiology [Guyton & Hall 2000]. At low BG levels, EGP should be high to restore normoglycaemia. Counter-intuitively, hyperglycaemia indicates stress and thus high EGP [McCowen et al. 2001]. Figure 5.1 shows the proposed shape of the EGP function, defined parametrically by four coordinates.

To reduce the scale of the identification process, four constraints were placed on the set of coordinates:

1. $x_1 = 0$ mmol/l
2. $x_2 = 4$ mmol/l
3. $y_2 = y_3$ mmol/min
4. $x_2 = 30$ mmol/l

The remaining four parameters (y_1, y_2, y_4, x_3) were identified using a non-linear least squares method minimising the sum of squared fitting errors. The non-linear least squares parameter optimisation was performed in MATLAB (2011a, Mathworks, Natick, MA) using the trust-region-reflective algorithm [Coleman & Li 1996].

The 200 SPRINT patients used in this investigation were split into 10 cohorts of 20 patients. The parameter identification was performed separately on each of these cohorts. This method allowed the independent results to be compared, providing a degree of cross-validation. The cohorts were populated so that they each had a similar distribution of maximum BG fitting errors.
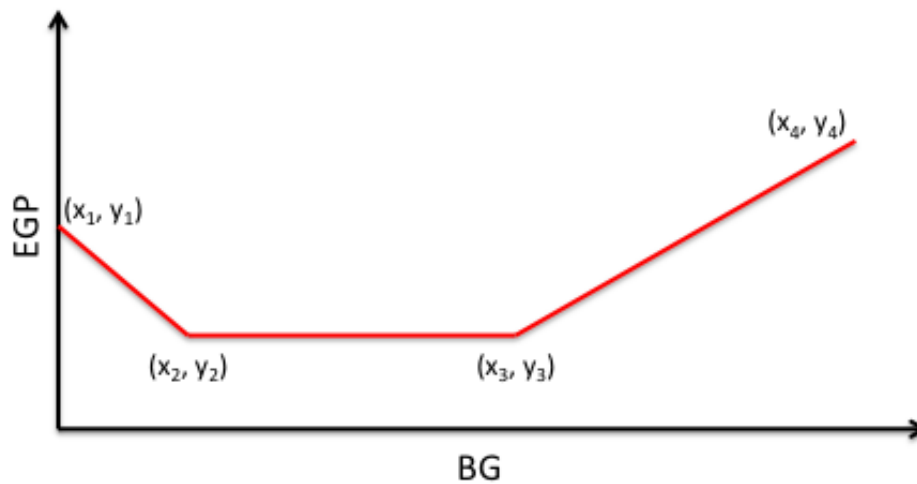
Figure 5.1 Schematic plot of proposed EGP(G) function.

Large BG fitting errors due to the non-negative constraint on *SI* predominantly occur during the first 24-48 hours of the SPRINT protocol, during the acute phase of critical illness [Frayn 1986; Weissman 1990]. To ensure an equal weighting from each patient-hour, the optimisation was performed over the first 48 hours of SPRINT. As the cohort consisted of patients that spent more than 48 hours on the protocol, this criterion prevented the results from being skewed by long-stay patients.

During this investigation, EGP was held constant at the mean value determined by the two surrounding BG measurements. Using the mean value ensured that the modelled EGP was able to capture rapid changes in BG. The mean BG value cannot be used in real-time clinical situations, limiting the utility of this approach. However, in this proof of concept analysis, this method is justified as a first attempt to assess the efficacy and utility of the overall model hypothesis and approach.

5.2.2.2 EGP as a function of time

To gauge the temporal, EGP(t) profile that would improve glucose dynamics modelling, the number of instances where *SI* was constrained to a non-negative minimum value was examined over time for both the 200 patient and poor fit cohorts. Further, the minimum value of EGP was determined that resulted in fitted *SI* = 10^{-5} l/mU.min. This value of *SI* is at the very low end of the typical physiological range for critically ill patients of 10^{-4} – 10^{-3} l/mU.min. The overall goal was to assess the potential range and inter-patient variability of EGP over the first 48 hours of SPRINT. Data was analysed in 6-hour blocks for each cohort from the commencement of the SPRINT protocol.

The SPRINT protocol is often commenced shortly after admission to the ICU. However, this early start is not always the case. When SPRINT is commenced later in a patient's stay, it typically follows an unexpected rise in BG concentration to above 8 mmol/l [Chase et al. 2008]. Thus, some significant change in patient state resulted in a spontaneous rise in the patient's blood glucose concentration, either by increased EGP, reduced glucose uptake or a combination of both. This dysregulation of glycaemic level may indicate increased stress levels [McCowen et al. 2001]. Hence, EGP was modelled as a function of time on the SPRINT protocol, rather than explicit time in the ICU.

5.3   Results and Discussion

5.3.1   EGP from the literature

To provide some context to the models of EGP proposed in this analysis, Table 5.2 presents results from a number of published studies on critically ill patients and healthy controls. The subjects varied in nutritional state from fasted to receiving approximately ACCP goal feed (25 kcal/kg.day) with 50% glucose via the parenteral route [Cerra et al. 1997]. Most of the studies measured EGP at a single point in time ranging from during surgery to 96 hours post-ICU admission. The range of reported mean values of EGP for critically ill patients was 0.10-2.36 mmol/min.

The published data from tracer studies with tabulated results was combined to calculate overall statistics. The resulting mean and standard deviation values for fasted and fed patients were 1.77 ± 0.55 mmol/min (N = 114) and 0.62 ± 0.36 mmol/min (N = 75), respectively. These values span the constant 1.16 mmol/min currently used in the ICING model.

Table 5.2 EGP values measured in critically ill patients and healthy controls from the literature. Where reported values were normalised by anthropomorphic data, 80 kg and 1.8 m^2 body surface area have been in this table. Abbreviations; Epi: Epidural block; N. anaes: Normal anaesthesia; TPN: Total parenteral nutrition; CHO: carbohydrate; IV: intravenous.

Study	Subject type	Nutritional information	N	EGP (mmol/min)
Wolfe et al. [1979]	Burn patients	Fasted	15	1.89
Wilmore et al. [1980]	Burn patients (non-infected)	Fasted	7	1.14
	Burn patients (bacteremic)	Fasted	8	1.50
	Burn patients (bacteremic with complications)	Fasted	4	0.65
Black et al. [1982]	Trauma patients	Fasted	3	1.51
Shaw et al. [1989]	Trauma patients	Fasted	43	1.68
	Healthy controls	Fasted	32	1.12
	Trauma patients	TPN (50% CHO)	43	0.88
Jeevanandam et al. [1990]	Trauma patients	Fasted	10	1.76
	Healthy controls	Fasted	6	1.22
Watters et al. [1997]	Healthy controls: Young	Fasted	5	1.73
	Healthy controls: Older	Fasted	6	1.82
	Trauma patients: Young	Fasted	14	2.00
	Trauma patients: Older	Fasted	8	2.27
Tappy et al. [1999]	Surgical ICU patients	TPN (75% CHO)	7	1.20
	Surgical ICU patients	TPN (28% CHO)	7	1.04
Chiolero et al. [2000]	Cardiac surgery patients with cardiogenic shock	Fasted	7	2.36
	Healthy controls	Fasted	7	0.86

Table 5.2-continued.

Study	Subject type	Nutritional information	N	EGP (mmol/min)
Lattermann et al. [2003]	Colorectal surgery patients: Epi. - pre-operative	Fasted (36hrs)	8	0.89
	Colorectal surgery patients: Epi. - peri-operative	0.89mmol/min IV glucose	8	0.10
	Colorectal surgery patients: Epi. - post-operative	0.89mmol/min IV glucose	8	0.24
	Colorectal surgery patients: N. anaes. - pre-operative	Fasted (36hrs)	8	0.85
	Colorectal surgery patients: N. anaes. - peri-operative	0.89mmol/min IV glucose	8	0.30
	Colorectal surgery patients: N. anaes. - post-operative	0.89mmol/min IV glucose	8	0.43
Thorell et al. [2004]	Trauma patients	Fasted	6	1.38
	Healthy controls	Fasted	6	1.07
	Trauma patients	TPN (50% CHO)	6	0.67
	Healthy controls	TPN (50% CHO)	6	0.36
Revelly et al. [2005]	ICU patients with severe sepsis/septic shock	Fasted	7	1.18
	ICU patients with cardiogenic shock	Fasted	7	1.20
	Healthy controls	Fasted	7	0.58

5.3.2   EGP as a function of BG

Figure 5.2 shows the results of the shape optimisation of EGP as a function of BG (EGP(G)). There are 10 separate lines on the plot representing the optimal functions for each of the 10 cohorts of 20 patients. The results show considerable variability in optimal EGP values across the cohort, both at high BG concentrations and at more normal levels of 4.0-6.0 mmol/l. In addition, many of the functions can result in EGP values much larger than those listed in Table 5.2, particularly for patients receiving nutrition.
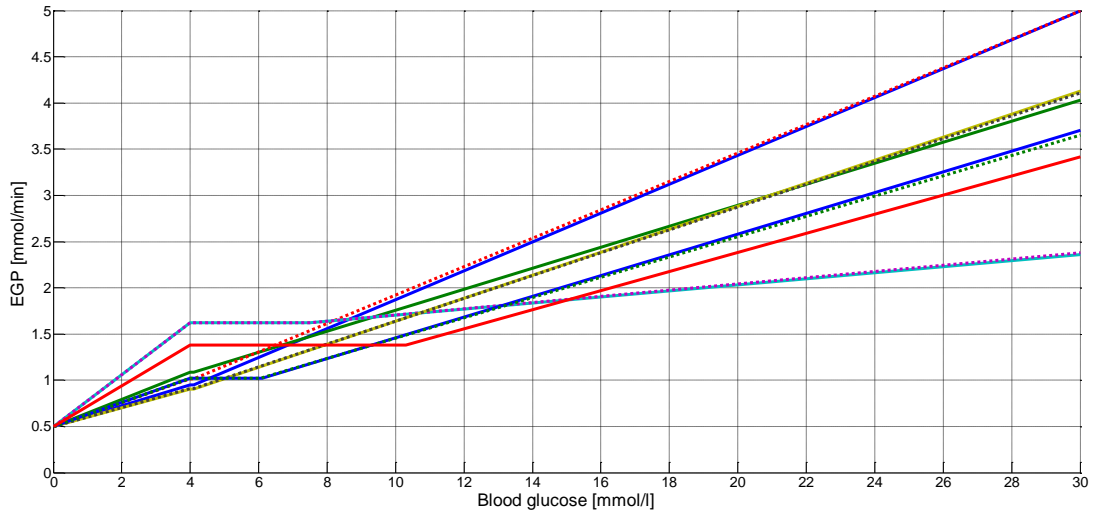
Figure 5.2 Results of the EGP(G) shape optimisation based on BG fitting error over 48 hours using 10 cohorts of 20 SPRINT patients.

Contrary to the initial reasoning presented, all the optimal EGP functions were monotonically increasing. The lack of a decreasing section at low-normal BG concentrations 2.0-4.0 mmol/l is likely a combination of the low number of hypoglycaemic episodes experienced during the SPRINT protocol [Chase et al. 2008] and the choice of BG fitting error as the performance metric.

Hypoglycaemia is uncommon to the SPRINT protocol. Chase et al. [2008] reported 3.8% of measurements below 4.0 mmol/l in an evaluation of the clinical implementation of the protocol. In the 200 patient cohort used for the optimisation of EGP, 3% (201 measurements) of the 6948 BG measurements were below 4.0 mmol/l and 0.16% (11 measurements) were below 3.0 mmol/l. Thus, there were only a small number of data points from a few patients contributing to the optimisation below 4.0 mmol/l. These limited points likely did not produce a strong signal for increased EGP at low BG concentrations.

More importantly, for a given pair of BG measurements, the minimum fitting error tends to occur at the lowest value of EGP that results in a non-negative SI. The non-negative constraint on SI results in a steep negative relationship between EGP and fitting error for $SI \rightarrow 0$. This relationship is a result of the

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constrained *SI* parameter being unable to balance glucose appearance and utilisation to correctly fit the measured glucose dynamics.

The relationship between EGP and fitting error is slightly increasing for *SI* > 0. As EGP increases, *SI* also increases. This increasing *SI* amplifies the relatively constant error between the linear BG trajectory assumed for parameter identification and the subsequent solution of the glucose dynamics equation.

Thus, for any given parameterisation of the EGP function, the sum squared fitting error and its gradient are dominated by those patient hours where the value of *SI* is close to zero. At these points, the model cannot capture the observed data and large fitting errors occur. Hence, there is a tendency towards lower EGP values and a non-decreasing EGP function as seen in Figure 5.2. This link between EGP and BG fitting error renders fitting error less than fully suitable as a performance metric for this analysis.

Modelling EGP as an increasing function of BG may also result in instability during virtual patient simulations. During virtual patient simulations, the *SI* profile is taken from a real patient and the glucose-insulin model is used in conjunction with a control algorithm to determine the interventions and the resulting BG concentration profile [Chase et al. 2010]. In this situation, an increasing EGP(G) function could provide a form of positive feedback leading to high, non-physiological simulated BG concentrations.

The aim of this part of the investigation was to model EGP as a function of BG concentration for critically ill patients. However, the relationship between EGP and BG fitting error and the possibility of positive feed-back during simulation render this approach unsuitable, given the available data and hypothesised form of EGP(G).

5.3.3   EGP as a function of time

Figure 5.3 shows the prevalence of instances where *SI* was forcibly constrained to non-negative values for both cohorts. The data are presented in 6-hour blocks

from the commencement of the SPRINT protocol. There is a clear relationship between the number of constrained *SI* values and time, in both cases. In particular, the exponential decay over time from the commencement of SPRINT is qualitatively similar for both cohorts.
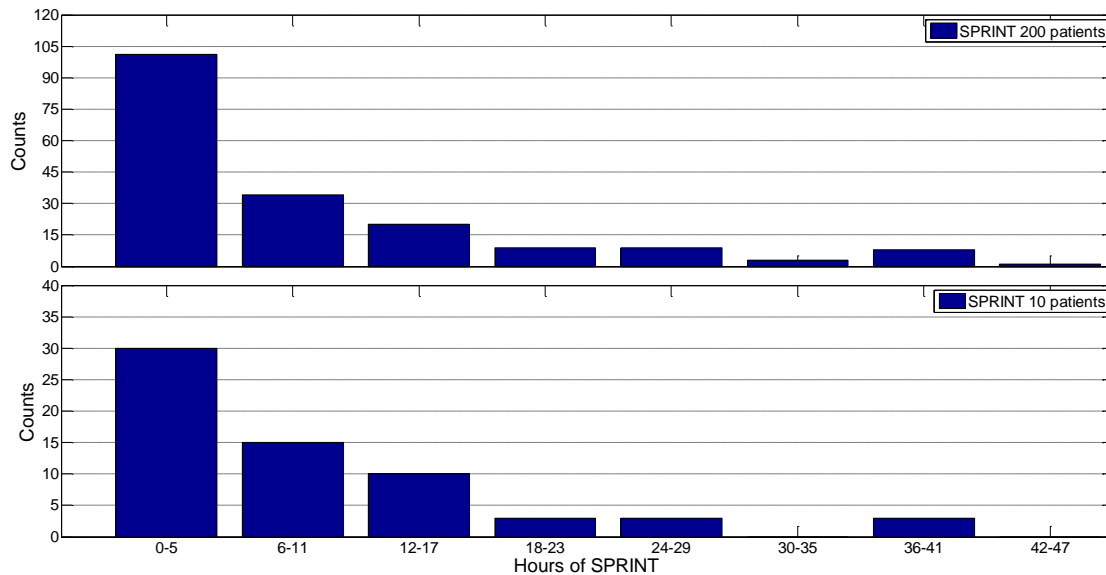
Figure 5.3 Time course of the number of instances where the fitted *SI* parameter was constrained to non-negative values during the first 48 hours of SPRINT. The top panel shows the results for the 200 patient SPRINT > 48 hours cohort. The bottom panel shows the 10 patient poor fit cohort.

Eight of the 10 patients in the poor fit cohort received no exogenous nutrition prior to the time at which the large BG fitting errors occurred. Thus, in these cases, the only possible source glucose appearance in the dynamics model was from endogenous production and there could be no error introduced through incorrectly modelling gastric absorption. The value of EGP used in the ICING model was clearly too low for these instances in particular as it could not provide a glucose rate of appearance high enough to match the measured data.

The poor fit cohort was used to define the time course of EGP suggested by Figure 5.3. Figure 5.4 presents the distributions of EGP values for each 6-hour block that resulted in the minimum fitted *SI* = 10^{-5} l/mU.min. There is a general reduction over time in both the level and variability of EGP required to maintain

this level of *SI*. It is clear that the necessary early, higher EGP levels are very patient specific and exhibit significant inter-patient variability. Using the 75th percentile values of EGP from Figure 5.4 to fit a function over time provided a good balance between reducing the number of constrained *SI* values and modelling EGP at supra-physiologic levels to include outliers.
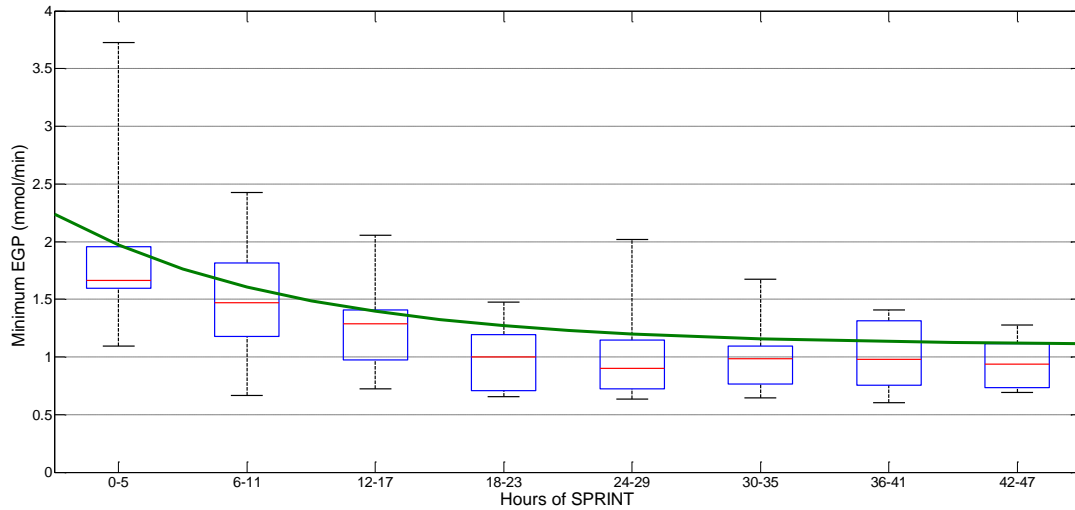
Figure 5.4 Time course of minimum EGP values required to prevent non-physiologic negative fitted *SI* values for the poor fit cohort. The whiskers indicate the full range of EGP values. The model is fitted to the 75th-percentile points $r^2 = 0.87$.

The least squares fitted exponential model of EGP is shown in Figure 5.4. The model was fitted to the 75th-percentile points located at the midpoints of the time intervals (3, 9, 15… hrs). Equation 5.1 defines the model and its parameters with *t* expressed in minutes. With a coefficient of determination, $r^2 = 0.89$, the model fitted the data points very well.

$$EGP(t) = 1.14 \times e^{-0.09t} + 1.10 \qquad\qquad 5.1$$

The values of EGP determined by the model approach 1.10 mmol/min asymptotically from 2.24 mmol/min at t = 0 hours. The value of EGP determined by the model is less than the currently used value of 1.16 mmol/min when t ≥ 33 hours. These values of EGP compare well with data from the literature shown in Table 5.2 and the calculated combined values for fasted and fed patients.

In the studies shown in Table 5.2, subjects receiving nutritional support generally had lower EGP levels than fasted subjects. This trend includes critically ill patients, where it may have been supposed that elevated levels of stress hormones might mitigate the suppression of EGP by exogenous glucose.

Eight of the 10 patients in the poor fit cohort received no nutrition prior to the time at which the large BG fitting errors occurred, so the proposed model may overestimate EGP for some patients when they are being fed. Equally, the values of EGP determined in the analysis are based on the minimum that drives SI to a very low physiological value. However, the unknown, true SI values may be anywhere in the typical range (10^{-4} – 10^{-3} l/mU.min) and, in this sense, the proposed model represents a minimum level and may underestimate EGP.

The SI parameter balances the glucose appearance from EGP and nutrition with utilisation by modifying insulin-mediated glucose uptake so that the modelled glucose dynamics best fit the measured data. Using a value of EGP that is too low causes obvious modelling errors due to the non-negative constraint on SI. However, when the value of EGP used in the model is too large, the model can still fit the data very well, as SI increases to maintain the glucose balance and match the observed data.

There is no obvious, physiological upper limit on this model-based SI parameter that can provide an indication that the value of EGP was too large. Hours where SI must be constrained to non-negative values provide extra data that suggest the value of EGP must be increased. However, once EGP has been raised to the point where $SI > 0$, there is little further information available to define the exact level. A prior distribution could be applied to place SI within the typical range (10^{-4} – 10^{-3} l/mU.min). However, this approach would still result in a wide range of EGP values. The problem thus becomes functionally unidentifiable once SI enters a physiologically reasonable range, as SI and EGP cannot be determined uniquely with just BG measurements.

The aim of this analysis was to model EGP as a function of time on the SPRINT protocol. However, arguments can be made that the proposed model may over- or under- estimate EGP depending on levels of nutrition and assumptions about the true *SI* level. Additionally, the model was developed on a small cohort of 10 patients with acute jumps in BG and may not generalise well to a normal ICU population. To properly define EGP over time and with different levels and types of nutrition, a series of studies would need to be conducted.

The fitted exponential function of Figure 5.4 matches clinical expectations. The acute phase of critical illness is characterised by a stress response diminishing over 12-48 hours as the concentrations of counter-regulatory hormones decline [Frayn 1986; Weissman 1990]. Overall, while the proposed model provides some insight into the possible behaviour of EGP over time, it is not well founded on measured data and suffers from an identifiability problem. Equally, the range of possible EGP levels is wide and patient-specific, even while the overall trend is clinically realistic. Therefore, the best course may be to continue using constant EGP for most applications. In special circumstances, during real-time control in clinical situations, it may be prudent to increase EGP temporarily.

5.3.4   EGP in control during special circumstances

During real-time control of BG in a clinical setting, particular circumstances may warrant a temporary increase in modelled EGP to ensure adequate control performance. When a patient has a poor fit to measured data due to a constrained value of *SI*, particularly if receiving no nutrition, then EGP is the most likely source of the error. In these situations, temporarily increasing EGP ensures that control performance and safety is maintained.

The duration and degree to which EGP should be increased likely varies between patients and over time. However, the results of this analysis and reported values from the literature suggest a wide range of possibilities. Hence, raising EGP up to 2.0 mmol/min to ensure $SI = 10^{-5}$ l/mU.min as a minimum value with good fit (<5% error) to measured BG data is potentially prudent. This change can be checked each hour to determine if it is still required.

5.4   Summary

Modelling EGP as a function of BG concentration, proved unsatisfactory in this investigation. The relationship between EGP and BG fitting error and the potential for positive feedback causing instability during simulation make modelling EGP as a function of BG unfeasible for this particular model and data set.

Modelling EGP as a function of time on the SPRINT protocol proved successful at reducing fitting error due to constrained *SI* values. While the values of EGP determined from the model compare well with those from published literature, arguments can be made that they may over- or under- estimate EGP, depending on levels of nutrition and assumptions about *SI*. Without additional data that are currently unavailable in clinical real-time, the problem is fundamentally unidentifiable when *SI* values are in the physiologic range. Additionally, this model was developed on a small cohort of 10 patients with acute jumps in BG and may not generalise well to a normal ICU population.

The best course may be to continue using constant EGP for most applications. However, during real-time control in clinical situations, if a patient has poor fit to measured data due to a constrained value of *SI* while receiving no nutrition, then EGP should be temporarily increased. Raising EGP up to 2.0 mmol/min and assessing the necessity hourly is proposed.

Finally, one major outcome of both analyses presented was confirmation of the wide inter- and intra- patient variability in EGP. This variability appeared in both functions of BG and time. This significant variability in EGP is a further aspect that confounds clinical glycaemic control efforts through intrinsic *SI* variability.

Chapter 6. ICING-2 Model Summary

6.1   Introduction

To conclude this section on intrinsic variability, the ICING model, modified with the proposed changes is presented. This modified model is designated ICING-2 to differentiate it from the original.

The changes to the original ICING model detailed in this section were:

- A model of pancreatic insulin secretion as a function of blood glucose concentration (Chapter 3).
- Improved insulin kinetics (Chapter 4).

Endogenous glucose production remains a population constant as discussed in Chapter 5.

6.2   Pharmacokinetic-pharmacodynamic model and parameters

The ICING-2 model is presented in Equations 6.1 - 6.7. The associated parameter values and descriptions are listed in Table 6.1. Table 6.2 shows the exogenous input variables to the model.

$$\dot{G}(t) = -p_G G(t) - S_I G(t) \frac{Q(t)}{1 + \alpha_G Q(t)} + \frac{P(t) + EGP - CNS}{V_G} \tag{6.1}$$

$$\dot{Q}(t) = n_I\big(I(t) - Q(t)\big) - n_C \frac{Q(t)}{1 + \alpha_G Q(t)} \tag{6.2}$$

$$\dot{I}(t) = n_K I(t) - n_L \frac{I(t)}{1 + \alpha_I I(t)} - n_I\big(I(t) - Q(t)\big) + \frac{u_{ex}(t)}{V_I} + (1 - x_L)\frac{u_{en}(G)}{V_I} \tag{6.3}$$

$$P(t) = \min(d_2 P2, P_{\max}) + PN(t) \tag{6.4}$$

$$\dot{P1}(t) = -d_1 P1 + D(t) \tag{6.5}$$

$$\dot{P2}(t) = -\min(d_2 P2, P_{\max}) + d_1 P1 \tag{6.6}$$

$$u_{en}(G) = \min\left(\max\left(u_{min}, k_1 G(t) + k_2\right), u_{max}\right) \tag{6.7}$$

Table 6.1 Parameter values and descriptions for the ICING-2 model.

Parameter	Value		Unit	Description
p_G	0.006		min^{-1}	Non-insulin mediated glucose removal
EGP	1.16		mmol/min	Endogenous glucose production rate
CNS	0.3		mmol/min	Central nervous system glucose uptake
V_G	13.3		L	Plasma glucose distribution volume
V_I	4.0		L	Plasma and interstitial insulin distribution volume
α_G	0.0154		L/mU	Insulin binding saturation parameter
α_I	0.0017		L/mU	Hepatic insulin clearance saturation parameter
n_I	0.006		min^{-1}	Trans-endothelial diffusion rate
n_C	0.006		min^{-1}	Interstitial insulin degradation rate
n_K	0.0542		min^{-1}	Renal insulin clearance rate
n_L	0.1578		min^{-1}	Hepatic insulin clearance rate
x_L	0.67			Fractional first-pass hepatic insulin extraction
d_1	0.0347		min^{-1}	Glucose transport rate from stomach to gut
d_2	0.0069		min^{-1}	Glucose transport rate from gut to plasma
P_{max}	6.11		mmol/min	Maximum glucose flux from gut to plasma
u_{min}	16.7		mU/min	Minimum pancreatic secretion rate
u_{max}	266.7		mU/min	Maximum pancreatic secretion rate
k_1	ND:	14.9	mU.L/mmol.min	Pancreatic insulin secretion glucose-sensitivity
	T2DM:	4.9		
	T1DM:	0.0		
k_2	ND:	-49.9	mU/min	Pancreatic insulin secretion offset
	T2DM:	-27.4		
	T1DM:	16.7		

Table 6.2 Exogenous input variables to the ICING-2 model.

Variable	Unit	Description
PN(t)	mmol/min	Intravenous glucose input rate (parenteral nutrition)
D(t)	mmol/min	Oral glucose input rate (enteral nutrition)
$u_{ex}(t)$	mU/min	intravenous insulin input rate

Chapter 7. Patient Type and Condition

In contrast with the previous thesis section, this section investigates extrinsic *SI* variability resulting from changes external to the specific pharmacokinetic-pharmacodynamic model. *SI* varies over time and between patients and patient groups as a result of physiological factors and measurement errors that are not explicitly modelled. To reduce the impact of these variations, while using the model for glycaemic control or analysis, the variability of these factors must be understood, and used to enable improved means of applying or implementing the model applied.

7.1   Introduction

The metabolism of critically ill patients evolves dynamically over time [Cuthbertson 1942; Frayn 1986; Weissman 1990]. The counter-regulatory hormones: cortisol, glucagon, the catecholamines, as well as growth hormone, are significantly elevated almost immediately post critical-insult, but decline rapidly over the first 12-48 hours [Chernow et al. 1987; Frayn 1986; Jaattela et al. 1975; Weissman 1990]. These hormones have a direct physiological impact on the *SI* parameter of the ICING-2 model, through altered endogenous glucose production, peripheral and hepatic insulin-mediated glucose uptake and endogenous insulin secretion. However, the specific level and time-course of the acute stress-response to critical illness varies significantly between patients. Hence, the level and variability of *SI* changes over time and between different patients and patient groups.

Understanding the variability of *SI*, over hours and days, is important for safely and effectively managing glycaemic levels with exogenous insulin. The metabolic balance represented by *SI* is an important consideration in clinical blood glucose control, as it determines a body's glycaemic response to exogenous insulin and nutrition. Several patient- and treatment related factors are thought to influence insulin sensitivity, such as cardiovascular surgery and glucocorticoid therapy.

Importantly, Bagshaw [2009] reported an association between hypoglycaemia and variability during the first 24 hours of ICU stay, and mortality. Not only does glycaemic variability pose a risk through hypoglycaemia, it is also detrimental in its own right. Several studies [Egi et al. 2006; Egi et al. 2010; Hermanides et al. 2010; Krinsley 2008] have shown that glycaemic variability is independently associated with mortality in critically ill patients. Hence, glycaemic variability is a critical factor to mitigate during control.

The objective of this study was to assess the evolution of insulin sensitivity level and variability over the first four days of ICU stay. Once this variability was understood, the means to reduce the impact on glycaemic control are proposed.

7.2 Subjects and Methods

7.2.1 Patients

This analysis was performed on a cohort of 164 patients from the SPRINT tight glycaemic control study in the Christchurch Hospital ICU [Chase et al. 2008]. All patients from the TGC cohort were included where SPRINT was commenced within 12 hours of ICU admission and continued for at least 24 hours.

A separate, sub-analysis was performed on cardiovascular surgery (CVS) patients from the full cohort. CVS patients form an important ICU population subgroup with regard to TGC [Van den Berghe et al. 2001], and are present in sufficient numbers in the SPRINT cohort to permit analysis. Table 7.1 presents a summary of the cohort details.

The Upper South Regional Ethics Committee, New Zealand granted approval for the audit, analysis and publication of this data.

Table 7.1. Summary details of the study subjects. The CVS patients are also included in the ICU cohort. Data are presented as median [interquartile range] where appropriate.

	ICU	CVS
N	164	22
Age (years)	65 [56-74]	73 [66-76]
Gender (M/F)	102/62	16/6
APACHE II score	19 [16-25]	17 [16-21]
APACHE II ROD (%)	32 [17-52]	21 [12-36]
Operative/Non-operative	66/98	22/0
Diabetic history: Type I/Type II	10/22	1/3
Hospital mortality	25%	18%
ICU length of stay (hours)	142 [70-308]	100 [67-257]

7.2.2   Analyses:

SI level was identified hourly using the ICING-2 model for each patient. Variability of *SI* was calculated as the hour-to-hour percentage change in *SI* ($\Delta\%SI$), defined in Equation 7.1. Use of percentage change, rather than absolute change, normalised the metric so that patients with very different absolute levels of *SI* could be compared fairly.

$$\Delta\%SI_k = 100 \times \frac{(SI_{k+1} - SI_k)}{SI_k} \qquad\qquad 7.1$$

SI level and variability were analysed on overall cohort and per-patient bases using two separate timescales. The evolution of *SI* over the first four days of ICU stay was analysed in 24-hour blocks. Bagshaw et al. [2009] reported an association between hypoglycaemia and variability during the first 24 hours of ICU stay, and mortality. Therefore, the acute evolution of *SI* over the first day using 6-hour blocks was also analysed.

Cohort analysis examined hourly values of *SI* and variability for the entire cohort grouped together and shows trends in the overall group behaviour. To quantify

per-patient variability, the interquartile range (IQR: 25-75th percentile) of Δ%*SI* was examined for each patient within each timescale. This metric captures the width of the variability distribution for each patient. Per-patient *SI* level was defined by the median value within each timeframe.

The analyses were linked to time on the SPRINT protocol, rather than time in the ICU, to ensure sufficient insulin and nutrition data to accurately identify *SI* hourly [Hann et al. 2005]. Therefore, day 1 comprises the first 24 hours of SPRINT. However, as patients were included only if they commenced SPRINT within 12 hours of ICU admission, a minimum of half of the day 1 results for each patient occur during their first 24 hours in the ICU. The median delay between admission and commencement of SPRINT for this cohort was 1.9 hours and 81% of the cohort had started SPRINT within 6 hours. When a patient was taken off the SPRINT protocol, their *SI* profile for the last day was included in the analysis if it contained six or more hours of data.

SI levels and variability are compared using cumulative distribution functions (CDFs) and non-parametric statistics. Distributed data was generally compared using the Wilcoxon rank-sum test (Mann-Whitney U-test), except for *SI* variability results. *SI* variability was compared using the Kolmogorov-Smirnov test as it has more power to detect differences in the shape of distributions than the rank-sum test when median values are similar. P-values of 0.05 were considered statistically significant.

7.3   Results

7.3.1   Twenty-four hour analyses:

7.3.1.1 Insulin sensitivity level

Figure 7.1 presents the cumulative distribution functions (CDFs) of hourly *SI* for each day by cohort (left panel) and median daily *SI* per-patient (right panel). Table 7.2 presents the increase in values from Figure 7.1 and associated p-values between successive days. Both per-patient and cohort analyses suggest that insulin sensitivity levels start low, but increase over time in the ICU. There was a

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particularly significant increase between days 1 and 2 (p < 0.001). On subsequent days the increase continues, but to a lesser extent. Per-patient comparisons between days 2, 3 and 4 were not statistically significant.
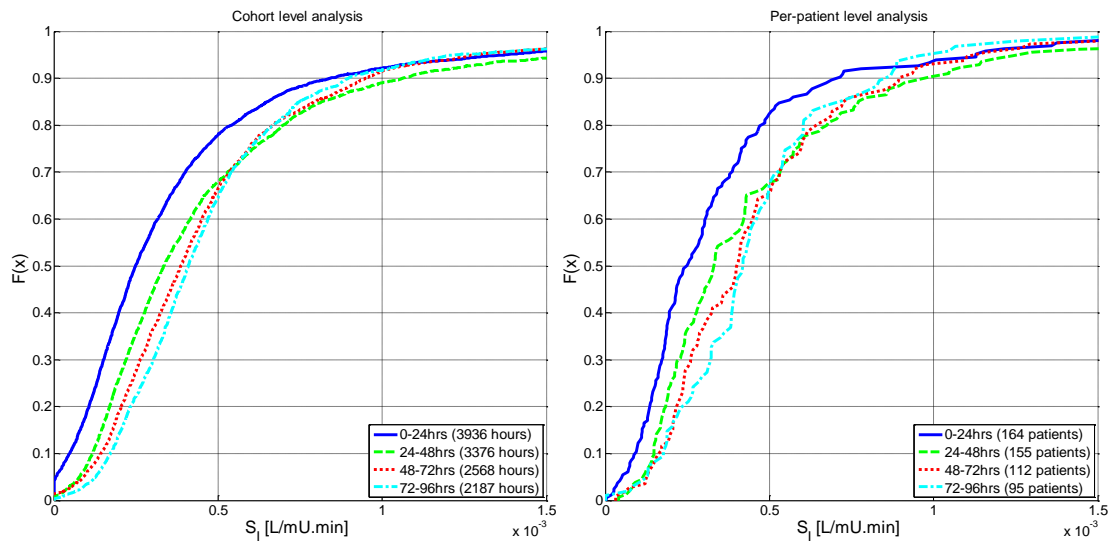
Figure 7.1. Insulin sensitivity level analyses by cohort (left) and per-patient median (right) using 24-hour blocks of data.

Table 7.2. Increasing cohort and per-patient median insulin sensitivity over time (24hr blocks). P-values calculated using Wilcoxon rank-sum test.

Level analysis	Cohort analysis		Per-patient analysis	
	% Increase at median	p-value	% Increase at median	p-value
Days 1-2	34	<0.0001	33	0.0004
Days 2-3	16	<0.0001	21	0.2559
Days 3-4	6	0.0013	4	0.6306

The results of Figure 7.1 and Table 7.2 are further reflected in Table 7.3, which shows that daily median insulin sensitivity increased for a large proportion of the cohort between days 1 and 2 with lesser proportions on subsequent days. Table 7.3 is a matrix where the value in a cell represents the proportion of patients for whom daily median insulin sensitivity is greater on the day of the associated column than the day of the associated row. For example, 72% of

patients showed an increase in median *SI* between days 1 and 2, and 54% when comparing days 2 and 3.

Table 7.3. Proportion of patients for whom median insulin sensitivity increases between the days indicated in the rows and columns.

	Day 2	Day 3	Day 4
Day 1	0.72	0.74	0.71
Day 2		0.54	0.64
Day 3			0.53

7.3.1.2 Insulin sensitivity variability

Insulin sensitivity variability reduced over time in the ICU, parallel to increases in *SI* level. Figure 7.2 and Table 7.4 present the CDFs and tabulated results for cohort and per-patient analyses of the hour-to-hour percentage changes in *SI* ($\Delta\%SI$). The cohort aggregate distributions of $\Delta\%SI$ by day are shown in the left panel of Figure 7.2. The right panel presents the CDFs of the per-patient IQRs by day.
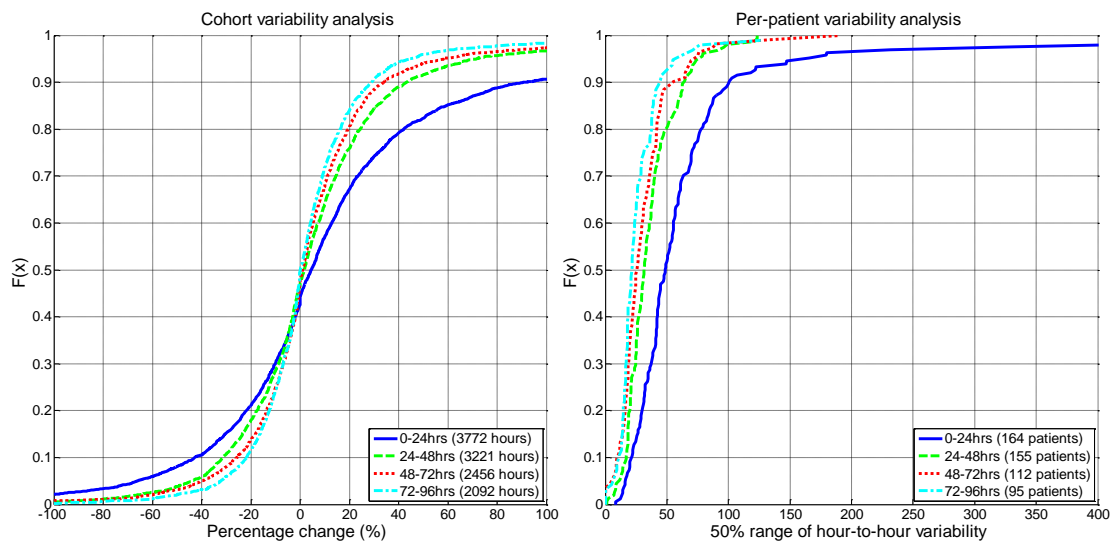
Figure 7.2. Insulin sensitivity variability analyses by cohort (hour-to-hour percentage change) and per-patient interquartile-range using 24-hour blocks of data.

As with *SI* level, the largest improvement in variability was between days 1 and 2. The reduction between days 2-3 and 3-4 was statistically significant or very nearly so for both cohort and per-patient analyses, but the change was much less than over the first day, and may not be clinically significant.

Table 7.4. Reductions in the IQR and median per-patient range of hour-to-hour percentage insulin sensitivity change over time. P-values calculated using Kolmogorov-Smirnov test for cohort comparisons and Wilcoxon rank-sum test for per-patient comparisons.

Variability analysis	Cohort analysis		Per-patient analysis	
	% Reduction of IQR	p-value	% Reduction at median	p-value
Days 1-2	34	<0.0001	35	<0.0001
Days 2-3	20	0.0022	18	0.0087
Days 3-4	14	0.0339	16	0.0543

7.3.2 Six hour analyses:

7.3.2.1 Insulin sensitivity level

Figure 7.3 presents the distributions of cohort and per-patient *SI* over the first 24 hours in 6-hour blocks. Also shown for comparison is the day 2 distribution from Figure 7.1 (labelled 24-28 hours). It is evident that insulin sensitivity level improves over the first day up to the level of the second day. Hence, the differences between day 1 and 2 seen in Figure 7.1 were a function of the low, but increasing insulin sensitivity during the first 12-18 hours.

Table 7.5 lists the differences in median insulin sensitivity levels from the distributions shown in Figure 7.3. The increases in *SI* during the first 18 hours were large and statistically significant. Subsequent increases are unlikely to be clinically significant at less than 10%. Of particular interest is the comparison between 18-24 hours and day 2, which indicates that by 18 hours, the rapid improvement in *SI* was largely complete.
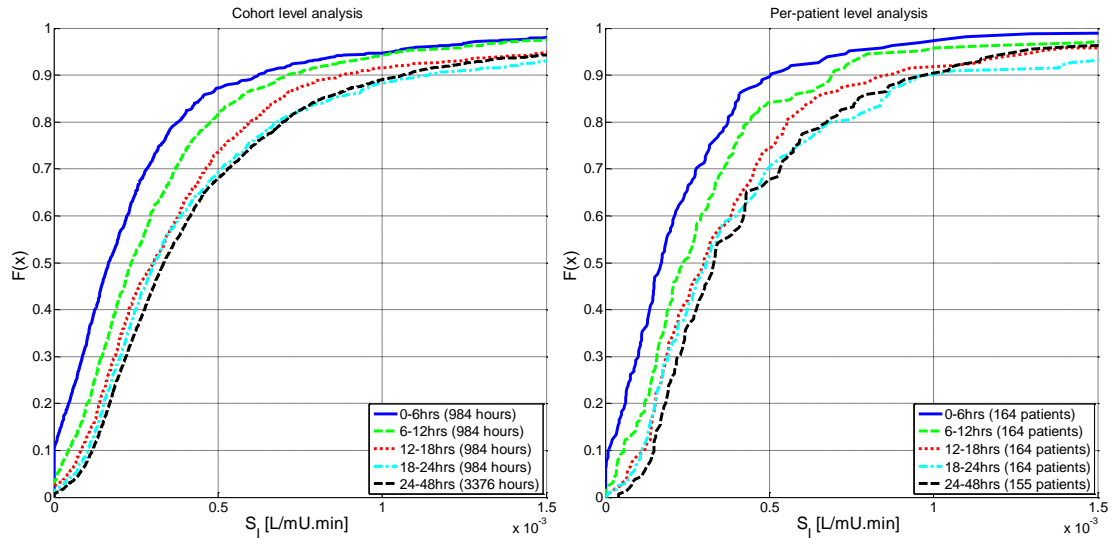
Figure 7.3. Insulin sensitivity level analyses by cohort (left) and per-patient median (right) using 6-hour blocks of data.

Table 7.5. Increasing cohort and per-patient median insulin sensitivity over time (6hr blocks). P-values calculated using Wilcoxon rank-sum test.

Level analysis	Cohort analysis		Per-patient analysis	
	% Increase at median	p-value	% Increase at median	p-value
Block 1-2 (0-6 vs 6-12hrs)	42	<0.0001	40	0.0007
Block 2-3 (6-12 vs 12-18hrs)	28	<0.0001	26	0.0123
Block 3-4 (12-18 vs 18-24hrs)	1	0.0335	3	0.4829
Block 4-5 (18-24 vs 24-48 hrs)	9	0.0451	7	0.3763

Table 7.6 shows that during the first 18 hours, a large proportion of the patients saw an increase in insulin sensitivity using the 6-hour timescale. Past 18 hours, the proportion of patients with increasing SI was similar to that seen between days 2, 3 and 4 (Table 7.3) at a little over 50%.

Table 7.6. Proportion of patients for whom median insulin sensitivity increases between the blocks indicated in the rows and columns.

	6 - 12hrs	12 - 18hrs	18 – 24hrs	24 – 48hrs
0 - 6hrs	0.74	0.78	0.77	0.79
6 - 12hrs		0.76	0.70	0.72
12 - 18hrs			0.55	0.64
18 - 24hrs				0.58

7.3.2.2 Insulin sensitivity variability

As with *SI* level, the majority of the improvement in *SI* variability occurred during the first 18 hours. Figure 7.4 shows the CDFs of the cohort and per-patient variability metrics. However, Table 7.7 shows that only the differences between 0-6 hours and 6-12 hours were statistically significant in both analyses.
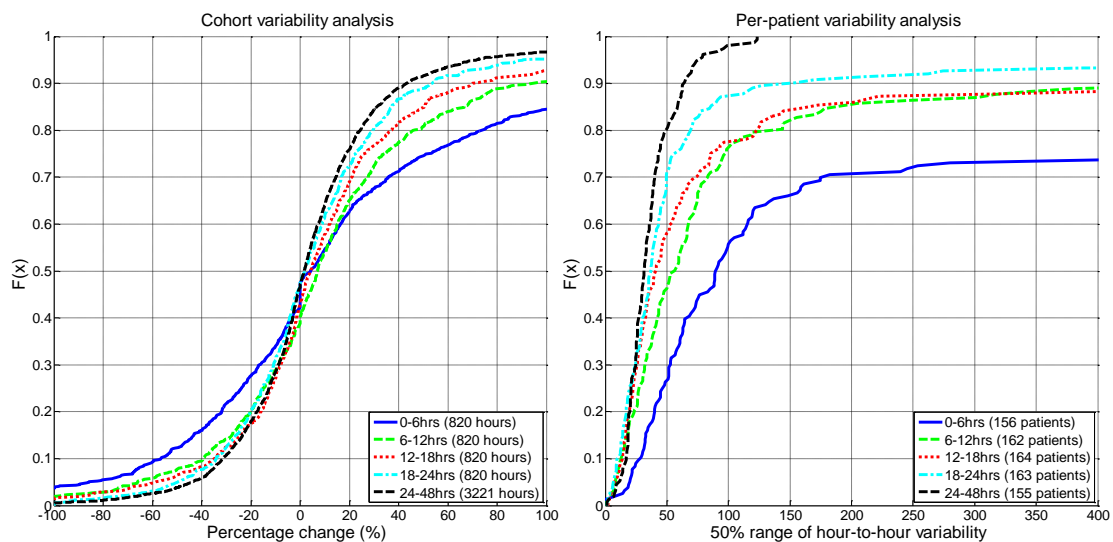
Figure 7.4. Insulin sensitivity variability analyses by cohort (hour-to-hour percentage change) and per-patient interquartile-range using 6-hour blocks of data.

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Table 7.7. Reductions in the IQR and median per-patient range of hour-to-hour percentage insulin sensitivity change over time. P-values calculated using Kolmogorov-Smirnov test for cohort comparisons and Wilcoxon rank-sum test for per-patient comparisons.

Variability analysis	Cohort analysis		Per-patient analysis	
	% Reduction of IQR	p-value	% Reduction at median	p-value
Block 1-2 (0-6 vs 6-12hrs)	36	0.0092	37	< 0.0001
Block 2-3 (6-12 vs 12-18hrs)	24	0.0806	27	0.1031
Block 3-4 (12-18 vs 18-24hrs)	-1	0.0806	10	0.868
Block 4-5 (18-24 vs 24-48hrs)	18	0.1639	15	0.1002

7.3.3 Cardiovascular surgery patients

Figure 7.5 and Figure 7.6 show the evolution of *SI* over the first four days of ICU stay for the 22 CVS patients. Also shown, for comparison, are the same data for the full 164 patient ICU cohort from Figure 7.1 and Figure 7.2, including these 22 patients.

The CVS patients exhibit similar trends over time to the full ICU cohort. Cohort analysis showed 21-32% increases in level for all days ($p < 0.003$) and a 34% reduction in variability between days 1 and 2 ($p < 0.02$). More importantly, the CVS patients also exhibit lower and more variable *SI* than the ICU cohort for the first few days of ICU stay. The CVS patients had 25-34% lower *SI* than the full cohort during days 1-3 of ICU stay ($p < 0.001$), and were also significantly more variable on day 1 ($p = 0.03$). By day 4, there were no statistically significant differences in level or variability between the CVS cohort and the ICU cohort.

The relatively small number of CVS patients that fulfilled the selection criteria for this study limited the reliability of the per-patient analyses. The 6-hour analyses were omitted altogether as both the cohort and per-patient data were sparse.
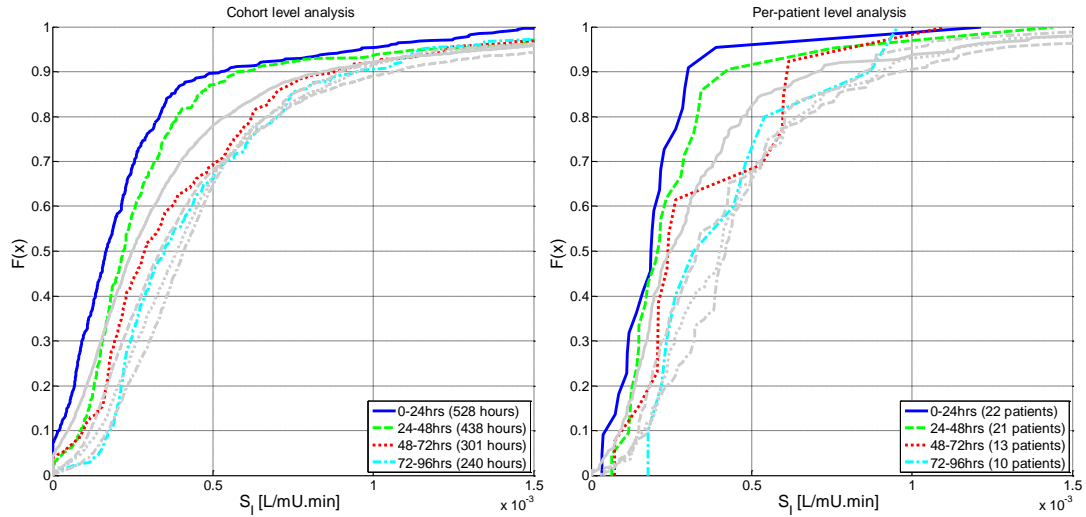
Figure 7.5. Insulin sensitivity level analyses by cohort (left) and per-patient median (right) for cardiovascular surgery patients. The grey lines show the data from the full 164 patient cohort for comparison.
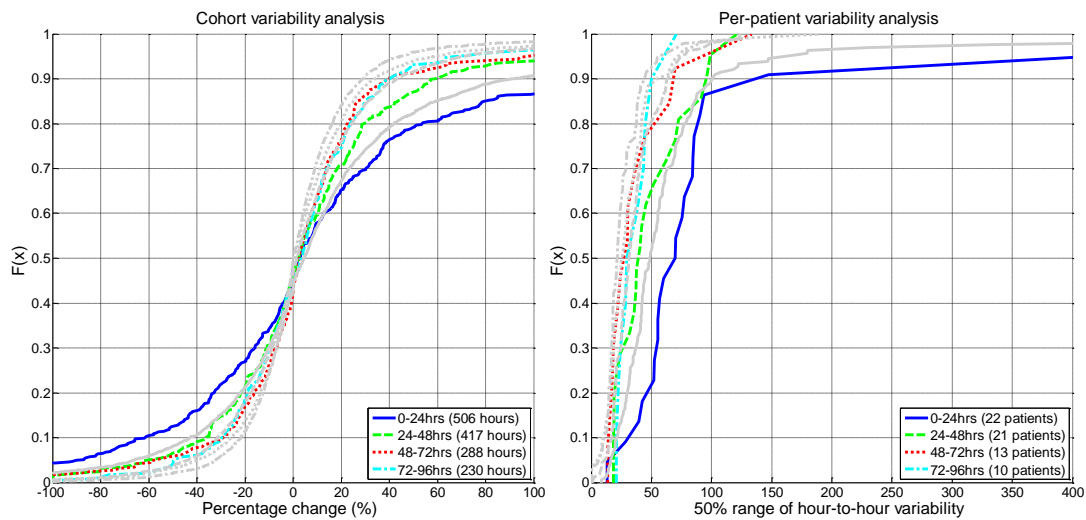
Figure 7.6. Insulin sensitivity variability analyses by cohort (left) and per-patient median (right) for cardiovascular surgery patients. The grey lines show the data from the full 164 patient cohort for comparison.

7.4   Discussion

7.4.1   Insulin sensitivity variability

Both cohort and per-patient results suggest that ICU patients have significantly lower and more variable insulin sensitivity on day 1 than later in their stay. Further analysis showed that this day 1 result was primarily influenced by the

first 12-18 hours of ICU stay. Over this time, rapid improvements in insulin sensitivity level and variability occur so that there was no statistically significant difference between 18-24 hours and day 2. From day 2 onwards, changes in *SI* level and variability are not as large and of limited clinical and statistical significance.

Within the analyses, there were some differences in significance between cohort and per-patient results for comparisons after day 2. The overall findings noted in the preceding paragraph are the only clear, consistent trends across both analyses.

The counter-regulatory hormones: cortisol, glucagon, the catecholamines, as well as growth hormone, are significantly elevated almost immediately post critical-insult, but decline rapidly over the first 12-48 hours [Chernow et al. 1987; Frayn 1986; Jaattela et al. 1975; Weissman 1990]. These hormones are known to cause increased hepatic glucose production, inhibition of insulin release and peripheral insulin resistance [Weissman 1990], all of which cause a reduction in the model-based *SI* metric used in this study. Hence, the low but rapidly increasing insulin sensitivity seen over the first 12-18 hours of ICU stay is likely due to the acute counter-regulatory response to critical illness.

Cardiovascular surgical patients were examined in particular, as they constitute one of the largest single diagnostic subgroups treated with the SPRINT protocol [Chase et al. 2008] and are common in many study cohorts. Additionally, they have shown potential benefit from TGC, independent of broader cohorts [Furnary et al. 1999; Van den Berghe et al. 2006a; Van den Berghe et al. 2001]. The CVS cohort demonstrated the same increased level and reduced variability of *SI* over time as the full cohort. More importantly, the CVS cohort exhibited lower and more variable *SI* than the full cohort for the first few days of stay.

The significantly lower and more variable results of the CVS cohort during the first 2 days may result from the high level of stress and inflammation inherent to cardiovascular surgery, particularly when cardiopulmonary bypass is used

[Warren et al. 2009]. Additionally, cardiovascular disease and insulin resistance (often undiagnosed) go hand-in-hand [Alberti et al. 2005; Cowie et al. 2009] and could account for some of the observed effect.

Time in this study was referenced from the commencement of SPRINT, rather than ICU admission. However, the difference between admission time and commencing SPRINT was generally very short as noted in Section 7.2.2. Hence, these results are applicable to the first few hours and days of ICU stay.

7.4.2 Reducing the impact of *SI* variability on outcome glycaemia

This analysis investigates *SI* variability resulting primarily from physiological changes in patients' external to the glucose-insulin system model. Equally, where the impact of the physiological and hormonal changes is evident in the model, they cannot be directly measured at the bedside or in real-time to enable better models. Hence, rather than modifying or expanding the model, improved means of applying or implementing it during control and analysis are necessary.

The primary use of this glucose-insulin system model is enabling model-based TGC in critical care. During TGC, greater variability with lower *SI* early in a patient's stay greatly increases the insulin required to maintain control. High levels of circulating insulin coupled with the observed variability in insulin sensitivity result in increased glycaemic variability and an increased risk of hypoglycaemia, particularly during the first 24 hours of ICU stay. Both glycaemic variability and hypoglycaemia have been associated with poor outcomes in the ICU [Egi et al. 2006; Egi et al. 2010; Hermanides et al. 2010; Krinsley 2008].

There are two complementary ways to reduce the impact of *SI* variability on outcome glycaemia. The simplest, intervention-based method relies on adapting the control protocol to minimise the impact of *SI* variability. Greater blood glucose measurement frequency and conservative insulin dosing can lower the impact of *SI* variability on glycaemia and risk [Lonergan et al. 2006]. Modulation of carbohydrate nutrition, within limits [Krishnan et al. 2003], can also reduce the need for exogenous insulin to better manage glycaemia [Suhaimi et al. 2010].

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Complementing the intervention-based methods are model-based methods for reducing the impact of *SI* variability. The controllers currently used in the Christchurch ICU are implemented on tablet computers and use the ICING-2 model to forecast outcome BG for a series of possible interventions and then select the most optimal [Evans et al. 2011]. This forward-prediction is enabled by a stochastic model of *SI* for hour *n+1*, based on the value identified for hour *n* [Lin et al. 2008]. With the understanding gained from this analysis, several stochastic models could be used based on day of stay and/or diagnosis, rather than just one to improve performance.

Using separate stochastic models where *SI* level and variability are atypical would allow the controller to capture this behaviour and titrate insulin and nutrition accordingly. Results from this investigation suggest that at least 3 stochastic models would be appropriate:

1. All patients, for use more than 24 hours after ICU admission (day 2 on).
2. All non-CVS patients for use between ICU admission and 24 hours.
3. CVS patients for use between ICU admission and 24 hours.

Further investigation may identify other important diagnostic subgroups that would benefit from separate stochastic models. However, to be effective, each stochastic model must be generated from a sufficient number of data points. As a guide to a possible lower limit, Lin et al. [2006] validated a model based on 1300 hours of data from 18 ICU patients.

The stochastic model for all patients more than 24 hours after ICU admission would likely look very similar to the current model. However, models for use during the first 24 hours in the ICU for both CVS and other patients would have wider bounds reflecting the increased hour-to-hour variability. The result of this widening, under the current STAR protocol [Evans et al. 2011] would be more conservative and consistent insulin dosing to manage the risk of glycaemic variability and hypoglycaemia.

7.5   Summary

The results of this study indicate that critically ill patients have significantly lower and more variable insulin sensitivity on day 1 than later in their ICU stay, particularly during the first 12-18 hours. Cardiovascular surgery patients were shown to be even lower and more variable than the general ICU cohort (including themselves). This effect is likely due to the acute counter-regulatory response to critical illness. Greater variability with lower *SI* early in a patient's stay greatly increases the insulin required, potential glucose flux due to variation in *SI*, and thus the risk of glycaemic variability and hypoglycaemia. Both glycaemic variability and hypoglycaemia have been associated with poor outcomes in the ICU.

To manage this extrinsic *SI* variability and its evolution over time, the use of several stochastic models was proposed. Using different models for the early part of ICU stay and for different diagnostic subgroups would permit control algorithms to reduce the impact of the *SI* variability on outcome glycaemia. The three models proposed from this analysis were:

1. All patients, for use more than 24 hours after ICU admission.
2. All non-CVS patients for use between ICU admission and 24 hours.
3. CVS patients for use between ICU admission and 24 hours.

Additionally, intervention-based measures such as greater blood glucose measurement frequency, conservative insulin dosing and modulation of carbohydrate nutrition can lower the impact of *SI* variability on glycaemia and risk.

Chapter 8. Drug Therapies

Similar to the impact of patient condition, a number of drug therapies often administered in the ICU are known to impact *SI* in healthy individuals. The use of these drugs may add to the extrinsic *SI* variability that needs to be mitigated for optimal use of the ICING-2 model in analysis and real-time control applications.

8.1   Introduction

Glucocorticoids and β-blockers are two drug therapies common to critical care. Glucocorticoid steroids are administered to treat a variety of inflammatory and allergic disorders [Rhen & Cidlowski 2005]. β-blockers are used to reduce cardiac output and essential hypertension [Khan 2007]. Both classes of drugs have been shown to have an effect on insulin sensitivity in healthy individuals [Binnert et al. 2004; Elliott & Meyer 2007; Jacob et al. 1996; Larsson & Ahren 1996; Nicod et al. 2003; Pagano et al. 1983; Perry et al. 2003; Pollare et al. 1989]. However, there is a lack of data about whether these effects are equally valid, or equally large, for critically ill patients

The effects of different glucocorticoids on the insulin sensitivity of healthy subjects are fairly consistent. Several studies reported 30-62% decreases in insulin sensitivity of healthy subjects after short-term administration of dexamethasone [Binnert et al. 2004; Larsson & Ahren 1996; Nicod et al. 2003; Perry et al. 2003]. Pagano et al. [1983] documented a similar change with prednisone.

In contrast, the reported effects of β-blockers on insulin sensitivity range from detrimental to beneficial, depending on the specific drug [Jacob et al. 1996; Sarafidis & Nilsson 2006]. Thus, while the impact of different glucocorticoids on *SI* can be analysed together, β-blockers must be treated separately. This study analyses the impact of metoprolol on *SI,* as it is currently one of the most commonly used β-blockers in the Christchurch intensive care unit (ICU)

Metoprolol is a competitive antagonist to the β1-adrenergic receptor [Kindermann et al. 2004] and is indicated for use in several diseases of the cardiovascular system. Three studies have investigated the effects of metoprolol on insulin sensitivity using the gold-standard euglycaemic-hyperinsulinaemic clamp method [Falkner & Kushner 2008; Jacob et al. 1996; Pollare et al. 1989]. Two of the studies [Jacob et al. 1996; Pollare et al. 1989] reported reductions in insulin sensitivity of 14-27% associated with metoprolol in non-diabetic individuals when used to treat hypertension. The study by Falkner et al. [2008] showed a statistically non-significant 2% reduction in insulin sensitivity due to metoprolol in type-2 diabetic subjects.

There is a lack of data about whether the impact of glucocorticoids and metoprolol on *SI* are equally valid, or equally large, for critically ill patients. In terms of glucose metabolism, critically ill patients are very similar to type 2 diabetic individuals, thus, studies on healthy individuals may not translate fully. The aim of this investigation was to assess the impact of these agents, on the level and variability of *SI* in critically ill patients. Once the effects were understood, means to mitigate the impact on glycaemic control could be implemented.

8.2   Subjects and Methods

These studies were conducted as retrospective analyses of data from patients admitted to the Christchurch Hospital ICU between 2005 and 2007. The analyses of glucocorticoid and metoprolol data were conducted independently. Two matched cohorts were used for each analysis. All of the patients spent at least 24 hours on the SPRINT glycaemic control protocol [Chase et al. 2008].

The Upper South Regional Ethics Committee, New Zealand granted approval for the audit, analysis and publication of this data.

8.2.1 Glucocorticoid study subjects

Two cohorts of 40 patients were used for the glucocorticoid analysis. The cohort details are shown in Table 8.1. The steroid cohort received one or more of the steroids listed in Table 8.2. Patients were excluded if they received β-blockers or ACE-inhibitors, as these therapeutic agents can affect glucose metabolism and insulin sensitivity [Deibert & DeFronzo 1980; Henriksen & Jacob 2003a; Rizza et al. 1980]. A control cohort of 40 patients, who did not receive any glucocorticoid, β-blocker or ACE-inhibitor therapy, was also selected so that the overall cohort parameters (age, sex, outcome, severity of illness), matched the steroid cohort as closely as possible.

Table 8.1. Glucocorticoid analysis cohorts. Data are shown as median [interquartile range] where appropriate. P-values were calculated using Fisher's exact test for categorical data and the Wilcoxon rank-sum test for continuous data.

	Control Cohort-S	Steroid Cohort	p-value
N	40	40	
Hospital Mortality (%)	38	40	1.00
Operative/Non-operative	12/28	11/29	1.00
Gender M/F	23/17	20/20	0.65
AGE (yrs)	65.5 [51-73]	61.5 [52-74]	0.74
Diabetic history (T1DM/T2DM)	3/5	1/4	0.67
APACHE II Score	20.0 [18-27]	22.5 [18-28]	0.83
APACHE II Risk of death (%)	38.3 [23-64]	39.7 [23-62]	0.95
Patient time on SPRINT (hrs)	103 [42-155]	102 [66-153]	0.63
Patient median blood glucose (mmol/l)	5.7 [5.3-6.1]	5.9 [5.3-6.3]	0.49
Total time on SPRINT (hrs)	5259	4914	
Total time on Steroids (hrs)	0	3489	
Equivalent daily dose of hydrocortisone (mg/d)	0	200 [80-200]	

Table 8.2 lists the potencies and half-lives used in analysis of the steroids for this research. Relative potencies and biological half-lives of the glucocorticoids were based on data for anti-inflammatory effects as these closely parallel the effects on glucose metabolism [Schimmer & Parker 2006]. The relative potencies enable calculation of the equivalent hydrocortisone dose in Table 8.1.

Table 8.2. Glucocorticoids and their properties used in this study [Derendorf et al. 1993; Melby 1977; Schimmer & Parker 2006].

Compound	Relative anti-inflammatory potency	Duration of action / Effective biological half-life (hrs)
Hydrocortisone	1	10
Prednisone	4	24
Prednisolone	4	24
Methyl-prednisolone	5	24
Dexamethasone	25	45

8.2.2 Metoprolol study subjects

Two cohorts of 17 patients were used for the metoprolol analysis. The cohort details are shown in Table 8.3. The treatment cohort did not receive any other β-blockers besides metoprolol (oral or intravenous) and did not receive glucocorticoid or ACE-inhibitor treatment. The restrictions on other treatments significantly reduced the number of patients eligible for consideration as hypertension is often treated with a combination of drugs. However, these other agents are known to affect glucose metabolism [Henriksen & Jacob 2003b; Lithell 1992; Lithell 1995; Pollare et al. 1989; Pretty et al. 2010] and thus may have confounded the results. Similarly to the glucocorticoid analysis, a control cohort was selected to match overall parameters.

Table 8.3. Metoprolol analysis cohorts. Data are shown as median [interquartile range] where appropriate. P-values were calculated using Fisher's exact test for categorical data and the Wilcoxon rank-sum test for continuous data.

	Control Cohort-M	Metoprolol Cohort	p-value
N	17	17	
Hospital Mortality (%)	35%	24%	0.71
Operative/Non-operative	4/13	4/13	1.00
Gender M/F	12/5	13/4	1.00
AGE (yrs)	63 [45-71]	57 [45-67]	0.69
Diabetic history (T1DM/T2DM)	1/2	0/1	0.60
APACHE II Score	19 [16-27]	20 [16-26]	0.70
APACHE II Risk of death (%)	33.6 [20-53]	40.8 [13-61]	0.74
Patient time on SPRINT (hrs)	141 [88-293]	178 [73-339]	0.45
Patient median blood glucose (mmol/l)	5.7 [5.0-6.4]	5.8 [5.1-6.5]	0.11
Total time on SPRINT (hrs)	3369	4126	
Total time on Metoprolol (hrs)	0	3079	
Daily dose of Metoprolol (mg/d)	0	100 [50-200]	

8.2.3   Analyses

SI level was identified hourly using the ICING-2 model for each patient. Variability of *SI* was calculated as the hour-to-hour percentage change in *SI* ($\Delta\%SI$), defined in Equation 8.1 from Chapter 7.

$$\Delta\%SI_k = 100 \times \frac{(SI_{k+1} - SI_k)}{SI_k} \qquad\qquad 8.1$$

SI level and variability were compared between matched cohorts to determine the impact of the drug therapies. Overall cohort comparisons of insulin sensitivity were possible with the matched cohorts. However, as individual patients could not be explicitly matched, *percentile patients* were used as a surrogate for explicit per-patient analyses as described by Pretty et al. [2010]. As the percentile patient distributions are not sampled data and are composed from an arbitrary number of points, they cannot fairly be compared with standard hypothesis tests for statistical significance. However, comparison of percentile patients between cohorts does provide confirmation of the cohort analysis results.

Where patients did not receive a drug therapy for the entire time they were on SPRINT, *SI* was considered to be affected by the drug for some period after the last dose. For glucocorticoids, this period was one effective biological half-life (Table 8.2). Metoprolol was considered to affect *SI* for 12 hours following the last dose. Both these periods are relatively short and the drugs have been reported to remain active for longer periods. The short periods ensured that any effects on *SI* had not decreased so far as to be undetectable.

The effective biological half-lives of the glucocorticoids listed in Table 8.2 are the median values of ranges reported by Melby [1977]. Metabolism of metoprolol is extremely variable between patients [Chrysostomou & Kazmerski 2008]. However, a number of studies have shown that oral doses of 100-200 mg/day result in a duration of action for heart-rate and blood-pressure effects of 12-24 hours [Åblad et al. 1975; Freestone et al. 1982; Johansson et al. 1980; Johnsson et al. 1975; Reybrouck et al. 1978]. Previous investigations have targeted the effects of chronic metoprolol dosing on insulin sensitivity, showing that a reduction in *SI* is present even 20 hours after the last dose [Jacob et al. 1996; Pollare et al. 1989]. The variable and prolonged effects of both drugs made comparison of the *SI* values within each cohort between periods on- and off treatment infeasible, as there were few hours of data that could confidently be considered unaffected by the treatment.

SI level and variability distributions are compared using CDFs and non-parametric statistics. Comparisons were generally made using the Wilcoxon rank-sum test (Mann-Whitney U-test) for continuous data and two-sided Fisher's exact test for categorical data. Hour-to-hour *SI* variability was compared using the Kolmogorov-Smirnov test as it has more power to detect differences in the shape of distributions than the rank-sum test when median values are similar. P-values of 0.05 were considered statistically significant.

8.3 Results

8.3.1 Glucocorticoid analysis

Analysis of changes to *SI* level and variability associated with glucocorticoid treatment were investigated using two cohorts with matched overall parameters. The temporal location of *SI* data compared in this Section was also similar between cohorts. For the steroid cohort, 18% and 35% of the *SI* values considered affected by the drug came from the first 24 and 48 hours of SPRINT, respectively. The corresponding proportions for the control cohort were 19% and 34%. Hence, the results are unlikely to have been confounded by the timing of the treatments.

8.3.1.1 SI level analysis

SI level in patients receiving glucocorticoids was lower than control patients in an overall cohort comparison. The median value of the 'on-steroid' data was 33% lower than the control data (2.83×10^{-4} and 4.19×10^{-4} l/mU.min, $p < 0.0001$). The left panel of Figure 8.1 shows the CDFs for both cohorts. There is a clear separation between the control cohort and the steroid cohort (while receiving steroids) distributions at all percentile values.

The CDF of *SI* level for the steroid cohort is also shown for periods when the patients were not receiving steroid treatment, for the purposes of comparison only. This data is primarily composed of *SI* values from periods after patients had completed glucocorticoid therapy. Only 2% of data was from the first 24 hours of SPRINT (compared to 18-19% for the on-steroid and control data). This data is likely biased by improved patient condition, as described in Chapter 7, and thus may not make a fair comparison with on-steroids hours. In addition, the chosen on/off steroids cut-off point of one half-life means that some of this data is likely still affected by exogenous glucocorticoids.
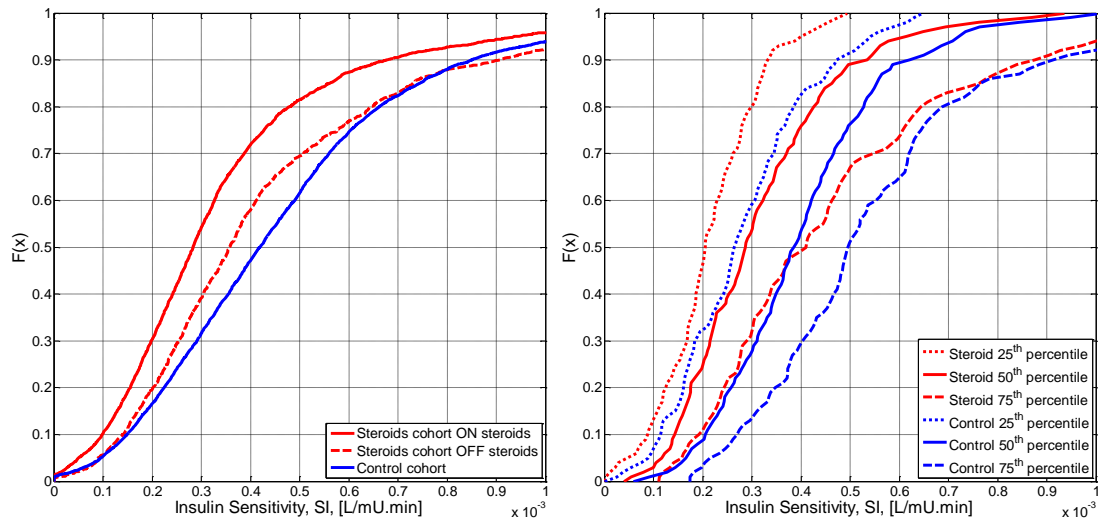
Figure 8.1. CDFs of *SI* level for the control and steroid cohorts. The left panel shows the overall cohort comparison. The right panel shows the 25th-, 50th- and 75th percentile patients.

Analysis of the percentile patient data also shows a reduction in *SI* at all percentiles for patients receiving glucocorticoids. Figure 8.2 (right panel) shows the CDFs for the 25th, 50th and 75th-percentile patients from both cohorts. The reductions in median *SI* for the percentile patients receiving steroids were 22%, 26%, and 17% for 25th-, 50th- and 75th percentile patients, respectively. While the percentile patient distributions cannot be compared with standard hypothesis tests, they do provide confirmation of the magnitude of the cohort result.

8.3.1.2 SI variability analysis

Figure 8.2 shows that glucocorticoid therapy was associated with an increase in the hour-to-hour variability of *SI* compared to the controls in both cohort and percentile patient analyses. The 90% range (5th-95th percentile) of Δ%*SI* for the steroid cohort was 50% larger than the control cohort ($p < 0.0001$). For the percentile patients, steroid treatment was associated with increases to the 90% range of 27%, 50% and 39% for the 25th-, 50th- and 75th percentile patients, respectively.
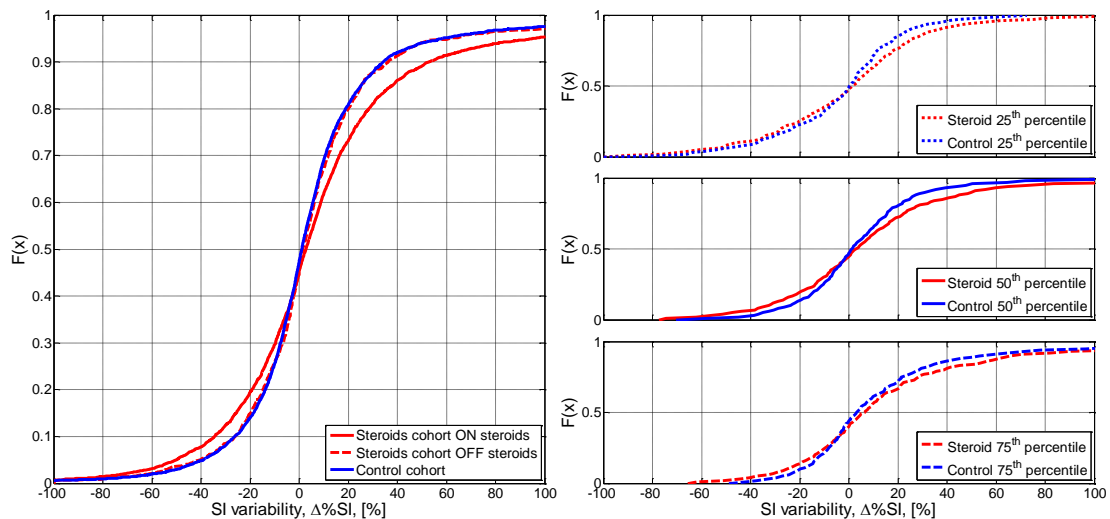
Figure 8.2. CDFs of *SI* hour-to-hour variability for the control and steroid cohorts. The left panel shows the overall cohort comparison. The right panel shows the 25th-, 50th- and 75th percentile patients (top to bottom).

It is interesting to note that the variability of the steroid cohort while not receiving steroids is almost identical to the control cohort. However, as mentioned in the preceding section, improving patient condition likely confounds this comparison.

8.3.2 Metoprolol analysis

The temporal location of *SI* data compared in this analysis was not as well matched as for the glucocorticoid analysis. For the metoprolol cohort, 6% and 10% of the *SI* values considered affected by the drug were during the first 24 and 48 hours of SPRINT, respectively. The corresponding proportions for the control cohort were 13% and 23%. The disparity between these values and those of the glucocorticoid analysis cohorts is primarily due to the median length of time spent on the SPRINT protocol being 40-80% longer for patients in the metoprolol analysis. The disparity between the treatment and control cohorts may be due to the clinical practise for administering metoprolol. However, with only 6-13% of the total hours occurring during the first 24 hours of SPRINT, evolving patient condition is unlikely to confound the results.

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8.3.2.1 SI level analysis

SI level in patients receiving metoprolol was typically lower than control patients in an overall cohort comparison, although the difference was noticeably less than in the glucocorticoid analysis. Median cohort insulin sensitivity was reduced 10.5% from 4.28×10^{-4} to 3.83×10^{-4} l/mU.min ($p < 0.0001$). Figure 8.3 (left panel) shows the CDFs for both cohorts. There was a clear separation between the control cohort and the metoprolol cohort (while receiving metoprolol) distributions between the 10th- and 90th percentile values. Outside this range, factors such as variable metabolism and dosing of metoprolol between patients, as well as patient condition, may be the cause of the *SI* distributions crossing over each other.
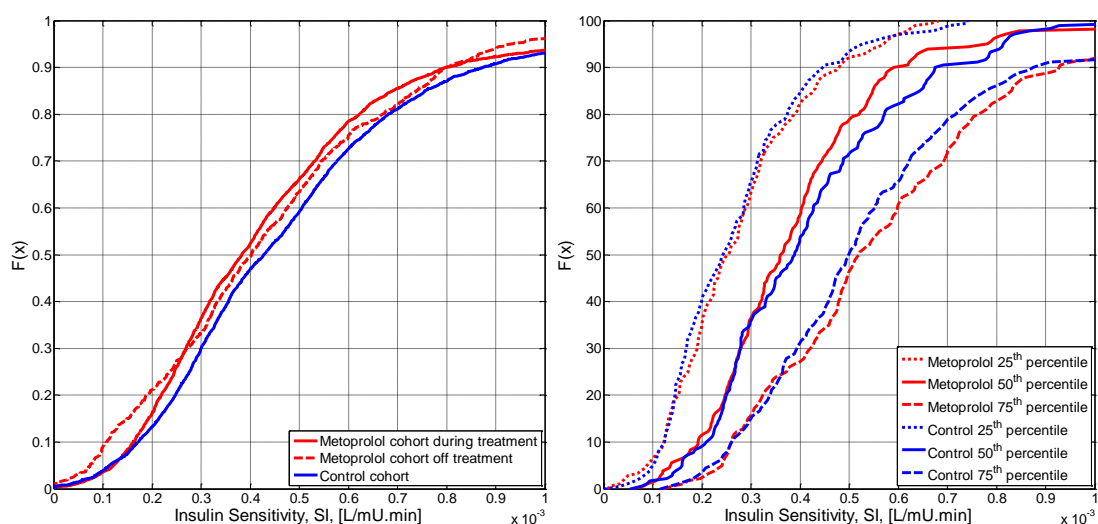
Figure 8.3. CDFs of *SI* level for the control and metoprolol cohorts. The left panel shows the overall cohort comparison. The right panel shows the 25th-, 50th- and 75th percentile patients.

The CDF of *SI* level for the metoprolol cohort is also shown for periods when the patients were not receiving treatment, although only for comparison. As with the glucocorticoid analysis, the variable metabolism and selected on/off metoprolol cut-off point of 12-hours means that some of this data is likely still affected by the drug.

Analysis of the percentile patient data showed no clinically significant reduction of *SI* for patients receiving metoprolol. Figure 8.3 (right panel) shows the CDFs of

the 25th, 50th and 75th-percentile patients from both cohorts, where the differences at the median were -5%, 7% and -4%, respectively. Note that a positive value represents a reduction in *SI* for the metoprolol percentile patient compared to the control.

8.3.2.2 SI variability analysis

Figure 8.4 shows that metoprolol was not associated with any change in hour-to-hour *SI* variability on an overall cohort basis (left panel). The 90% range of Δ%*SI* for the metoprolol cohort was 8.5% lower than the control cohort. However, this difference was not statistically significant (p = 0.44, Kolmogorov-Smirnov test).
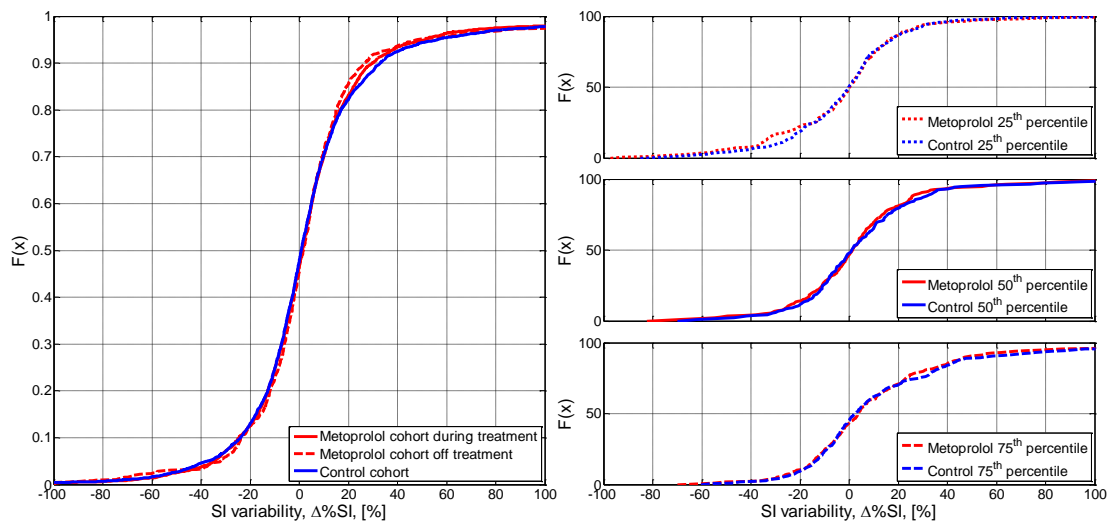
Figure 8.4. CDFs of *SI* hour-to-hour variability for the control and metoprolol cohorts. The left panel shows the overall cohort comparison. The right panel shows the 25th-, 50th- and 75th percentile patients (top to bottom).

The variability of the metoprolol percentile patients was not very different from the controls. Differences in the 90% ranges were 12%, 12% and -8% for 25th-, 50th- and 75th percentile patients, respectively. The negative value indicates that the 90% range was smaller for the metoprolol percentile patient than the control percentile patient.

8.4 Discussion

These analyses indicate that both glucocorticoid and metoprolol administration in critically ill patients are associated with reductions in *SI* level. However, the reductions are considerably less than those reported by studies on healthy subjects. Additionally, there is an increase in hour-to-hour variability of *SI* associated with glucocorticoid use, but not with metoprolol.

8.4.1 Glucocorticoids

Both cohort and percentile patient analyses indicate reductions in *SI* associated with glucocorticoid treatment of 17-33%. These values are significantly less than the 30-62% reductions in insulin sensitivity reported in healthy subjects [Binnert et al. 2004; Larsson & Ahren 1996; Nicod et al. 2003; Pagano et al. 1983; Perry et al. 2003]. Differences in steroid dosages are unlikely to be responsible for the disparity, as the patients in this study received higher equivalent daily doses than the healthy subjects in the published studies referenced.

The dosage and particular drug received by patients in this study varied between individuals and over the course of treatment. However, over the entire cohort the median daily dose of glucocorticoid was equivalent to 200 mg/d (IQR: 80-200 mg/d) of hydrocortisone per patient. In contrast, healthy subjects in the published studies [Binnert et al. 2004; Nicod et al. 2003; Pagano et al. 1983; Perry et al. 2003] were administered either 2 mg/d of dexamethasone, equivalent to 50 mg/d of hydrocortisone [Binnert et al. 2004; Nicod et al. 2003; Perry et al. 2003], or 15 mg/d of prednisone, equivalent to 60 mg/d of hydrocortisone [Pagano et al. 1983]. Larsson and Ahren [1996] reported a 54% reduction in insulin sensitivity with 6 mg/d dexamethasone (equivalent to 150 mg/d hydrocortisone). Hence, the results of this study show lower reductions in *SI* compared to results reported for healthy individuals, despite glucocorticoid doses that are 1.3-4.0 times larger. This result indicates a significantly reduced impact of glucocorticoids on insulin sensitivity in the critically ill.

In addition to the reduced *SI* level, a 27-50% increase in hour-to-hour variability was also associated with glucocorticoid treatment. However, there are no known

published studies investigating the effects of glucocorticoids on *SI* variability with which to compare these results.

Although a great deal of research has been conducted on the effects of glucocorticoids on insulin sensitivity, very little is known about the specific mechanisms of action. Glucocorticoids reduce insulin sensitivity directly, as well as disrupting glucose metabolism at the liver, pancreas and peripheral tissues. Several studies have indicated that decreased cellular glucose uptake is at least partly responsible [Pagano et al. 1983; Paquot et al. 1995; Tappy et al. 1994]. Impaired intracellular glucose oxidation has also been shown to have a role in glucocorticoid induced insulin resistance [Paquot et al. 1995; Tappy et al. 1994]. In addition, endogenous glucose production is enhanced by glucocorticoids [Besse et al. 2005; Binnert et al. 2004; Nicod et al. 2003; Pagano et al. 1983], possibly through their enhancement of the synthesis and action of catecholamines [Barth et al. 2007; Paquot et al. 1995; Rizza et al. 1980; Taylor & Hancox 2000].

Delaunay et al. [1997] and Lambillotte et al. [1997] showed that glucocorticoids suppress insulin secretion through a direct action on the pancreatic β-cells. However, the results from Binnert et al. [2004], Besse et al. [2005] and Nicod et al. [2003] show a clear increase in glucose-induced insulin secretion after administration of dexamethasone. It is possible that there are competing pathways with the net effect depending upon specific physiological conditions.

In summary, the elevated levels of counter-regulatory hormones often present in critically ill patients [Bessey & Lowe 1993; Mizock 2001] may cause saturation of the physiological impact of these agents. For example, the increased endogenous glucose production associated with glucocorticoids may be blunted as EGP is often already significantly enhanced in critically ill patients. Healthy individuals, in contrast, typically have much lower levels of circulating catecholamines and cortisol. Therefore, they may show more significant reductions in *SI* and increases in EGP with additional, exogenous glucocorticoids than critically ill patients.

8.4.2 Metoprolol

Both cohort and percentile patient analyses indicate changes to *SI* associated with metoprolol treatment ranging from a 5% increase to a 10.5% decrease, compared with controls. These values are significantly less than the 14-27% reductions in insulin sensitivity due to metoprolol, when used to treat essential hypertension in otherwise healthy individuals [Jacob et al. 1996; Pollare et al. 1989]. A similar study in hypertensive subjects with non-insulin dependent diabetes mellitus [Falkner & Kushner 2008] reported a statistically non-significant 2% reduction in insulin sensitivity associated with metoprolol. Differences in metoprolol dosages are unlikely to be responsible for the disparity as the patients in this study received similar daily doses to the healthy subjects in the previously published studies.

The dosage received by patients in this study varied between individuals and over the course of treatment. However, over the entire cohort the median daily dose of metoprolol was 100 mg/d (IQR: 50-200 mg/d). This dose range is comparable to the doses of 200, 100 and 50-200 mg/d administered in the studies by Pollare et al. [1989], Jacob et al. [1996] and Falkner et al. [2008], respectively. Hence, the reduction in impact of metoprolol on *SI* is unlikely to be a result of the dosing.

In the study by Falkner et al. [2008], metoprolol was added to the participants' existing hypertension treatment regime. Studies have indicated that these other hypertension treatments; angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs), lead to improved insulin sensitivity [Lithell 1992; Perkins & Davis 2008]. Therefore it is possible that reductions in insulin sensitivity associated with metoprolol were mitigated by increases in insulin sensitivity due to the concomitant use of ACE-inhibitors and ARBs, resulting in no significant change, as reported by Falkner et al. [2008].

The mechanisms by which β-adrenoceptor antagonist treatment (β-blockade) modifies insulin sensitivity are not fully understood. Both Pollare et al. [1989] and Jacob et al. [1996] suggest a possible haemodynamic explanation for the

reduced insulin sensitivity. The reduced heart-rate and contractility caused by metoprolol lowers blood flow to the skeletal muscles. Thus, there is lower glucose availability to these prime target tissues for glucose disposal at given insulin levels [Jacob et al. 1996; Pollare et al. 1989], and an apparent reduction in insulin sensitivity, as defined by the rate of insulin mediated glucose uptake. Jacob et al. [1996] also suggest that β-blockade appears to reduce insulin clearance rates and the resulting hyperinsulinaemia may down-regulate insulin receptors, directly lowering insulin sensitivity. The actual mechanism of action may be a combination of these factors or an as yet unidentified pathway.

As discussed in Section 8.4.1, the critical condition of the patients in this study may moderate the physiological impact of the proposed mechanisms of action attributed to metoprolol. Critically ill patients already have significant peripheral insulin resistance [Black et al. 1982] and may thus be less likely to show further large reductions caused by reduced blood flow or receptor down-regulation compared to healthy subjects. This saturation of the physiological effect may explain the limited reduction of *SI* in critically ill patients seen in this study, compared with 'healthy' individuals.

8.4.3   Impact of drug therapies on *SI* and outcome glycaemia

The results presented in this study indicate that metoprolol is associated with a small effect on the insulin sensitivity of critically ill patients, but it is unlikely to be clinically significant. The 17-33% reduction in *SI* level and increased variability associated with glucocorticoids is clinically significant and large enough to warrant measures to mitigate these changes on outcome glycaemia.

The primary use of this glucose-insulin system model is enabling model-based tight glycaemic control in critical care. In this context, increased variability and lower levels of *SI* greatly increases the insulin required to maintain blood glucose concentrations in a desired band. High levels of circulating insulin coupled with the observed variability in insulin sensitivity result in increased glycaemic variability and an increased risk of hypoglycaemia. Importantly, glycaemic variability and hypoglycaemia have been associated with poor

outcomes in the ICU [Egi et al. 2006; Egi et al. 2010; Hermanides et al. 2010; Krinsley 2008].

The 17-33% reductions in *SI* level and 27-50% increases in *SI* variability associated with glucocorticoids are of similar magnitude to the changes seen over the first few days of ICU stay reported in Chapter 7. Therefore, the two measures proposed in Chapter 7 are also applicable to reducing the variability of outcome glycaemia for patients receiving glucocorticoids.

Intervention-based methods rely on adapting the control protocol to minimise the impact of *SI* variability. Greater blood glucose measurement frequency and conservative insulin dosing can lower the impact of *SI* variability on glycaemia and risk [Lonergan et al. 2006]. Modulation of carbohydrate nutrition, within limits [Krishnan et al. 2003], can also reduce the need for exogenous insulin to better manage glycaemia [Suhaimi et al. 2010].

Model-based methods, employing separate stochastic models where *SI* level and variability are atypical were also proposed. Separate models would allow the controller to capture this behaviour and titrate insulin and nutrition accordingly. Results from this investigation suggest that an additional stochastic model to the three proposed in Chapter 7 be generated for patients receiving glucocorticoid treatment.

The limited reduction in *SI* seen in this investigation is thought to result from the saturation of the physiological impact of endogenous cortisol and the catecholamines due to elevated levels in critical illness. The impact of exogenous glucocorticoids on *SI* during the acute phase of critical illness (0-24 hours) may thus be further reduced. Hence, a single additional stochastic model for use more than 24 hours after ICU admission, while receiving glucocorticoids, is likely sufficient.

8.5   Summary

The results presented in these analyses indicate that two drug therapies, relatively common to the ICU, have less impact on *SI* in critically ill patients than would be presumed from published studies on healthy subjects. Treatment with glucocorticoids was associated with 17-33% reductions in *SI* level, significantly less than the 30-62% reductions in insulin sensitivity reported in healthy subjects. In addition to the reduced *SI* level, glucocorticoid treatment was also associated with 27-50% increased hour-to-hour variability.

Treatment with metoprolol was associated with changes to *SI* level ranging from a 5% increase to a 10.5% decrease compared with the control cohort. These values were also less than the 14-27% reductions reported for otherwise healthy, hypertensive subjects. At the levels observed in this study, the effects of metoprolol on *SI* are unlikely to be clinically significant in critically ill patients.

The limited reductions in *SI* observed in these analyses may be due to the saturation of the physiological impact of glucocorticoids and metoprolol in critically ill patients. Critically ill patients already have significant peripheral insulin resistance, and other metabolic changes captured by the *SI* parameter and may therefore be less likely to show further large reductions caused by these drugs in healthy subjects.

To manage the extrinsic *SI* variability associated with glucocorticoid treatment, and reduce the impact on outcome glycaemia, the two methods described in Chapter 7 are applicable. A single additional stochastic model for use more than 24 hours after ICU admission, while receiving treatment, would permit control algorithms to mitigate the effects. Additionally, intervention-based measures such as greater blood glucose measurement frequency, conservative insulin dosing and modulation of carbohydrate nutrition can lower the impact of *SI* variability on glycaemia and risk.

Chapter 9. Measurement Errors

The final source of extrinsic *SI* variability investigated in this thesis results from errors in blood glucose measurement timing and concentration. These factors can alter the identified values of *SI*, which in turn may impact glycaemic variability during control.

9.1   Introduction

In the busy ICU environment, blood glucose measurements are rarely taken at the exact, scheduled time during glycaemic control. Sensor errors add uncertainty to measured BG concentration. Both errors propagate through to the value of *SI* during parameter identification and impact overall *SI* variability.

SI variability from timing error can affect glycaemic control through the stochastic models in two ways. Stochastic models are currently built with data from the SPRINT tight glycaemic control study [Chase et al. 2008]. The maximum resolution for measurement data during SPRINT was one hour. Therefore, any discrepancies between scheduled and actual measurement times smaller than one hour are unknown and can impact the level and variability of *SI*, and thus, the form of the resulting stochastic model.

The one-hour resolution of SPRINT necessitates a corresponding resolution for stochastic models derived from the data. Thus, while the more recent, computerised and model-based, STAR protocol [Evans et al. 2011] records more accurate measurement times, the interventions are determined by 1, 2 and 3 hour forward prediction of BG, based on the stochastic models derived from SPRINT. Therefore, if measurements are not performed at the scheduled time, the likelihood of achieving the predicted BG concentration is reduced, particularly for infused insulin, where the total insulin administered is time dependant.

Even with perfect timing, BG measurement errors also affect the identified values of *SI*. Typical point-of-care glucometers have measurement errors in the

range 2-10% [Abbott 2010; Arkray 2007; Roche 2007,2008; Solnica et al. 2003]. The glucometer used in the Christchurch Hospital ICU (Super-Glucocard II, Arkray Inc., Japan) typically has an error of less than 10% [Arkray 2007]. The uncertainty in BG concentration resulting from sensor error impacts the identified values of *SI* through altering the glucose flux that must be balanced by the insulin-mediated glucose disposal term in the glucose-insulin system model.

The objective of this investigation was to assess the impact of both measurement timing and sensor error on *SI* variability. Having quantified the impact on *SI*, decisions could be made about whether means to reduce the magnitude of these errors, such as improved BG sensors, are necessary for improved control or safety. Equally, existing or new protocols might be optimised to be robust in the face of these errors.

9.2   Subjects and Methods

9.2.1   *Patients*

This study was conducted as retrospective analyses of data from 270 patients admitted to the Christchurch Hospital ICU between 2005 and 2007. All patients were on the SPRINT protocol for at least 24 hours [Chase et al. 2008]. Table 9.1 shows a summary of the cohort details.

Table 9.1. Cohort details summary. Data are shown as median [interquartile range] where appropriate.

N	270
Age (yrs)	65 [49-73]
Gender (M/F)	165/105
Operative/Non-operative	104/166
Hospital mortality (%)	27%
APACHE II score	19 [16-25]
APACHE II ROD (%)	30 [17-53]
Diabetic status (T1DM/T2DM)	10/34
ICU length of stay (hrs)	160 [77-346]

The Upper South Regional Ethics Committee, New Zealand granted approval for the audit, analysis and publication of this data.

9.2.2 Error modelling

9.2.2.1 Timing error

Measurements and interventions during the SPRINT protocol were 1 or 2-hourly and intended to be taken on the hour. These measurements were recorded by hand and attributed to the nearest hour on the standard paper 24-hour charts used in the Christchurch Hospital ICU. Hence, any discrepancies between the actual measurement time and the 'nearest hour' were lost.

Recent pilot trials of the STAR protocol at Christchurch Hospital ICU [Evans et al. 2011] provide data to generate a timing error model (1651 measurements on 20 patients). Measurements and interventions during STAR are designed to be 1, 2 or 3-hourly, as selected by clinical staff. However, because the protocol is implemented on a tablet computer, the exact time when BG measurements are entered is recorded. Using the discrepancies between scheduled and actual BG measurements, a model of timing error can be generated and applied to data from the SPRINT protocol. Although the STAR protocol is different to SPRINT, particularly with its computerised interface, it is used by the same clinical staff, in the same unit. Hence, it may be assumed that timing errors in making measurements will be similar.

From the STAR data, a vector of timing errors was extracted for each measurement interval. There were 765 one-hour measurement error values, with a mean value of -0.5 minutes. The two and three-hour errors (886 errors) were combined and applied to the SPRINT 2-hour measurements. These values had a mean value of +0.1 minutes. The low mean values indicate that the errors reflected both early and late measurements relatively equally. Errors were limited to a maximum of 20 minutes. The empirical error distributions are shown in Figure 9.1.
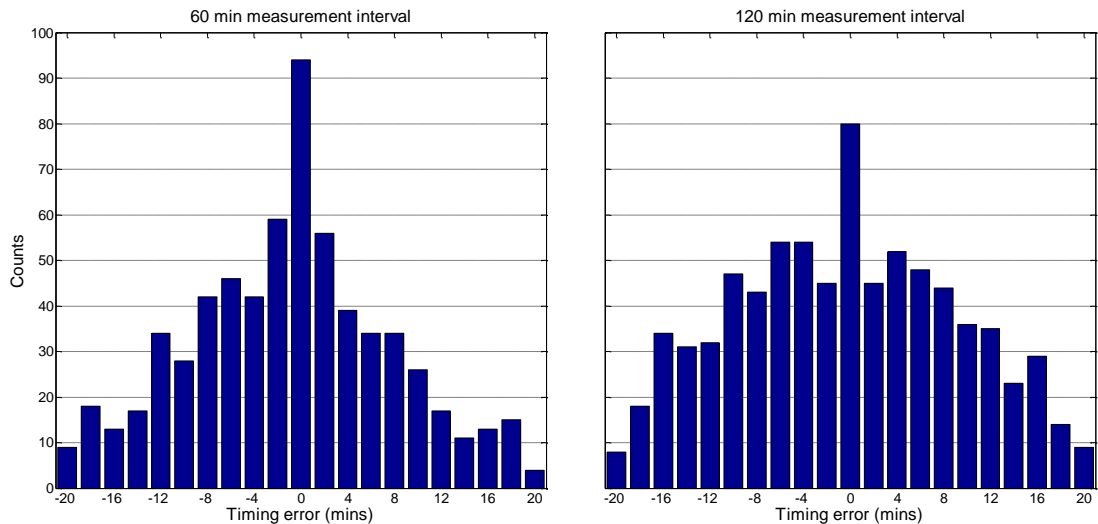
Figure 9.1. Timing error models based on data from the STAR pilot trials [Evans et al. 2011]. Errors from 1-hour measurements are shown on the left and 2-hour measurements on the right.

Errors from these distributions were applied additively to the SPRINT data by randomly sampling from the error vectors. The errors were applied to both the measurement and intervention timing. Thus, the measurements and interventions remained synchronised, as they would in the hospital.

9.2.2.2 BG sensor error

Sensor error consists of two components that vary independently, depending on the BG concentration being assayed. Bias is an offset defined as the difference between the mean of a set of measurements from a single sample and the reference value. Precision defines the spread of measured values about the mean and is often reported as a coefficient of variation (CV = standard deviation/mean).

Bias was determined from the correlation data reported for the glucometer test strips, [Arkray 2007] and was therefore known at all BG concentrations. Precision was reported at three BG concentrations, 4.3, 6.9 and 21.0 mmol/L. For this analysis, the CV was interpolated for BG concentrations within the reported range and held constant outside this range. These data were used to construct an

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additive error model for the glucometer used in this investigation. Table 9.2 presents the bias and precision components for a range of glycaemia.

Table 9.2. Error components of the Arkray Super-Glucocard II glucometer [Arkray 2007].

Blood glucose (mmol/L)	2.0	4.3	6.9	10.0	21.0	30.0
Bias (%)	+7.9	+2.1	+0.2	-0.8	-2.0	-2.3
Precision, CV (%)	3.5	3.5	2.8	2.8	2.7	2.7

The data used in the study was collected by trained clinical staff, minimising the potential for additional error through device misuse [Bergenstal 2008]. Blood samples tested were typically arterial, although, when an arterial line was not present, capillary blood was used.

9.2.3 Analyses

To assess the effects of random timing and sensor errors on *SI*, Monte Carlo simulations were performed. The *SI* profile of each patient in the cohort was refitted 100 times with randomly sampled errors applied to the observed timing and BG concentrations. The *SI* profiles identified without additional random errors were thus considered the 'true' profiles, and the Monte Carlo profiles were compared to these to assess their impact. Comparisons of both *SI* level and hour-to-hour variability were made.

Three separate sets of Monte Carlo simulations were performed for this analysis. Each set had either BG sensor error, timing error or both applied to the SPRINT data. *SI* level and variability of the simulated data were compared to the true data to assess the impact of each of the sources of error, both individually and combined.

To facilitate comparisons when timing errors were applied, *SI* was identified in 60-minute intervals, rather than between BG measurements. This use of fixed, 60-minute fitting intervals is consistent with the methodology used for glycaemic control by the STAR protocol.

9.2.3.1 SI level analyses

To analyse the impact of errors on the identified *SI* level, the variation induced by the simulated errors at each hour was compared. To characterise the distribution of differences in *SI* level at each hour, between the true and simulated profiles, the width of the IQR was used. Figure 9.2 illustrates the methodology for *SI* level comparisons between the n = 100 Monte Carlo simulations and the true data.

This analysis method resulted in one 'IQR width' per patient hour. For the 270 patient SPRINT cohort, there were 47120 hours of data. These 47120 IQR widths were presented as cumulative distributions to show the overall effect of the errors on the cohort.
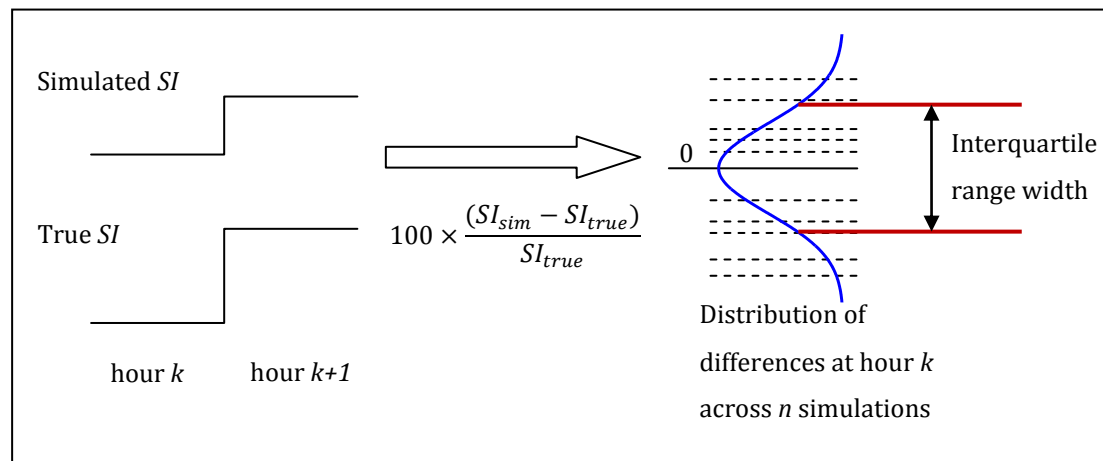
Figure 9.2. *SI* level comparison method for the Monte Carlo simulations with added sensor and timing error. The width of the IQR of differences, expressed as percentages, was used to characterise the variability in level induced by the errors.

9.2.3.2 SI variability analyses

The hour-to-hour variability of simulated data could not be compared to the true variability using ratios, as the variability distribution of any given patient was

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centred on approximately zero. Therefore, many values are close to zero, causing any comparison ratio to approach zero or infinity, providing an effectively meaningless metric. Hence, another method of comparison was necessary.

For any given patient and hour, the median *SI* variability across the (n = 100) Monte Carlo simulations was approximately equal to the true value. This equivalence is a consequence of the approximately zero-mean error distributions and a large number of Monte Carlo simulations. This fact was utilised to characterise the variability of the variability as the IQR width for each hour, across the n = 100 Monte Carlo simulations, without explicit comparison to the true value. Hence, the *SI* variability analysis data can be interpreted in a similar way to the level analysis.

A comparison to the actual variability is provided by the distribution of 'ΔMedian *SI*.' For any given hour, this metric is defined as the difference between the median hour-to-hour variability (%), across the simulations, and the actual value (%). Typically, the distribution was tightly centred about zero, justifying the use of simulation IQR width without explicit reference to the actual variability.

9.3   Results and Discussion

9.3.1   Timing error

Figure 9.3 shows the impact of timing errors on identified *SI* level (left panel) and variability (right panels). For 95% of hours, the IQR width of *SI* level was less than 12.4%. Thus, for those 44334 hours, half the simulations resulted in *SI* values within approximately ±6.2% of the true value, assuming a symmetrical distribution. Similarly, for variability, 95% of hours had an IQR width of hour-to-hour changes of less than 17.8%, or ±8.9% about the simulation median. The top right panel of Figure 9.3 shows the simulation median was typically very close to the true value for variability, justifying the assumptions made.
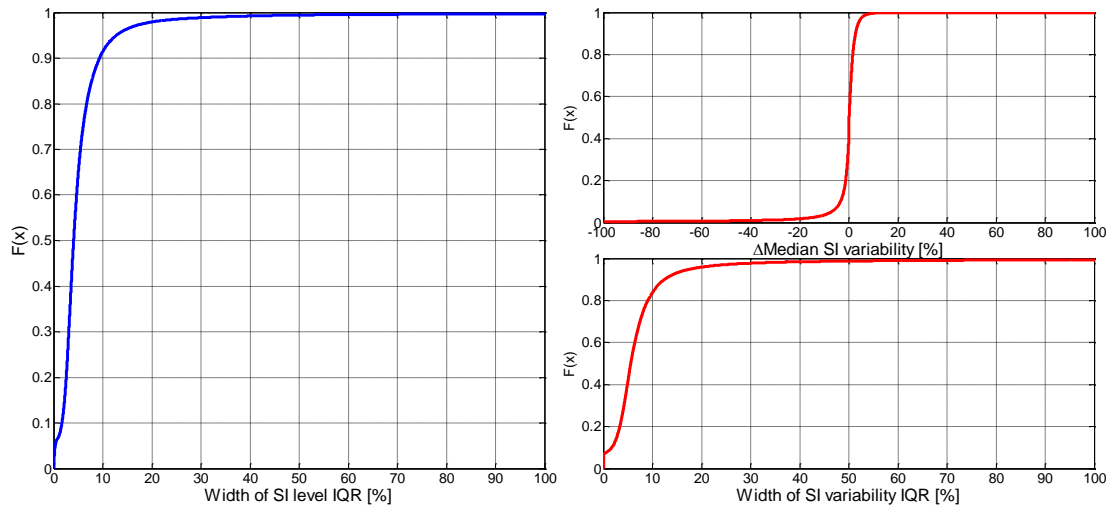
Figure 9.3. The impact of timing error on *SI* level (left panel) and variability (right panels), characterised by the variability of these parameters determined by Monte Carlo simulation. The panels on the right show the location of the median simulated variability, compared to the actual (top) and the variability about that median (bottom).

These results suggest that typical timing errors in isolation have limited impact on the level and variability of *SI*. With a median absolute difference between the simulated and actual measurement intervals of 9 minutes and using bolus insulin delivery, this result is not too surprising. Unlike infused insulin, bolus delivery ensures that the entire prescribed dose is always administered, regardless of the time between measurements. In addition, timing discrepancies only affect the later parts of the interstitial insulin profile, where concentrations are lowest and thus contribute least to the area under the curve used in fitting *SI* [Hann et al. 2005].

9.3.2 Blood glucose measurement error

Figure 9.4 shows the impact of BG sensor errors on *SI* level (left panel) and variability (right panels). The variability induced in both *SI* level and variability is greater than that due to timing error. The increases at the median values for level and variability compared to timing error of Figure 9.3 were 4.9% and 2.2%, respectively ($p = 0$, Wilcoxon rank-sum test). However, with so many data points, a statistically significant difference is almost guaranteed.
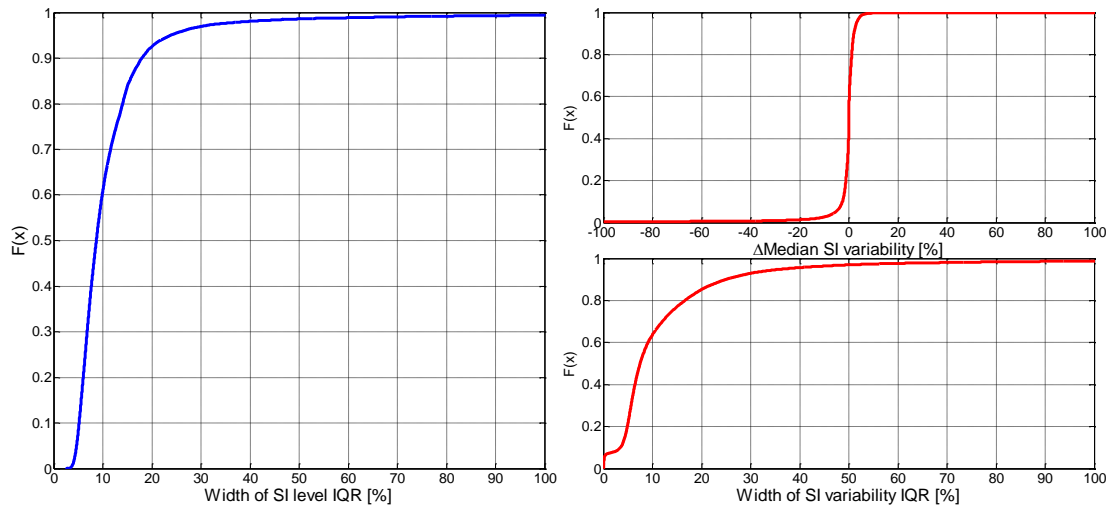
Figure 9.4. The impact of BG sensor error on *SI* level (left panel) and variability (right panels), characterised by the variability of these parameters determined by Monte Carlo simulation. The panels on the right show the location of the median simulated variability, compared to the actual (top) and the variability about that median (bottom).

The effect of the sensor bias is evident in the minimum value of the level IQR seen in the left panel of Figure 9.4. The minimum value was 2.7%. This non-zero minimum value was not present with the zero-mean timing error simulations of Figure 9.3.

9.3.3   Combined measurement error

Figure 9.5 shows the impact of the combined timing and BG sensor errors on *SI* level (left panel) and variability (right panels). The previous two sections have characterised the individual contributions of timing and sensor error. This analysis combines them, simulating errors seen in the real, clinical situation.

For 95% of hours, the IQR width of *SI* level was less than 23.9%. Thus, assuming a symmetrical distribution, half the simulations resulted in *SI* values within approximately ±12% of the true value. Similarly for variability, the 95th percentile was 34.9%, indicating that for half the simulations the hour-to-hour variability of *SI* was within ±17.5%.
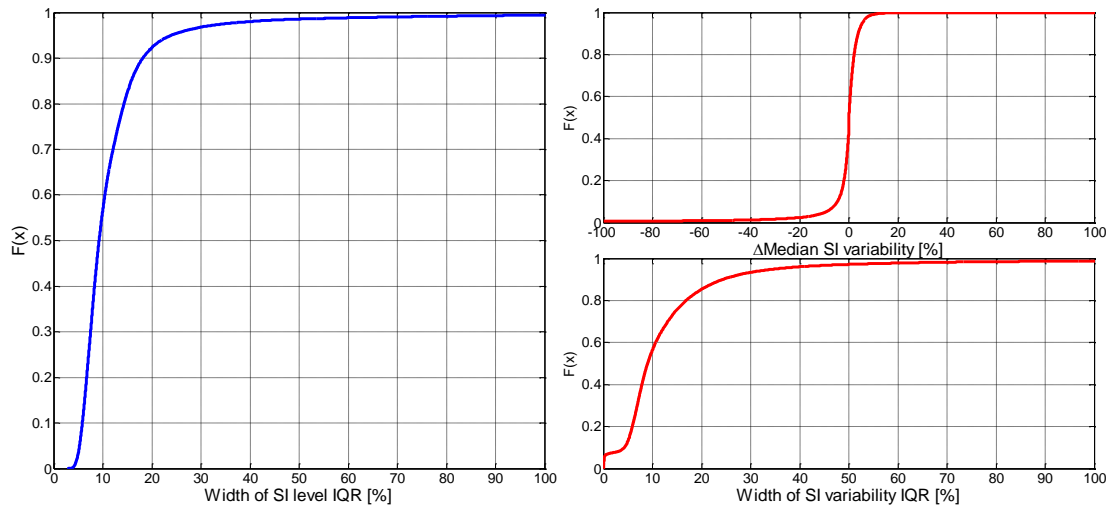
Figure 9.5. The impact of combined timing and BG sensor error on *SI* level (left panel) and variability (right panels), characterised by the variability of these parameters determined by Monte Carlo simulation. The panels on the right show the location of the median simulated variability, compared to the actual (top) and the variability about that median (bottom).

9.3.4 Implications of results

The clinical impact of changes to *SI* level induced by sensor and timing errors is likely to be limited. Given the hour-to-hour variability and longer-term evolution of *SI* in critically ill patients discussed in the previous chapters, deviations from the true *SI* caused by these errors are likely to be swamped by changes due to physiological variability. For example, changes in *SI* greater than 20% were seen with glucocorticoid treatment (Chapter 8) and improving patient condition over the first 18 hours of ICU stay (Chapter 7).

There is no way to reduce the impact of these errors as they are random and apply equally to all patients. The only available option is to reduce the magnitude of the errors. The timing error distribution shown in Figure 9.1 shows that more than 85% of measurements are within 10 minutes of the scheduled time, which is a very good result in a busy ICU environment. In contrast, BG sensor errors can be reduced with better, more accurate, but likely more expensive equipment.

To compare the impact of sensor errors from glucometers with a state of the art blood gas analyser (BGA), an error model was developed for the Bayer RapidLab

860 (Bayer Diagnostics, Tarrytown, NY) [2004; Peet et al. 2002]. Errors for this BGA consist of very little bias (≤ 0.06 mmol/L) and CV in the range 1.7%-4.9%, depending on BG concentration. The RapidLab 860 is used in the Christchurch Hospital Neonatal ICU [Le Compte 2009], and thus represents a realistic option for the adult ICU in Christchurch. An n = 50 run Monte Carlo simulation was performed with both timing and BG sensor errors from the BGA for a basic comparison.

The results show only a minor improvement by using the BGA. The 95th percentile of IQR widths reduced from 23.9% to 21.0% and from 34.9% to 30.2% for level and variability, respectively. These limited improvements hardly warrant investing NZ$50,000-100,000, plus per-sample costs [Pearson et al. 2006], for the device, solely for BG measurement.

The cause of the close results between glucometer and BGA appear surprising. They may be due to the relatively low reported errors of the glucometer. Data for the error model was taken from the manufacturer's data-sheet [Arkray 2007]. However, a published report [Solnica & Naskalski 2005] failed to recreate these results, possibly due to user error, sample type, abnormal hematocrit or interfering substances [Bergenstal 2008].

In contrast to *SI* level, the increase in hour-to-hour variability may be clinically significant. The relatively large, ±17.5%, range of variability about the median caused by errors, indicates that much of the IQR of a stochastic model at a given *SI* level may be dominated by these errors, rather than physiological variability. Hence, to avoid inadvertently basing control decisions on this artificial variability, the 5-95 range of the stochastic model should be used. *SI* values at these more extreme percentiles are less likely to be influenced by random sensor or timing errors.

A second potential clinically significant impact is on analytical use of *SI* as a marker of injury or change in state. Much of the true hour-to-hour change of this SPRINT cohort was smaller than the variability induced by sensor and timing

errors. The IQR of true hour-to-hour variability across the entire cohort was -9.7% to 13.9% and 63% of all values lay in the range ±17.5%. Thus, using changes in *SI* level as a diagnostic must be done with caution, potentially looking at longer-term trends, where the effects of random errors may be cancelled by averaging over time.

9.4   Summary

The objective of this chapter was to assess and quantify the impact of typical timing and BG sensor errors on the level and variability of model-based *SI*. Specifically, the variability of level and the variability of *SI* hour-to-hour variability were investigated under the influence of these sources of error, both separately and combined. Measurement timing errors were shown to have a relatively small impact on the *SI* parameter. The BG concentration errors of the Arkray glucometer had a larger effect on *SI* and tended to dominate the combined analysis.

The results of this study indicate that the impact of errors on *SI* level is unlikely to be clinically significant and probably swamped by physiological factors arising from the critical condition of the patients. In contrast, the impact of errors on hour-to-hour *SI* variability is more pronounced and may impact the way the *SI* parameter is utilised for control and analysis.

This analysis indicated that for a given *SI* level, variability induced by errors might dominate the IQR of the probability density function describing *SI* for the subsequent hour. Hence, to avoid inadvertently basing control decisions on this artificial variability, the 5-95 percentile range of the stochastic model should be used. In addition, using changes in *SI* level as a diagnostic must be done with caution, potentially looking at longer-term trends, where the effects of random errors may be cancelled by averaging over time.

Given the random nature of these errors, the only feasible method of mitigation is to use BG sensors with smaller errors. However, a comparison with results

from a state of the art, clinical blood gas analyser showed that the limited improvement in performance probably doesn't justify the significantly increased cost of the device. However, understanding the effect of sensor and timing errors on *SI* allows their impact to be taken into account when using the parameter for control and analysis.

Chapter 10.   Model Validation

Having enhanced the model to reduce intrinsic variability and proposed means to mitigate the effects of extrinsic variability of *SI*, these developments must be validated. The validation is conducted in two stages, described in the following two Chapters. This Chapter presents the validation of the model itself and thus its suitability for 'virtual trials' following the changes to reduce intrinsic variability of *SI*.   Chapter 11 validates the proposals to mitigate extrinsic variability by analysing the outcomes of a (validated) virtual trial.

10.1   Introduction

The key parameter of the ICING-2 model is *SI*, characterising the whole-body glycaemic response to exogenous insulin and glucose inputs over time. In an effective glucose-insulin system model, *SI* permits accurate fitting and forward prediction of blood glucose, while being independent of the insulin and glucose inputs used to identify it. These characteristics enable successful model-based glycaemic control in clinical real-time. In addition, an accurate *SI* profile over time that is independent of exogenous inputs can be used in 'virtual trials' to enable rapid testing of new glycaemic control protocols and analysis of existing protocols in different clinical or implementation scenarios.

In this study, validation of the ICING-2 model is carried out in two parts. First, BG fitting and one-hour-ahead prediction performance is assessed to validate *SI* for forward prediction in control decision-making. The second part is a self- and cross- validation analysis between two separate, clinically matched cohorts, indicating the suitability of the model and independence of *SI* to insulin and nutritional inputs.

This validation is performed on clinically matched cohorts based on clinical data from an ICU independent to that used in the development of the model. The cohorts used for validation are a subset of the Glucontrol trial from Liege, Belgium [Preiser et al. 2009]. These cohorts were treated with two different

glycaemic control protocols. The independence of the ICU ensures a cohort that may be different in treatment, insulin sensitivity or other factors [Suhaimi et al. 2010] from patients in the Christchurch ICU whose data underlie the development of the models and methods validated in this study [Chase et al. 2007; Lin et al. 2011].

The objective of this study is to validate the ICING-2 model for clinical glycaemic control and 'virtual trial' purposes. The validation is performed by assessing the BG fitting and forward prediction, as well as self and cross-validation performance on cohorts independent to those on which the model was developed. In effect, this study is an updated version of that conducted by Chase et al. [2010], using the ICING-2 model instead. Hence, the overall validation approach has previously been published, and this work focuses solely on model validation.

10.2 Subjects and Methods

10.2.1 Patients

Data was used from a subset of the 350 patients treated using the Glucontrol protocol at CHU de Liege, Belgium, between March 2004 and April 2005. Thus, the Glucontrol data used in this study is from only one centre out of the full study, but represents approximately 25% of all patients [Preiser et al. 2009]. The Glucontrol trial randomised patients to two different protocols (A and B), each with different glycaemic targets. Patients were eliminated from this analysis if they received no insulin for their entire stay (per protocol), had less than 5 BG measurements or received little or no (recorded) carbohydrate administration (in any form) for more than 48 hours of their stay. Of the 350 patients enrolled in both arms of the study in Liege, 211 were included in this analysis.

Clinical details of the resulting cohorts are shown in Table 10.1 and Table 10.2 totalling 29,777 hours and 7,391 BG measurements. Patients in Population A were slightly older than Population B. However, there were no significant differences in sex, weight, BMI, severity of illness as measured by APACHE II

score, or initial BG level. Population B received less insulin and more carbohydrate, in alignment with its higher glycaemic target.

Table 10.1. Glucontrol cohort characteristics. Data are shown as median [interquartile range] where appropriate. P-values were calculated using the Chi-squared test and Wilcoxon rank-sum test.

	Population A	Population B	P-value
N	142	69	
Gender (M/F)	92/50	39/30	0.25
Age (years)	71 [61 – 80]	69 [53 – 77]	0.035
Weight (kg)	72 [62 - 85]	75 [68 - 81]	0.38
BMI	25.4 [22.6 –29.3]	26.0 [23.2 - 29.3]	0.46
APACHE II score	17 [14 – 22]	17 [14 – 21]	0.76
Initial BG (mmol/L)	6.6 [5.6 – 8.6]	6.6 [5.7 – 9.4]	0.58

Table 10.2. Clinical glucose control characteristics. Data are shown as median [interquartile range] where appropriate.

	Population A	Population B
Total hours	16, 831	12, 946
Length of treatment (hrs)	68 [38 - 138]	89 [43 – 229]
BG measurements	4, 571	2, 820
BG (mmol/L)	6.3 [5.3 – 7.6]	8.2 [6.9 – 9.4]
BG target band (mmol/L)	4.4 - 6.1	7.8 - 10.0
Insulin rate (U/hr)	1.5 [0.5 – 3.0]	0.7 [0.0 – 1.7]
Carbohydrate admin (all sources) (mmol/min)	0.30 [0.00 – 0.90]	0.60 [0.10 – 1.00]

This validation is performed on cohorts matched for overall clinical parameters. The clinical data is from an ICU independent to that used in the development of the ICING-2 model. These cohorts were treated with two different glycaemic control protocols, which are also very different to that used on the development cohort. These factors ensure a cohort different in treatment, insulin sensitivity or other factors [Suhaimi et al. 2010] from patients in the Christchurch ICU whose

data underlie the development of the models and methods validated in this study [Chase et al. 2007; Lin et al. 2011].

Figure 10.1 shows the cumulative distributions of *SI* for the two cohorts. The SPRINT cohort on which the model was largely developed tends to have a lower, more variable *SI* distribution than the Glucontrol cohort (Populations A and B combined) used for validation in this study. Hence, the patients used for this model validation are not only independent from the data used to create the model, but are also metabolically different.
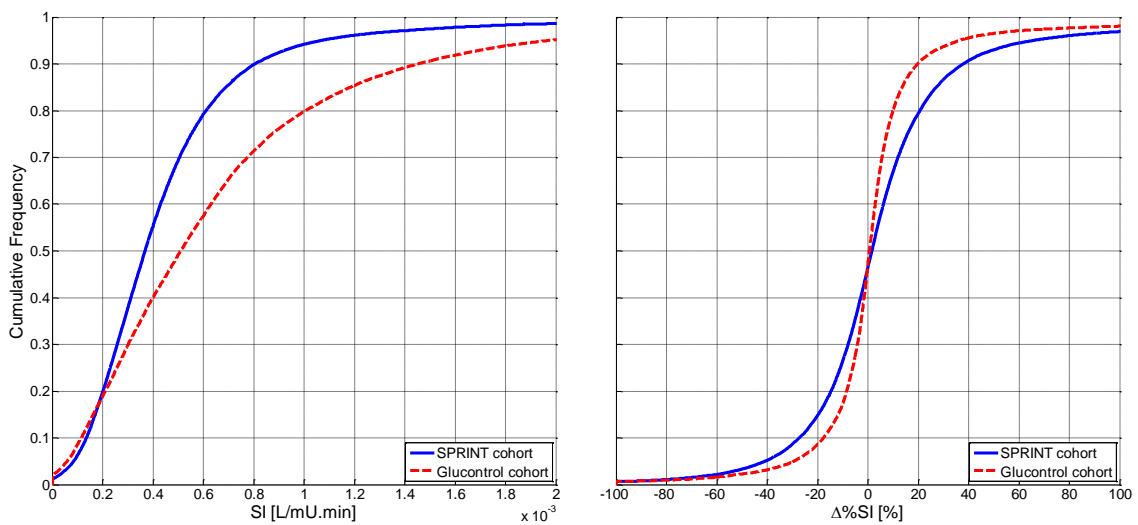
Figure 10.1. *SI* level (left panel) and hour-to-hour variability (right panel) distributions of SPRINT and Glucontrol patients.

10.2.2 Glucontrol protocols

The Glucontrol trial [Preiser et al. 2009] randomised patients into two groups: Populations A and B. Population A received intensive insulin therapy and Population B received conventional insulin therapy, with target ranges of 4.4-6.1 mmol/L and 7.8-10.0 mmol/L, respectively. Insulin was administered by continuous intravenous (IV) infusion.

The protocol specified insulin infusion rates are shown in Table 10.3 for the intensive protocol used on Population A, and Table 10.4 for the conventional protocol used on Population B. Nutritional input was left to local and/or clinician

standards, and was not explicitly considered in the Glucontrol glycaemic control protocols [Suhaimi et al. 2010].

Table 10.3. Glucontrol A protocol. The starting insulin infusion rate is shown in the top part of the table. The maintenance infusion rates or increments are shown in the lower part. All values have been converted to mmol/L from mg/dL.

STARTING INSULIN INFUSION RATE SCALE	
Glycaemia	Insulin infusion rate
< 6.1 mmol/L	On hold
6.1 – 7.8 mmol/L	1 U/hr
7.8 – 10.0 mmol/L	2 U/hr
> 10.0 mmol/L	4 U/hr
MAINTENANCE INFUSION RATE CHANGES	
Glycaemia	Incremental insulin infusion rate
> 16.7 mmol/L	+ 3 U/hr
10.0 – 16.7 mmol/L	+ 2 U/hr
7.8 – 10.0 mmol/L	+ 1 U/hr
6.1 – 7.8 mmol/L	+ 0.5 U/hr
4.4 – 6.1 mmol/L	+ 0 U/hr (target range)
2.2 – 4.4 mmol/L	Stop insulin, Hourly measurement of glycaemia until > 4.4 mmol/L
< 2.2 mmol/L	Stop insulin, 10gr glucose IVD, Call physician immediately, Hourly measurement of glycaemia until > 4.4 mmol/L

Table 10.4. Glucontrol B protocol. The starting insulin infusion rate is shown in the top part of the table. The maintenance infusion rates or increments are shown in the lower part. All values have been converted to mmol/L from mg/dL.

STARTING INSULIN INFUSION RATE SCALE	
Glycaemia	Insulin infusion rate
< 10.0 mmol/L	On hold
10.0 - 13.9 mmol/L	1 U/hr
13.9 - 16.7 mmol/L	2 U/hr
> 16.7 mmol/L	4 U/hr
MAINTENANCE INFUSION RATE CHANGES	
Glycaemia	Incremental insulin infusion rate
> 16.7 mmol/L	+ 3 U/hr
13.9 - 16.7 mmol/L	+ 2 U/hr
10.0 - 13.9 mmol/L	+ 1 U/hr
7.8 – 10.0 mmol/L	+ 0 U/hr (target range)
4.4 – 7.8 mmol/L	Decrease 50% rate insulin
2.2 – 4.4 mmol/L	Stop insulin, Hourly measurement of glycaemia until > 4.4 mmol/L
< 2.2 mmol/L	Stop insulin, 10gr glucose IVD, Call physician immediately, Hourly measurement of glycaemia until > 4.4 mmol/L

Hourly BG measurements were taken when the glycaemic level was not within the target range. Otherwise, 2-hourly measurements were taken in the case of limited variation of glycaemia, defined as less than a 50% change from the previous glycaemia in 2-hour range. 4-hourly measurements were permitted when the glycaemic level was less than 50% of the highest glycaemia of the four last hours.

10.2.3 Fitting and prediction

To validate *SI* for forward prediction in control decision making, BG fitting and one-hour-ahead prediction errors were assessed. Model fit and prediction errors were used to show the ability of the model to fit the data and predict the expected patient state. Fitting error was calculated by solving the model equations with the identified *SI* profile and known insulin and nutritional inputs and comparing these results with the clinically measured data. Thus, fit error quantifies the ability of the model to capture the observed dynamics.

Prediction results were generated by holding *SI* constant for one hour into the future. Specifically, taking the identified value of *SI* for hour *n* and holding it constant for hour *n+1*, then simulating BG one hour into the future using recorded clinical insulin and nutritional inputs. This BG prediction was compared to clinically recorded BG or a linear interpolation between 2-hourly measurements. Prediction errors assess the ability of the model and identified parameters to predict intervention outcomes and are highly relevant for validating models used in model-based TGC [Chase et al. 2007; Kovatchev et al. 2009].

10.2.4 Self and cross-validation

As described in Chase et al. [2010], the self- and cross- validation procedures rely on the 'virtual trial' method. The *SI* profile identified from clinical data for a given patient ('virtual patient') is used to simulate the glycaemic response to other combinations of insulin and glucose inputs, specified by a different protocol. The critical assumption of a virtual trial is that the identified *SI* profiles are (largely) independent of the clinical data used to derive them.

10.2.4.1   Self-validation

Self-validation tests the ability of the in silico virtual patient modelling method to reproduce the clinical data from which a virtual cohort was derived. For the self-validation on Glucontrol A, the Glucontrol A protocol defined in Table 10.3 was simulated on Population A virtual patients. These virtual trial results were then compared to the clinical data from Population A. This step was repeated for self-validation on Glucontrol B.

Differences between clinical and virtual trial results can be attributed to model errors, and/or lack of perfect compliance in the clinical study compared with the perfect compliance and timing in silico. Hence, two self-validation virtual trials were simulated on each group considering:

- Actual measurement timing used in the clinical trials (clinical timing).
- Measurement timing strictly dictated by the protocol (protocol timing).

Because the Glucontrol protocols modify insulin incrementally, different measurement timing could significantly change dosing and thus impact the results of the virtual trials [Chase et al. 2010].

10.2.4.2   Cross-validation

Cross-validation uses the matched A and B cohorts to determine the ability of the modelling method to reproduce the clinical data on a matched, but independent, cohort. Thus, Protocol A is simulated on virtual patients derived from Population B clinical data, with results compared to clinical data from Glucontrol Population A. Similarly, Protocol B is tested on virtual patients from Population A and the results are compared to Population B clinical data.

In theory, if patients were perfectly matched in all ways, the in silico and clinical data would also match if the in silico virtual trials method were exact. Differences using large matched cohorts can thus be largely ascribed to how well the assumption holds that these virtual patient *SI* profiles are independent of the clinical insulin and nutrition inputs used to derive them. If cross-validation

results match the clinical results well, for clinically matched cohorts, then this assumption can be considered valid. Hence, this validation tests the underlying assumption of this virtual trial method.

10.3   Results and Discussion

10.3.1 Fitting and prediction validation

Table 10.5 shows the model fit and prediction errors for the Glucontrol populations. Results are shown on a cohort and a per-patient basis. Model fit error was consistent across all both groups, with median fit error ≤ 0.3%. Population B had the lowest prediction error at almost half that of population A. However, median cohort and per-patient results are considerably less than typical sensor errors of 10% (Chapter 9).

Table 10.5. Fitting and one-hour-ahead prediction errors for Glucontrol populations with ICING-2 model. Data are shown as median [interquartile range].

Population	Fit error		Prediction error	
	Cohort (%)	Patient median (%)	Cohort (%)	Patient median (%)
A	0.3 [0.1 - 0.7]	0.3 [0.2 - 0.4]	2.7 [1.1 - 5.8]	3.0 [2.2 - 4.1]
B	0.2 [0.1 - 0.4]	0.2 [0.1 - 0.3]	1.5 [0.6 - 3.3]	1.6 [1.1 - 2.2]
A+B	0.2 [0.1 - 0.6]	0.3 [0.2 - 0.4]	2.1 [0.9 - 4.6]	2.6 [1.7 - 3.6]

Fitting errors are typically very small and a result of assumptions made during the identification of *SI*. Larger values (typically > 2%) indicate instances where the model cannot fit clinical data, for instance when an identified value of *SI* should be negative (mathematically), but is constrained to a non-negative value, as discussed in Chapter 5.

Prediction errors are an assessment of the models ability to make accurate patient-specific predictions of the outcomes of known interventions. Given low fit errors, prediction error indicates whether the identified and constant model parameters are accurate. In this study, prediction error serves to validate the

model identification method [Kovatchev et al. 2009] and approach [Chase et al. 2007; Lonergan et al. 2006] used to create virtual patients and virtual trials.

10.3.2 Self and cross validation

Figure 10.1 shows the distributions of measured and simulated blood glucose on a cohort basis. The distributions show a clear separation between the Glucontrol A and B clinical results, as expected, but also for all the respective simulations using those protocols.

The Glucontrol A clinical median cohort BG value of 6.3 mmol/L agrees well with the 6.1 mmol/L medians for both the self-validation trials. The cross-validation median BG of 6.4 mmol/L is also in close agreement with the clinical result. The overall curves, and thus median and variability, are very similar.
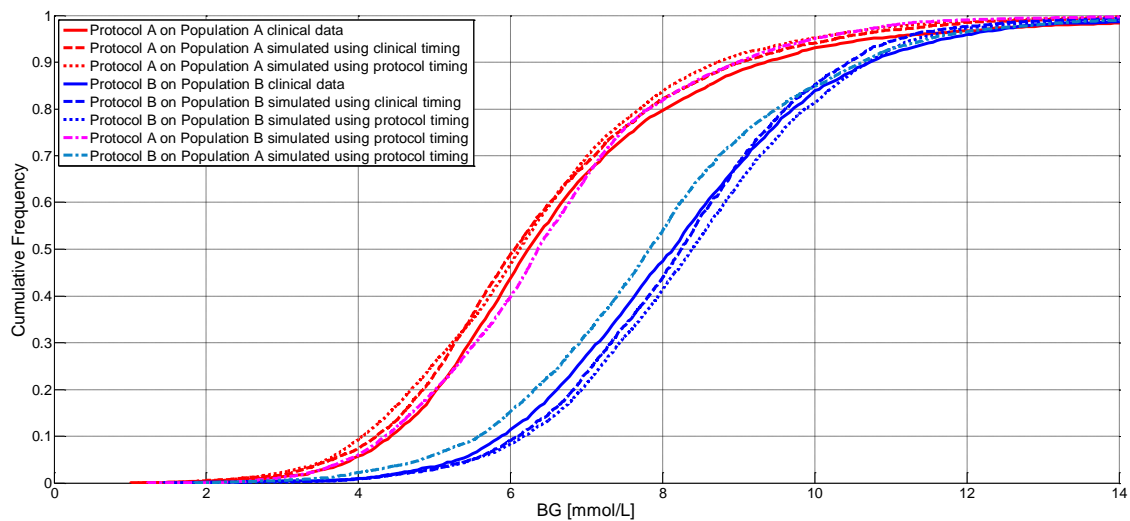
Figure 10.2. Distributions of blood glucose results of clinical Glucontrol data and virtual trials on a cohort basis.

The four BG distributions for the Glucontrol B protocol show a slightly wider spread in results, particularly below the Group B target of 8.0 mmol/L. However, the median cohort clinical BG value of 8.2 mmol/L still agrees well with the medians of 8.2 and 8.4 mmol/L for Glucontrol B self validation with clinical and per-protocol measurement frequency, respectively. It also agrees well with the cross-validation median result of 7.8 mmol/L. Overall, the curves agree very well, in general.

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For the cross-validation, Protocol A on Population B is a very good match with errors similar to the self-validation results for Population A. Protocol B on Population A is only just outside the range of the Population B self-validation, but still very close to the slope and trends of the clinical data. Thus, the insulin sensitivity independence assumption behind this virtual trials approach is valid, independently validating this concept and the virtual trial method based on this model.

Figure 10.3 shows similar results for the CDFs of the per-patient median blood glucose levels across all patients in each group. This per-patient comparison has the same whole-cohort trend seen in Figure 10.2, where the variation in BG distributions under a given protocol is significantly less than the variation between protocols. The differences between the clinical and simulated cross-validation results are more obvious in this per-patient analysis, but the median values are still within 8% of the clinical in both cases, and as with the cohort results, the slope, or variability is also similar.
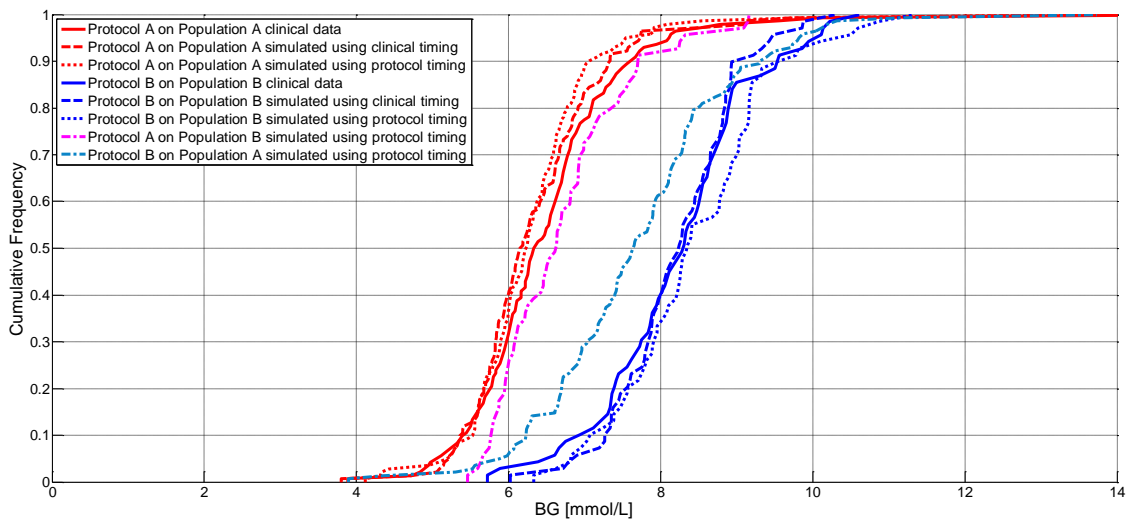
Figure 10.3. Distributions of per-patient median blood glucose results of clinical Glucontrol data and virtual trials.

Figure 10.4 presents the distributions of absolute paired differences between clinical and simulated median BG values for each patient. As expected, the differences are generally smaller for the simulations using clinical timing

compared to those following strict protocol timing. For the clinical timing simulations, 90% of patients had median simulated BG within 12% and 9% of their clinical results for protocols A and B, respectively. The corresponding values for the strict protocol timing were 14% and 13% for protocols A and B, respectively. These results indicate good self-validation, but also provide insight to the level of protocol violation that occurred.

In a perfect trial, with no protocol violations, the distributions of paired differences should approach the fitting error distributions (Table 10.5). However, once a simulation BG trajectory deviates from the clinical trajectory, modelling errors can add to the differences between the final results. Hence, the differences between median fitting errors of 0.2-0.3% and the medians of Figure 10.4 at 2-6% may be a result of both compliance and modelling issues and thus indicates a moderate level of non-compliance.
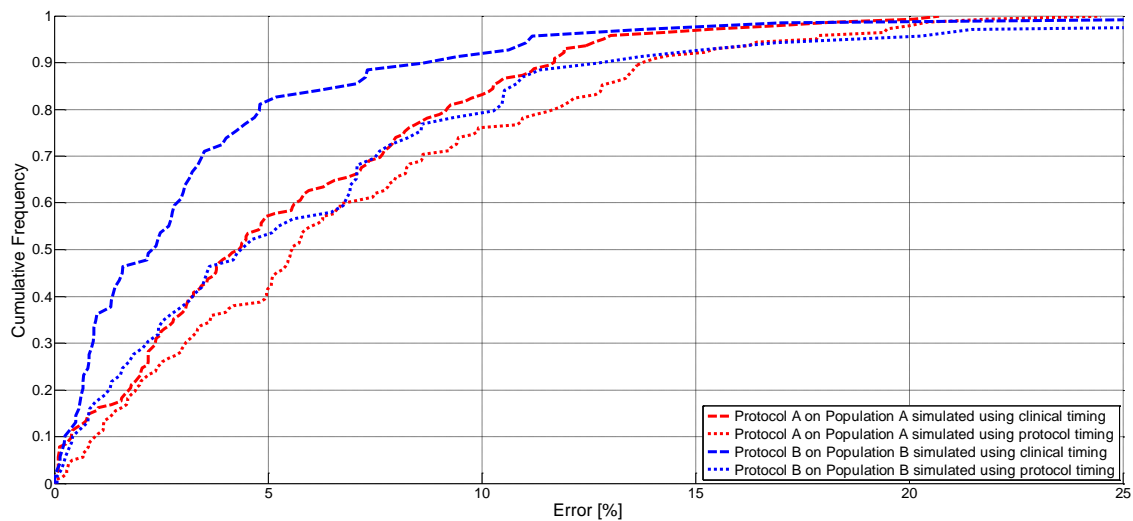
Figure 10.4. Per-patient median absolute BG comparison between simulated and clinical results.

This study focuses on the Glucontrol protocol from one centre (Liege, Belgium; pilot centre). Glucontrol was a multi-centre study stopped early to a high rate of unintended protocol violations [Preiser et al. 2009]. The self-validation results, in particular, capture and show the impact of these protocol violations.

Table 10.6 shows the comparison of outcomes between the actual clinical data and the self- and cross- validation simulations for the Glucontrol A protocol. These per-patient results show very good agreement between the actual data and the clinical timing self-validation. The increased measurement and insulin rates seen for the self-validation with protocol timing result are closely related. Given the incremental nature of the protocol insulin specification, timing non-compliance automatically translates into different insulin rates as more measurements provide more opportunities to increase the insulin rate, per the protocols in Table 10.3 and Table 10.4.

Table 10.6. Glucontrol A clinical and simulation results. Data are shown as median [interquartile range] where appropriate.

Glucontrol A	Clinical	Self-validation		Cross-validation
		Clinical timing	Protocol timing	Protocol timing
No. of patients	142	142	142	69
Insulin rate [U/hr]	1.4 [0.9-2.1]	1.7 [1.1-2.8]	2.7 [1.4-4.7]	6.2 [3.2-10.1]
Glucose rate [g/hr]	1.1 [0.5-7.6]	1.1 [0.5-7.6]	1.2 [0.5-7.5]	3.0 [0.7-7.4]
BG [mmol/L]	6.4 [5.9-6.9]	6.2 [5.8-6.8]	6.2 [5.8-6.7]	6.6 [6.0-7.1]
BG measurements	4571	4560	9907	7614
BG meas. freq. [/patient/day]	6.5	6.5	14.1	14.1

The high insulin dosing for Population B in the cross-validation is likely a result of using the clinically administered nutritional data. Population B received almost 3-times the glucose administration as population A, and therefore required significantly more insulin to control glycaemia to the protocol A target. In addition, cross-validation can only be performed with protocol timing and thus the associated increased measurement and insulin rates. These results are mirrored in the complementary cross-validation of protocol B on Population A shown in Table 10.7.

Comparison of clinical trials with self and cross-validation on Glucontrol B is summarised in Table 10.7. The trends are similar to those seen for Glucontrol A, where the clinical timing simulations closely match the actual clinical results and the protocol timing simulations have high measurement and insulin rates. However, protocol B clinical data had a measurement rate much closer to the strict protocol rate than protocol A. Hence, this lesser degree of measurement non-compliance translated into closer insulin rates between the clinical and protocol timing simulations.

Table 10.7. Glucontrol B clinical and simulation results. Data are shown as median [interquartile range] where appropriate.

Glucontrol B		Self-validation		Cross-validation
	Clinical	Clinical timing	Protocol timing	Protocol timing
No. of patients	69	69	69	142
Insulin rate [U/hr]	0.6 [0.3-1.2]	0.6 [0.3-1.3]	0.8 [0.2-2.1]	0.1 [0.0-0.8]
Glucose rate [g/hr]	2.9 [0.7-7.4]	2.9 [0.7-7.4]	2.9 [0.7-7.4]	1.1 [0.5-7.4]
BG [mmol/L]	8.3 [7.6-8.8]	8.2 [7.8-8.8]	8.4 [7.8-9.1]	7.7 [6.9-8.3]
BG measurements	2820	2818	4076	5282
BG meas. freq. [/patient/day]	5.2	5.2	7.5	7.5

The self-validation results of Table 10.6 and Table 10.7 clearly indicate significant measurement non-compliance. Comparison between the protocol timing simulation and clinical results show 54% and 31% fewer measurements in the clinical data for protocols A and B, respectively. Although it is not strictly correct to simply compare the tabulated numbers of measurements, due to potentially different BG trajectories, the outcome BG distributions are similar in these cases. Hence, these values likely provide a good estimate of the level of measurement timing non-compliance.

Differences between self- and cross- validation results can mostly be attributed to any remaining differences between patient groups, despite clinical matching.

More importantly, the relatively small differences show the strength of the *SI* parameter as a description of patient metabolic state, rather than as a therapy-specific parameter value.

Other causes for remaining differences may also be a function of model approximations or errors. Inter- and intra- patient variability in some fixed model parameters and insulin secretion rate (Chapters 3 and 4) is at least one cause of model limitations and errors. However, the limited blood glucose data with no added or real time plasma insulin data limits the ability to uniquely identify these parameters [Hann et al. 2005; Hann et al. 2008].

Despite these model approximations, the close correlation of self- and cross-validation results to clinical data validates both the ICING-2 model and independence of the *SI* parameter from insulin and nutritional inputs. In addition, these results validate the idea that these in silico virtual trial simulations can accurately predict the expected clinical results of a glycaemic control protocol.

10.4 Summary

The objective of this study was to validate the ICING-2 model for clinical glycaemic control and virtual trial purposes. The validation was accomplished by assessing the BG fitting and forward prediction as well as self- and cross-validation performance on cohorts independent to those on which the model was developed.

The low fitting and prediction errors, considerably less than typical 10% BG sensor errors, indicated that the model captured the clinically observed BG dynamics and variation. In particular, the low prediction error validates the ability of the model and identified *SI* parameter to predict intervention outcomes. This forward predictive ability is highly relevant for model-based glycaemic control.

The close correlation of self- and cross- validation results to clinical data validates both the ICING-2 model and independence of the *SI* parameter from insulin and nutritional inputs. Self-validation indicated a clinically insignificant error in these virtual trial methods due to model and/or clinical compliance. They also showed the impact of some non-compliance independent of model error. Cross-validation clearly showed that the virtual patient methods and models enabled by patient-specific *SI* profiles are effective and the assumption that the *SI* profiles are independent of the clinical inputs used to generate them is valid. Together, these results validate the concept that these virtual trial simulations can accurately predict the expected clinical results of a glycaemic control protocol.

Chapter 11. Implementation Validation

Chapter 10 validated both the ICING-2 model and the independence of the *SI* parameter from insulin and nutritional inputs, enabling accurate virtual trial simulations. Virtual trial simulations are used in this Chapter to validate the implementation of the model using separate stochastic models to reduce the impact of the extrinsic *SI* variability during glycaemic control.

11.1 Introduction

Extrinsic *SI* variability derives from factors external to the specific pharmacokinetic-pharmacodynamic model, such as changes in patient condition, drug therapies and measurement errors. These factors were discussed and quantified in Chapters 7, 8 and 9. The common, model-based method proposed to reduce the impact of this variability, while using the model for glycaemic control, was to use more than one stochastic model. However, this approach requires validation.

The objective of this study was to validate the use of separate stochastic models to reduce the impact of extrinsic *SI* variability during glycaemic control. A number of separate stochastic models were proposed in the preceding Chapters for different patient conditions, diagnostic categories and drug therapies. However, there is currently not enough data to create all these models, while ensuring the data used in each one is independent of the others and comprehensive.

The results of Chapter 7 showed that the first 24 hours of ICU stay were characterised by significantly reduced *SI* level and increased variability for all patients. There are enough data points from the first 24-hours to ensure an accurate, comprehensive stochastic model for this group. Hence, this study presents a limited validation using a specific model generated for the first 24 hours of ICU stay.

This validation was conducted using the virtual trial method validated in the previous Chapter. These virtual trials were conducted with the STAR protocol [Evans et al. 2011], employing the ICING-2 model and two separate stochastic models. The outcome glycaemia of these virtual trials was assessed and compared with the results using a single stochastic model.

11.2   Subjects and Methods

11.2.1 Patients

This study used data from 371 patients admitted to the Christchurch Hospital ICU between 2005 and 2007 and treated with the SPRINT glycaemic control protocol [Chase et al. 2008]. This cohort was essentially the same as that used in the studies by Chase et al. [2008] and Evans et al. [2012], enabling comparison with these previously reported results. Of the 371 patients, 293 commenced SPRINT within 24 hours of ICU admission. Hence, these patients contribute data to, and would be controlled for some period by the 0-24 hour stochastic model. Table 11.1 shows a summary of the cohort details. The Upper South Regional Ethics Committee, New Zealand granted approval for the audit, analysis and publication of this data.

Table 11.1. Cohort and sub-cohort summary statistics.

	All patients	Patients that started SPRINT within 24 hrs of ICU admission
N	371	293
Age (years)	65 [49-74]	65 [52-74]
Gender (M/F)	236/135	184/109
APACHE II score	18 [15-24]	18 [15-24]
APACHE II ROD (%)	26 [13-49]	26 [13-48]
ICU length of stay (hrs)	98 [41-251]	77 [29-191]
Operative/Non-operative	170/201	136/157
Diabetic status (T1DM/T2DM)	14/49	12/41
Hospital mortality	16%	17%

11.2.2 Virtual trial simulation

The method of virtual trial simulation was described in detail by Chase et al. [2010] and validated for this model in the previous Chapter. Briefly, the method involves using *SI* profile of one or more patients, identified from actual clinical data, as the underlying bases of virtual patients. A virtual trial consists of simulating the BG trajectory for the virtual patients by solving the ICING-2 model equations with the known *SI* profile and a control algorithm to select insulin and nutrition interventions

Virtual trial simulations, from a validated model, provide accurate information about expected glycaemic levels and interventions resulting from a given controller. This information can be used to assess the performance of the controller or aspects of it, such as the possible benefits of using separate stochastic models.

11.2.3 STAR protocol

The STAR (Stochastic TARgeted) glycaemic control protocol recommends insulin and nutrition interventions based on the predicted BG response over a 1-3 hour timeframe using forecasted *SI* from one or more stochastic models. The STAR approach explicitly targets a BG range by maximising the likelihood of achieving that range given certain constraints, such as an acceptable risk of hypoglycaemia and insulin and nutritional limits. The STAR protocol is described in detail by Evans et al. [2012; 2011], and its targeting approach illustrated in Figure 11.1.

With relatively stable BG, the STAR protocol allows 2 and 3-hour BG measurement options. In clinical use, nurses select the next measurement time from the permitted intervals. For this analysis, the in silico STAR controller always selects the longest available measurement interval, as this represents both the optimum balance between the level of control and nurse workload, and a likely scenario given heavy nurse workloads [Aragon 2006].
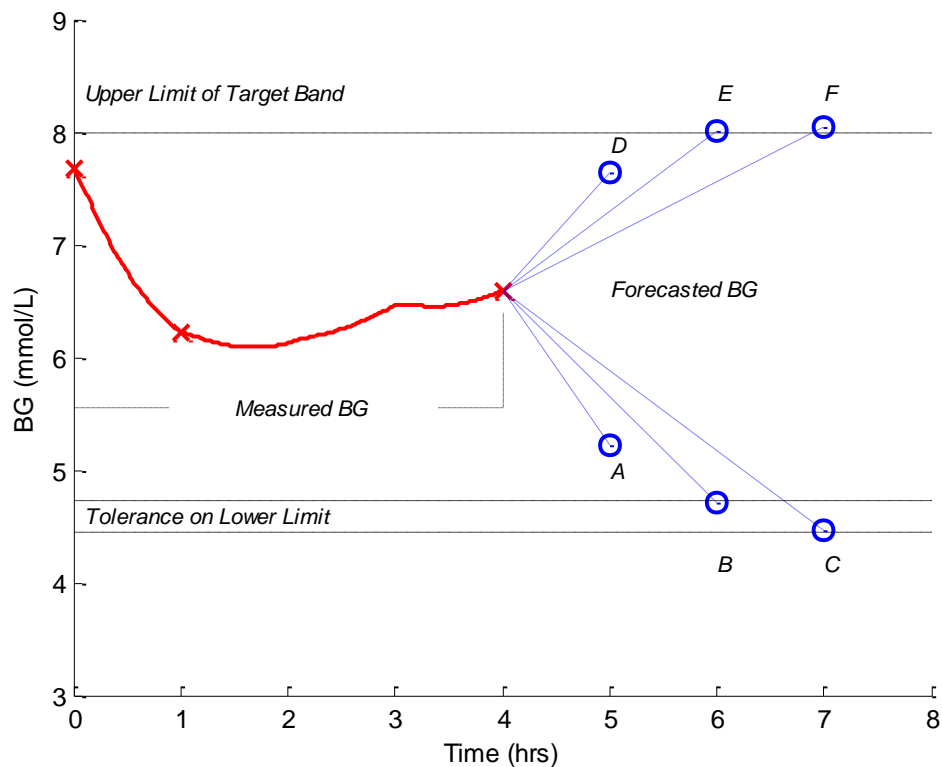
Figure 11.1. Controller forecast schematic for BG targeting the range 4.4 − 8.0 mmol/L. A BG measurement was taken at 4 hours, and forecasts of BG have been generated (points A-F) for 1-3 hours ahead using the 5th and 95th percentile *SI* values from the stochastic model and some possible insulin and nutrition intervention.

During the clinical pilot trials of the STAR protocol [Evans et al. 2011], a single stochastic model was used for all patients for the entire duration of glycaemic control (general stochastic model). For this study, a specific model was generated from, and used only during the first 24 hours of patient stay in the ICU. In practise, a 24+-hour model would cover all subsequent time. For example, if a patient commenced SPRINT 13 hours after ICU admission, only data from the first 11 hours of glycaemic control would contribute to the 0-24 hour stochastic model, and the remainder to the 24+-hour model. Similarly, during control, or a virtual trial with the STAR protocol, only the first 11 hours would employ the 0-24 hour stochastic model.

The 0-24 hour model was generated from data contributed by 293 patients that commenced SPRINT within 24 hours of ICU admission. The general model was generated from all 371 patients. The generation and validation of stochastic

models are described in detail elsewhere [Le Compte et al. 2009; Lin 2007; Lin et al. 2006; Lin et al. 2008].

11.2.4 Analyses

The objective of glycaemic control is to drive patient blood glucose levels into a target band, while avoiding hypoglycaemia. Therefore, the appropriate metric to assess methods of mitigating the impact of extrinsic *SI* variability is outcome glycaemia. This study compares outcome glycaemia from virtual trials only for the first 24 hours of ICU stay, as this time period is where the additional variability captured by the specific 0-24 hour stochastic model can have an impact. The 24+-hour stochastic model is sufficiently similar to the general model that the results are essentially identical for this latter part of patient stay. Including these latter days in the results would only swamp the relatively few data points from the first 24 hours. Both stochastic models and virtual trials used the ICING-2 model in this analysis.

11.3   Results and Discussion

Figure 11.2 shows the 0-24 hour and general stochastic models used in this analysis. The lines represent the 5th, 25th, 50th, 75th and 95th percentiles, from the lower part of the plot, upwards. The 0-24 hour model is noticeably wider than the general model and the data points are concentrated at lower *SI* levels, corresponding with the reduced level and increased hour-to-hour variability reported in Chapter 7.

Figure 11.3 presents the outcome glycaemia results of the virtual trials for the first 24 hours of ICU stay. Thus, this plot only contains data from 293 patients. Clinical data from the SPRINT protocol are also shown for context, although the target band of SPRINT differed from that of STAR (Table 11.2).
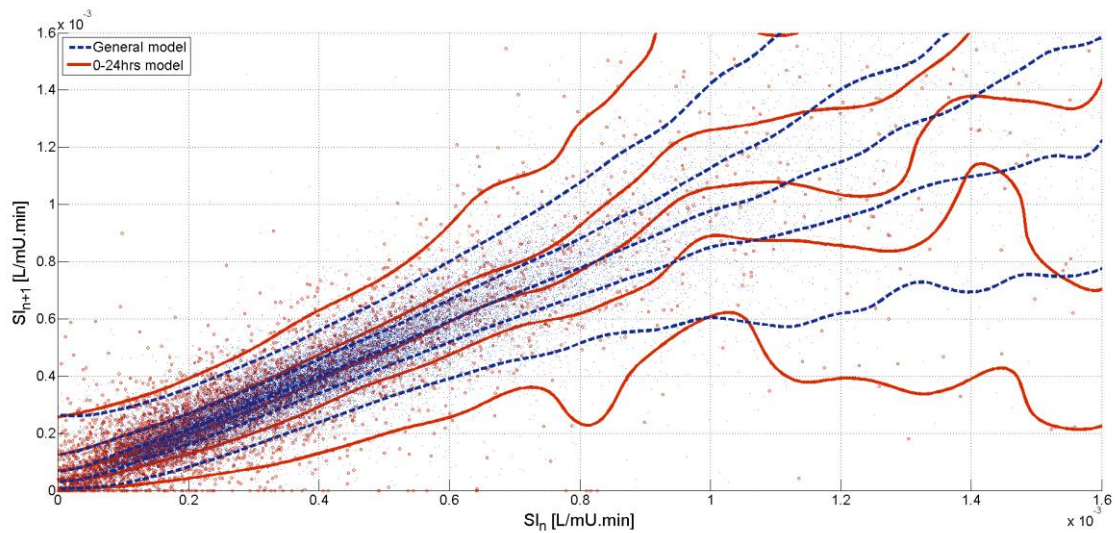
Figure 11.2. Comparison of 0-24hr and general stochastic models generated from the ICING-2 model.
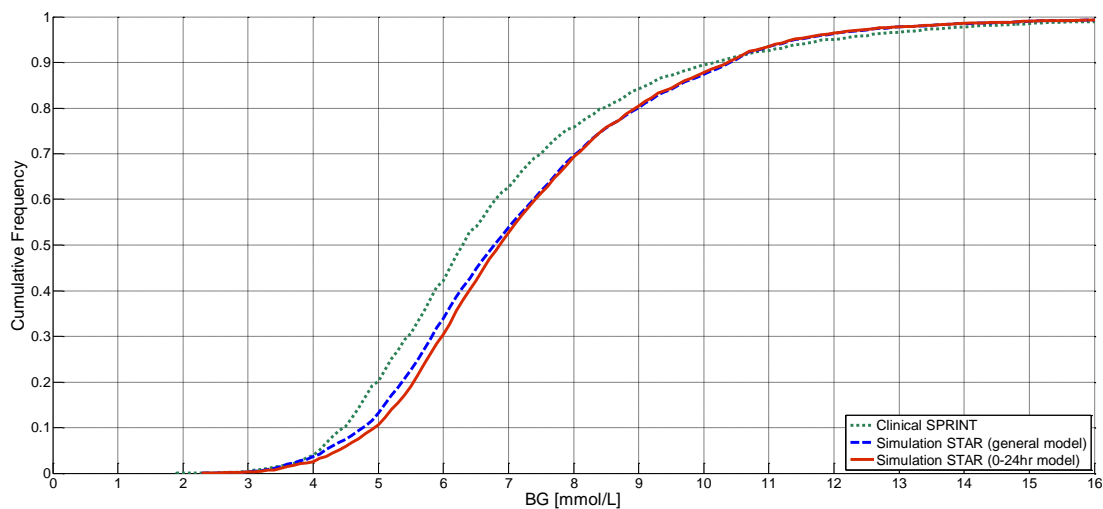
Figure 11.3. Virtual trial simulation BG results during the first 24 hours of ICU stay. The corresponding SPRINT clinical data are shown for context.

The results for the simulation using the 0-24 hour stochastic model show a slight rightward shift in the BG distribution at low BG levels (< 7 mmol/L) compared to the general model. This result was expected, given the increased width of the 0-24 hour stochastic model. To prevent hypoglycaemia, the STAR protocol constrains the 5th percentile BG prediction to a lower limit. Hence, the increased width of the stochastic model, particularly the 5th percentile causes a shift in the

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BG distribution at lower levels. This shift represents a small reduction in overall cohort glycaemic variability.

Table 11.2 shows that in general, the normoglycaemic and hyperglycaemic results were comparable between the two STAR simulations. The median BG of the 0-24 hour model result is still well within the target band and only 0.1 mmol/L higher than the result from the general model. Additionally, the interquartile range of the simulation using the 0-24 hour model is narrower, quantifying the reduction in overall variability seen in Figure 11.3.

Table 11.2. Virtual trial simulation BG results comparison for data within 24 hours of ICU admission.

Whole cohort control statistics	SPRINT Clinical	STAR General model	STAR 2 0-24hrs model
Num patients	293	293	293
Total hours	4662 hours	4662 hours	4662 hours
Num BG measurements	3915	3121	3204
Target BG band (mmol/L)	4.0 - 6.1	4.4 - 8.0	4.4 - 8.0
BG median [IQR] (mmol/L)	6.30 [5.20 - 7.90]	6.80 [5.70 - 8.50]	6.90 [5.80 - 8.50]
% BG within 4.0 - 6.1 mmol/L	41.6	33.2	30.4
% BG within 4.0 - 7.0 mmol/L	59.3	50.8	50.4
% BG within 4.4 - 8.0 mmol/L	67.7	63.6	64.9
% BG within 8.0 - 10 mmol/L	14.2	19.3	20.3
% BG > 10 mmol/L	10.5	12.5	12.2
% BG < 4.4 mmol/L	8.1	6.0	4.4
% BG < 4.0 mmol/L	3.4	3.1	2.2
% BG < 3.0 mmol/L	0.3	0.3	0.2
Num patients < 2.2 mmol/L	2	0	0

More importantly, the 0-24 hour stochastic model reduces the proportion of hypoglycaemic measurements. Absolute reductions of 1.6%, 0.9% and 0.1% were achieved for the amount of time spent below 4.4, 4.0 and 3.0 mmol/L, respectively. With 300-400 patients per year receiving glycaemic control in the Christchurch Hospital ICU, these results could reduce the number of patients experiencing a hypoglycaemic episode by up to 6, annually. The STAR protocol prevented any severe hypoglycaemic episodes, defined as BG < 2.2 mmol/L.

The SPRINT clinical data were shown in Table 11.2 for context. The SPRINT results show a slightly increased time in target band compared with STAR. However, the increased number of hypoglycaemic episodes offsets this result. It is also worth noting that the STAR results were achieved with approximately 20% fewer BG measurements than SPRINT.

Table 11.3 shows the insulin and glucose administration results from the virtual trials. Results for the two STAR trials were very similar. The slightly lower insulin administration during the trial with the 0-24 hour stochastic model may account for the slightly higher outcome glycaemia. It is interesting to note that very little nutrition was administered during this first 24-hour period. This was likely a consequence of low *SI* level while the controller was trying to bring BG down into the target band. Nutrition administration later in patient stay was generally much higher [Evans et al. 2012; Evans et al. 2011].

Table 11.3. Virtual trial simulation interventions within 24 hours of ICU admission. Data are shown as median [interquartile range]

Whole cohort control statistics	SPRINT Clinical	STAR General model	STAR 2 0-24hrs model
Insulin rate (U/hr)	3.0 [1.0 - 4.0]	3.0 [1.5 - 5.0]	2.5 [1.0 - 4.0]
Glucose rate (g/hour)	0.0 [0.0 - 2.8]	0.0 [0.0 - 4.2]	0.0 [0.0 - 4.2]
Glucose rate (% goal)	0.0% [0.0% - 40.0%]	0.0% [0.0% - 61.4%]	0.0% [0.0% - 63.8%]

These virtual trial results indicate that the impact of extrinsic *SI* variability can be reduced, to some extent, by using more than one stochastic model. This study demonstrated a reduction in the prevalence of hypoglycaemia during the first 24 hours of ICU stay, when patients tend to be more variable, using a specific stochastic model for that period. Additionally, a reduced BG interquartile range indicated a small reduction in overall cohort glycaemic variability.

As noted in Chapter 7, Bagshaw [2009] reported an association between hypoglycaemia and variability during the first 24 hours of ICU stay, and mortality. Not only does glycaemic variability pose a risk through

hypoglycaemia, it is also detrimental in its own right. Several studies [Egi et al. 2006; Egi et al. 2010; Hermanides et al. 2010; Krinsley 2008] have shown that glycaemic variability is independently associated with mortality in critically ill patients. Hence, the reduced hypoglycaemia and variability results using a specific stochastic model for the first 24 hours of ICU stay may appear small, but are potentially very important.

Chapters 7, 8 and 9 have shown that a number of factors are associated with increased extrinsic *SI* variability and thus proposed separate stochastic models to reduce the impact on outcome glycaemia. Currently, there is not enough data to create specific stochastic models for all the proposed cases, while ensuring the data used in each one is independent of the others. For example, there are currently only 904 hours of data for cardiovascular surgery patients that commenced SPRINT within 24 hours of ICU admission. This data is too sparse to generate a reliable stochastic model. Hence, this study validated the concept using only one additional stochastic model. However, as more data becomes available, models could be generated for all the proposed circumstances, and potentially others that may come to light.

11.4   Summary

This study has validated the concept that using more than one stochastic model during control can reduce the impact of extrinsic *SI* variability on outcome glycaemia. Virtual trials were simulated with the STAR protocol using stochastic models generated with data taken from both entire ICU stay and only the first 24 hours. Using a stochastic model specifically generated for the first 24 hours of ICU stay resulted in reduced variability and hypoglycaemia during this period, without adversely affecting the overall level of control. The increased variability and reduced level of *SI* during the first 24 hours was evident in the stochastic model, providing further justification for this approach. When more data becomes available, more models could be generated and used for specific diagnostic categories or drug therapies.

Chapter 12.   Conclusions

Tight glycaemic control in critical care has been shown to confer significant benefits on patient outcome. However, maintaining safe, effective control in critically ill patients has proven difficult, due to considerable inter- and intra-patient variability. Model-based control currently provides the only robust, adaptive and patient-specific solution to manage these highly dynamic patients.

The model-based control practised in the Christchurch Hospital ICU uses a physiological model that relies on a single, time-varying parameter, *SI*, to capture the patient-specific glycaemic response to insulin. As an identified parameter, *SI* is prone to also capturing other, unwanted, dynamics that add variability on multiple timescales. The objective of this thesis was to understand and reduce unwanted variability of the *SI* parameter, and thus improve glycaemic control performance.

Unwanted variability in *SI* was separated into two broad categories, intrinsic and extrinsic variability. The first part of this thesis addressed intrinsic variability by enhancements to reduce the influence of unmodelled artefacts within the model. The second part addressed extrinsic variability, by proposing ways of using the model in control to mitigate the effects on outcome glycaemia. The proposed changes to the model were validated in-silico.

A simple model of insulin secretion as a function of blood glucose concentration was developed using data collected from a recent study at the Christchurch Hospital ICU. Separate models were identified for non-diabetic patients and diagnosed, or suspected type II diabetic patients, with R^2 = 0.61 and 0.69, respectively. The gradients of the functions identified were comparable to data published in a number of other studies on healthy and diabetic subjects. These improved models provide a much better description of insulin secretion than the previous, relatively constant model and thus reduce unwanted intrinsic *SI* variability*.

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The population constant parameters describing key insulin kinetics were reviewed using data from published microdialysis studies. Specifically, values of the transcapilliary diffusion (n_I) and cellular clearance (n_C) rate parameters were optimised, as interactions between them determine maximum interstitial insulin concentrations available for glucose disposal, and thus directly influence *SI*. The optimal values of these parameters were determined to be $n_I = n_C = 0.0060$ min^{-1}. These optimal parameter values are associated with an 'effective' interstitial insulin half-life $t_{\frac{1}{2}} = 58$ mins, within the range of 25-130 mins reported by others.

A sub-model of endogenous glucose production was investigated to better capture the enhanced glucose appearance rate characteristic of the acute stress response to critical injury. Models of EGP as functions of blood glucose concentration and time were assessed, but proved unsatisfactory due to difficulties in identifying reliable functions with the available data set. Thus, until further information becomes available, the best course is to continue treating EGP as a population constant, despite the impact on intrinsic *SI* variability. However, during real-time control in clinical situations, if a patient has poor fit to measured data due to a constrained value of *SI* while receiving no nutrition, then EGP should be temporarily increased.

The proposed insulin kinetic parameters and secretion enhancements were incorporated into the model and this updated definition was re-designated ICING-2. The ICING-2 model was subsequently validated for clinical glycaemic control and virtual trial purposes using self- and cross- validation analyses on a critically ill cohort, independent to that on which the model was developed.

Several suspected causes of extrinsic *SI* variability were investigated with the ICING-2 model: Patient type and condition, drug therapies and measurement errors. As these factors are not explicitly modelled, they could be addressed by improved modelling. Hence, the impact of these elements could only be mitigated through understanding, and smarter use of *SI* in control and analysis applications.

The first 24 hours of ICU stay proved to be a period of significantly increased *SI* variability, both in terms of hour-to-hour changes and longer-term evolution of level. This behaviour was evident for the entire study cohort as a whole and was particularly pronounced during the first 12-18 hours. The subgroup of cardiovascular surgery patients, in which there was sufficient data for analysis, mirrored the results of the whole cohort, but was also found to have even lower and more variable *SI*.

In addition to patient type and condition, the use of glucocorticoid steroids was also found to be associated with clinically significant reductions in overall level and increases in hour-to-hour variability of *SI.* To manage the extrinsic *SI* variability and its changes over time and between patient groups, the use of several stochastic models was proposed. Using different models for the early part of ICU stay and for different diagnostic subgroups as well as when patients were receiving certain drug therapies would permit control algorithms to reduce the impact of the *SI* variability on outcome glycaemia. Additionally, intervention-based measures such as greater blood glucose measurement frequency, conservative insulin dosing and modulation of carbohydrate nutrition can be used to lower the impact of *SI* variability on glycaemia and thus risk.

An analysis of the impact of measurement timing and BG concentration errors on the variability of *SI* was also conducted. Results indicated that the impact of both sources of errors on *SI* level was unlikely to be clinically significant and probably swamped by physiological factors arising from the critical condition of the patients. The impact of BG sensor errors on hour-to-hour *SI* variability was more pronounced. However, given the random nature of these errors, the only feasible method of mitigation is to use more accurate BG sensors, but the cost of these devices may be prohibitive.

Understanding the effect of sensor and timing errors on *SI* allows their impact to be taken into account when using the parameter for control and analysis. For a given *SI* level, variability caused by measurement errors might dominate the IQR of the probability density function describing *SI* for the subsequent hour. Hence,

to avoid inadvertently basing control decisions on this artificial variability, the 5-95 percentile range of the stochastic model should be used. In addition, using changes in *SI* level as a diagnostic must be done with caution, potentially by looking at longer-term trends, where the effects of random errors may be cancelled by averaging over time.

The concept of using more than one stochastic model to reduce the impact of extrinsic variability on outcome glycaemia was validated using virtual trials. Virtual trials were simulated with the STAR protocol using stochastic models generated with data taken from both entire ICU stay and only the first 24 hours. Using a stochastic model specifically generated for the first 24 hours of ICU stay resulted in reduced glycaemic variability and hypoglycaemia during this period, without adversely affecting the overall level of control.

The analyses of intrinsic variability led to improvements in the model that provided a more physiological basis and increased accuracy. The performance of the model incorporating these changes was validated for clinical glycaemic control and virtual trial purposes. The study of extrinsic variability addressed factors that were outside the explicit physiological model. The use of multiple stochastic models to reduce the impact of this extrinsic variability during glycaemic control was validated using virtual trials.

Chapter 13. Future Work

The work presented in this thesis addressed several major causes of intrinsic and extrinsic *SI* variability. However, there remain other elements, both within the model and in the way it is used, that contribute to this variability that may provide avenues for further improvement in the future.

13.1 Gastric model

For patients being receiving nutrition through the enteral route, glucose appearance in current ICING family of models is handled by a gastric sub-model. This sub-model was adapted from that used by Wong et al. [2008] for type 1 diabetic subjects. Being a compartment model, the total mass of glucose is conserved, and thus must eventually appear in the blood glucose compartment. However, inaccurate kinetic parameters may result in an incorrect rate of appearance, which could impact identified values of *SI*.

Additionally, recent work within this research group suggests that an incretin effect is observable in the *SI* parameter. Incretins are a group of gastrointestinal hormones that potentiate insulin secretion in response to food. Thus, changes in nutritional content or rate may affect *SI*, through pathways independent of glucose appearance.

Verification of the gastric model kinetics and an analysis of the potential impact of incretins on *SI* in critically ill patients would provide valuable information on other sources variability that may affect glycaemic control.

13.2 Insulin delivery method

Bolus insulin delivery is preferred in the Christchurch Hospital ICU. Most other hospitals typically favour constant infusions. Both methods have their advantages and disadvantages. However, the choice of delivery method may have an impact on *SI*.

The high, transient insulin concentrations associated with bolus delivery can interact with modelled saturation dynamics, but also ensure a rapid rise in the interstitial insulin concentration and receptor-bound fraction. A preliminary (unpublished) study comparing the efficacy of both delivery methods with the ICING model found that bolus insulin resulted in greater glucose disposal than the same dose given as an infusion over one hour. Thus, a study into the possible effects of delivery method on *SI* level and variability would be worthwhile.

13.3 High frequency BG measurements

With the recent, rapid, improvement in continuous glucose monitoring (CGM) sensor technology, these devices may soon become common in intensive care units. CGM devices offer a much higher measurement frequency, but currently, with lower accuracy than typical bedside glucometers. As the technology matures, and accuracy and reliability increase, the high data density available from these devices may enable other model parameters to be identified or, at least, characterised in a more patient-specific manner. For example, an accurate BG profile measured every 1-2 minutes following a bolus of insulin could potentially provide valuable information about the insulin kinetics and/or glucose-insulin dynamics of individual patients. This information could then be used to further reduce intrinsic *SI* variability and thus improve patient-specific glycaemic control. Thus, a study into the trade-off between measurement frequency and model parameter identifiability would be worthwhile.

13.4 Endogenous insulin secretion and glucose production

The analyses of insulin secretion and EGP presented in this thesis are by no means complete. The wide range of disorders and variability characteristic of critically ill patients ensure that more data and analyses will always be valuable. A refined study of pancreatic insulin secretion would combine greater measurement frequency with better knowledge about when best to take C-peptide and insulin samples to accurately define the secretion profile. In addition, laboratory BG measurements, coinciding with the other samples would

provide a better basis for a model as a function of both BG and its time derivative.

Accurate information about endogenous glucose production is difficult to obtain due to the complicated and intensive experiments required. This fact is further complicated in ICU patients, where variability over time and between patients means that a single value of EGP at a point in time is of limited utility. However, developments and new techniques may come along to improve access to the endogenous glucose production rate. In addition, high frequency data from CGMs may enable better, real-time, estimation of EGP. Thus, with new data and methods, the treatment of EGP within the ICING family of models should be reviewed.

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