Robust Modelling of the Glucose-Insulin System for Tight Glycemic Control of Less Critical Care Patients

Normy Norfiza Abdul Razak

A thesis submitted in fulfilment
of the requirements for the Degree of
Doctor of Philosophy
in
Bio-Engineering
at the
University of Canterbury,
Christchurch, New Zealand.

9 January 2012

Acknowledgements

It is my utmost pleasure to thank those who made this thesis possible. Professor Geoffrey Chase, my principal supervisor in the Department of Mechanical Engineering, UC, it has truly been an honour for me to be under your guidance and support from the initial stage of this research until the completion of this thesis. There is so much more that i wish to continue learning from you, and you have inspired me to remain active and be a part of a research community.

Dr Jessica Lin, you have taught me to become a better student/researcher. Your continuous guidance, motivation, idea and knowledge helped me throughout this research. I appreciate it immensely. The best co-supervisor and friend anyone could have wished for.

To Dr Geoff Shaw, thank you for your insight, the associated experience have broadened my perspective in this area. I am also forever indebted to my research team members particularly Dr Aaron Le Compte and a future doctorate himself, Christopher Pretty, thank you so much.

To the rest of the bio-engineering team, particularly the glycaemic team, thank you for your friendship, being in lab is always a joy and enriching, my time in New Zealand won't be as memorable without all of you, Ummu, Fatanah, Jacqueline, Paul and Chiew.

I wish to extend my gratitude to the generous support of my sponsor, UNITEN. I hope my newly acquired knowledge would prove to be beneficial to them.

My deepest gratitude and love to my family. My father, Abdul Razak Osman, you have my admiration and the source of my inspiration. Nothing i could do would match to what you and mama have done. My beautiful mama, my teacher,

Jamilah Anum, i love you so much, thank you for always being there.

Most of all for my smart, loving, supportive and patient husband, Nazree Hisyam whom without his consent and by putting his career on hold for 3 years, this PhD would not be accomplished. Thank you so much for your time and effort in looking after our son Adam Armand while i concentrated upon this study. You keep me happy and sane. I deeply appreciate every single meal you cooked and every diaper you changed. Thank you.

Contents

List of Figures

List of Tables

Nomenclature

AACE	American Association of Clinical Endocrinologists
ADA	American Diabetes Association
APACHE	Acute Physiology and Chronic Health Evaluation
BG	blood glucose
BMI	body mass index
cdf	cumulative distribution function
C_{max}	maximal plasma insulin concentration
EGP	endogenous glucose production
FDA	US Food and Drug Administration
GLUT	glucose transpoter
ICU	intensive care unit
ICING	intensive control insulin-nutrition glycaemic
IQR	inter-quartile range
IV	intravenous
IVGTT	Intravenous Glucose Tolerance Tests
LOS	length of stay
MC	Monte Carlo
MPC	model predictive control
NICE-SUGAR	normoglycaemia in intensive care evaluation and survival using glucose algorithm regulation
NIRTURE	neonatal insulin replacement therapy in Europe
NRLS	non-linear recursive least square
NPH	Neutral Protamine Hagedorn
PD	pharmacodynamic
PK	pharmacokinetic
PID	proportional integral derivative
POC	Point of Care
RABBIT	randomized study of basal-bolus insulin therapy
RCT	randomised controlled trial
SC	subcutaneous
SPRINT	Specialized Relative Insulin and Nutrition Tables
SSE	sum square error
std	standard deviation
TGC	tight glycaemic control
T_{max}	time to maximal concentration

α_{gla}	Fraction of glargine as precipitate
α_G	Michaelis-Menten constant for insulin-stimulated glucose removal saturation
α_I	Michaelis-Menten constant for plasma insulin disappearance saturation
CNS	central nervous system
d_1	transport compartment rates
d_2	transport compartment rates
D	diffusion constant of hexameric and dimeric/monomeric insulin
D_t	dextrose from enteral feeding
EGP	endogenous glucose production rate
EGP_b	theoretical maximum endogenous glucose production
G_t	absolute (total) blood glucose level
G_E	equilibrium blood glucose level
I	blood plasma insulin concentration
k	rate of insulin transport and utilisation in the interstitium
k_{pr}	rise rate of exogenous plasma glucose appearance
k_{pd}	decay rate of exogenous plasma glucose appearance
$k_{prep,gla}$	Glargine precipitate dissolution rate [min-1]
k_1	Hexamer dissociation rate [min-1]
$k_{1,gla}$	Glargine hexamer dissociation rate [min-1]
k_2	Dimeric/monomeric insulin transport rate into interstitium [min-1]
k_3	Interstitium transport rate into plasma [min-1]
k_{di}	Rate of loss from interstitium [min-1]
k_d	Rate of diffusive loss from hexameric and dimeric/monomeric state compartments [min-1]
n	plasma insulin decay rate
n_I	transcapillary diffusion rate
n_C	cellular insulin clearance rate from interstitium
n_L	liver clearance rate
n_K	kidney clearance rate
$P1$	stomach
$P2$	gut
p_G	rate of endogenous glucose removal
P_t	glucose appearance

P_{max}	maximal out flux
$p_{gla}(t)$	Mass in glargine precipitate compt. [mU]
Q	interstitium insulin concentration
r	radius of the sc depot
$r_{dis,max}(t)$	Max glargine precip. dissolution rate [mU/min]
S_I	insulin sensitivity index
u_{ex}	exogenous insulin input
u_{en}	endogenous insulin production
$u_{total,gla}(t)$	Insulin glargine input [mU/min]
$u_{p,gla}(t)$	Glargine precipitate state insulin input [mU/min]
$u_{h,gla}(t)$	Glargine hexamer state insulin input [mU/min]
$u_{m,gla}(t)$	Glargine dimer/monomer state insulin input
V_G	glucose distribution volume
V_I	insulin distribution volume
V_P	plasma volume
V_Q	interstitial fluid volume
$x_{h,gla}(t)$	Mass in glargine hexameric compt. [mU]
$x_i(t)$	Mass in the interstitium compartment [mU]
x_L	first pass endogenous insulin hepatic uptake
$x_{dm}(t)$	Mass in dimer/monomer compartment [mU]

Abstract

In the intensive care units, hyperglycaemia among the critically ill is associated with poor outcomes. Many studies have been done on managing hyperglycaemia in the critically ill. Patients in the ICU continue to benefit from the outcome of extensive studies including several randomized clinical trials on glycaemic control with intensive insulin therapy. Tight glycaemic control has now emerged as a major research focus in critical care due to its potential to simultaneously reduce both mortality and cost. Although the debate on tight glycaemic control is on going, managing glycaemic level in ICUs is gaining widespread acceptance as the adverse effects are well known. However, in the less acute wards, to date there have only been a single randomized, controlled study to examine the benefit of glycaemic control. Patients in the less acute wards do not receive the same level of care, as glycaemic control is not regarded as important and not a priority. Glycaemic goals in the less acute wards are often judged based on clinical experience rather than adhering to a standard protocol or a treatment guideline.

It is important that patients in the less acute wards received the level of care as practised in the ICU. If hyperglycaemia worsens outcome in the ICU, a similar effect is seen within less acute wards. Hence, tight glycaemic control needs to be extended in the less critical setting as well. To support the establishment of a control protocol for patients in less acute wards, a method that has been successful in the critical care and can be adapted to the less acute wards, is the model-based or model-derived control protocol. Model-based protocol can deliver a safe and effective patient-specific control, which means the glycaemic control protocol can be devised to each individual patient. Hence, a physiological model that represents the glucose-insulin regulatory system is presented in this thesis. The developed model, Intensive Control Insulin-Nutrition-Glucose (ICING) is based on the best aspects of two previous clinically-validated glucose-insulin models.

Glucose utilisation and its endogenous production are more distinctly expressed. A more realistic model for gastric glucose absorption accounting for the stomach, gut and saturable glucose appearance is also introduced. Finally, the model also includes explicit pathways of insulin clearance and transport from plasma, which reflects biological mechanisms.

The ICING model is capable of accurately capturing long term dynamics and evolution of a critically ill patient's glucose-insulin response. The model achieved low fitting and, most importantly, low prediction error when fitted to blood glucose data from critically ill patients. Fitting errors and the 75^{th} percentile prediction errors were all well below measurement error for 173 patients and 42,941 hours of data. The new model outperforms its critical care predecessors, and has greater physiological relevance and more detailed insulin kinetics.

A subcutaneous insulin absorption model for Glargine is also developed. Glargine, a new type of insulin analog is incorporated in the study due to its unique once or twice a day basal coverage. Glargine has been used for Type 1 and Type 2 diabetic patients and the take of Glargine for the basal coverage of recovering critically ill patients is an interesting and promising approach. If Glargine can be used successfully in less acute wards, the high nursing effort frequently associated with tight glycaemic control can be greatly reduced. Hence, an improved pharmacokinetics and pharmacodynamics of subcutaneous Glargine model is developed and validated in this thesis. A further measure of validation is performed in which the model output of Glargine plasma insulin curve is validated using data from external independent studies. To account for intra- and inter-patient variability in the absorption kinetics of Glargine, variability is introduced to Glargine-specific parameters. The impact of variability is assessed with Monte Carlo analysis and increases the potential of the subcutaneous absorption model to be used effectively in a glycaemic control protocol.

Virtual trial provides a safe mean to develop and analyze glycaemic control protocols prior to clinical validation in pilot trials. Protocols may be optimised virtually to save time, save money and, most important of all, yield a better patient outcome in clinical implementation. Employing the ICING and subcutaneous Glargine insulin absorption model, *in silico* virtual trials were done on 15 metabolically stable ICU patients. Glargine's efficacy in this patient population was tested by comparing simulation results to SPRINT clinical data, dose

to dose. No control measure was adapted at this stage. Further virtual trials on 30 metabolically stable patients, combined an intravenous insulin protocol practised in the Christchurch ICU Hospital, New Zealand with subcutaneous Glargine doses as a basal background. This approach is targeted for patients in transition, from the ICU to less acute wards. It is expected that Glargine daily doses would eventually replace the intravenous insulin bolus, once patients insulin sensitivity is high and stable.

The transition protocol, with nutrition adjustments further looks into the efficacy in terms of nursing intervention frequency. Aside from managing patient's glycaemic level, which is the main priority, this research looks further into the nursing effort as the success of TGC protocol largely depends on human factor, specifically the nursing resources. Current guidelines for switching patients to a subcutaneous insulin are adhoc and often fail. A system is required to maintain good blood glucose control outside of the ICU and allows a smooth transition of patients from the ICU to less acute wards, while keeping nursing effort to a minimum – a major and heretofore an insoluble task. Thus, a protocol that does not burden nurses which is often limited in the less acute wards is highly required and practical. The solution created in this thesis will be the first attempt to generalize tight glycaemic control to less acute wards.

Monte Carlo analysis provide a further valuable approach to test the robustness of the control protocol and robustness is achieved with the ability of the control protocol accounting for possible blood glucose concentrations and variations of Glargine absorption. Overall, the results meet the primary goal of the analysis to justify a clinical pilot study to fully validate these *in silico* results.

Hence, a protocol 'Proof of Concept Study of Insulin Glargine in the Intensive Care and the High Dependency Units' which has been granted ethics is presented in this thesis. Having taken the modeling approach to a successful analytical endpoint, it is a critical and unique opportunity to clinically validate these *in silico* results.

Chapter 1

Introduction

Stress-induced hyperglycaemia is prevalent in critical care and can occur in patients with no history of diabetes [Krinsley, 2004; Capes et al., 2000; Van Den Berghe et al., 2001]. Hyperglycaemia occurs when the glucose concentration in the blood plasma is higher than a basal level of 5.5 mmol/L or 99 mg/dL [Mizock, 1995]. In which therapy should be initiated, hyperglycaemia is defined as being consistently higher than fasting blood sugars of >7mmol/L (>126 mg/dL) or random blood sugars of >11mmol/L (>200 mg/dL) as adapted from the American Diabetes Association Expert Committee on the Diagnosis and Classification of Diabetes Mellitus [Care, 2003]. Critically ill patients exhibit increased endogenous glucose production, erratic insulin production, and significantly increased insulin resistance [Capes et al., 2000; Esposito et al., 2003; Finney et al., 2003; Krinsley, 2003; McCowen et al., 2001; Van Den Berghe et al., 2001; Van den Berghe et al., 2003].

The occurrence of hyperglycaemia in critically ill patients is associated with increases in counter regulatory hormones such as catecholamines, growth hormone, cortisol and cytokines [McCowen et al., 2001; Barth et al., 2007a]. These counter-regulatory hormones antagonize insulin production and stimulate endogenous glucose production. They also decrease immune function response at high blood glucose levels [Marik and Raghavan, 2004; Turina et al., 2005; Weekers et al., 2003]. In addition, a combination of other factors also affect the patient's glycaemic level, mainly the severity of the patients underlying illness itself. Their underlying glucose tolerance may also play a role with individuals with Type 2 diabetes having a higher incidence of ICU-related hyperglycaemia [Irwin and Rippe, 2009].

Other than that, the administration of some medications play a role. In particular, steroids [Bradley, 2002], noradrenaline [Lewis et al., 2004] and beta blockers [Freeman et al., 2001] are commonly used drugs that have been recognized to exacerbate hyperglycaemia. Thus all these factors significantly increase effective insulin resistance. Finally, high glucose content nutritional regimes exacerbate hyperglycemia and thus mortality [Weissman, 1999; Krishnan et al., 2003; Elia et al., 2005], whereas reducing glucose intake from all sources has reduced glycemic levels [Patiño et al., 1999; Elia et al., 2005; Ahrens et al., 2005; Krajicek et al., 2005] and can alleviate the impact of the hyperglycemic counter-regulatory response that drives the problem [McCowen et al., 2001; Mizock, 2001; Thorburn et al., 1995; Larsen et al., 2002].

Extensive studies have therefore linked hyperglycaemia to worse outcomes [Krinsley, 2004] and higher hospital care cost [Furnary et al., 2004]. It is strongly associated with increased mortality [Krinsley, 2003; Laird et al., 2004; Jeremitsky et al., 2005]. Increament in fasting plasma glucose for every 1 mmol/L, is related with 33% increase in mortality in a study by Baker et al. [2006]. In particular, hyperglycaemic patients are at a higher risk of severe infection [Bistrian, 2001], myocardial infarction [McCowen et al., 2000] and critical illnesses such as polyneuropathy and multiple organ failure [Chase et al., 2010b; Van Den Berghe et al., 2001]. Hyperglycaemia has also been known to induce damage at a cellular level including immunosupression, inflammation, thrombosis and increased oxidative stress [Brownlee, 2001; Hirsch and Brownlee, 2005; Preiser and Devos, 2007]. Although not conclusive, several studies suggested that patients with no prior history of diabetes are even at a higher risk for adverse complications compared to patients with existing diabetes [Smiley and Umpierrez, 2008; Dungan et al., 2009; Tonks et al., 2010]. Hence, hyperglycaemia has a significant physiological impact via multiple routes on the critically ill patient that can by this impact add significant difficulty and complexity to their care and management.

A number of studies have investigated the effects on patient outcomes when blood glucose levels are controlled with insulin, and revealed markedly mixed results with some very positive reports showing the clear potential of this approach. Hyperglycaemia used to be seen as a positive adaptive response in the critically ill [Mesotten and Van den Berghe, 2009]. Since the landmark study in surgical intensive care unit (ICU) patients by Van Den Berghe et al. [2001], which reduced mortality by 18-45% using tight glycaemic control (TGC), the attitude towards

tolerating hyperglycaemia in critically ill patients has changed. Insulin, with TGC, can ameliorate inflammatory responses and improve insulin sensitivity and glycemic response [Weekers et al., 2003; Jeschke et al., 2004; Vanhorebeek et al., 2005; Langouche et al., 2005]. Van Den Berghe et al. [2001], obtained significant mortality reductions for a cardiovascular surgery cohort, as well as reducing other outcomes and treatments. It was matched by the retrospective study of Krinsley [2004]. TGC has now emerged as a major research focus in critical care due to its potential to simultaneously reduce both mortality and costs. Specifically, TGC is defined as having blood glucose range between 4.4–6.1 mmol/L (80-110 mg/dL). This is the normal range of blood glucose level of a healthy individual. Table 1.1 lists the glycaemic target range employed by several different studies to achieve normoglycaemia. The various glycaemic targets portray the widespread acceptance of TGC, yet at the same time questions on the best TGC target still remain. The final TGC band is yet to be established, with each study having its own approach on protocol implementation and target goal.

In contrast to the physiological impact noted, other benefits demonstrated from implementing TGC are lower rates of bacteremia, multiorgan failure, surgical site infection, renal failure and shorter duration of ventilation [Chase et al., 2010b; Van Den Berghe et al., 2001, 2006b]. The anti-inflammatory effects of insulin in reducing cellular level damage have also been noted [Van Den Berghe et al., 2001, 2006b].

However, repeating these results that reduced mortality and other outcomes has been difficult [Griesdale et al., 2009]. Several large trials [Finfer and Heritier, 2009; Brunkhorst et al., 2008; Preiser et al., 2009] were unable to repeat the early results of Van Den Berghe et al. [2001] or other success by Krinsley [2004] and Chase et al. [2008c]. For example, Brunkhorst et al. [2008] was stopped for safety due to hypoglycaemia while Preiser et al. [2009] had unintended protocol violations. Thus, the role of tight glyceamic control during critical illness and suitable glycaemic ranges have been under scrutiny in recent years [Schultz et al., 2008; Kalfon and Preiser, 2008; Preiser, 2009; Moghissi et al., 2009; Chase and Shaw, 2007; Van Den Berghe et al., 2006b]. Overall, conclusions are varied with both success [Van Den Berghe et al., 2001; Chase et al., 2007, 2008c; Krinsley, 2004], failure, [Finfer and Heritier, 2009] and, primarily, no clear outcome [Van Den Berghe et al., 2006b; Chase and Shaw, 2007; Preiser and Devos, 2007; Vanhorebeek et al., 2007; Brunkhorst et al., 2008; De La Rosa et al., 2008; Schultz et al.,

2008; Wiener et al., 2008; Treggiari et al., 2008], as summarised in Griesdale et al. [2009].

Below are few important methodological differences identified to be the cause of deficiency or varying level of success and failure among TGC studies.

- Differences in target range of BG between control and intervention groups.
- Differences in routes of insulin administration.
- Differences in sampling sites.
- Differences in types of instrument for BG measurements.
- Differences in nutritional strategies.
- Differences in level of expertise among ICU nurses.

The study by Chase et al. [2010a] states that all the controversy surrounding around TGC and its application are due to lack of understanding of both the problem and the patient-specific dynamics that hinder clarity on the issues. More specifically, the study reviews the basic known physiological and clinical aspects of TGC, in terms of their impact on glycemia and thus outcome.

Table 1.1 Tight glycaemic control range in ICU

Reference	TGC Range (mmol/L)	TGC Range (mg/dL)
Chase et al. [2008c]	4.4–6.1	80–110
Krinsley [2004]	<7.7	<140
Saager et al. [2008]	5.0–8.3	90–150
Rood et al. [2005]	4.0–7.0	72–126
Dortch et al. [2008]	4.4–6.1	80–110
Hermayer et al. [2007]	4.4–7.1	80–129
Thomas et al. [2005]	5.4–7.1	97–128
Vogelzang et al. [2005]	4.0–7.5	72–135
Davidson et al. [2005]	5.5–7.7	100–140
Meynaar et al. [2007]	4.5–7.5	81–135
Pachler et al. [2008]	4.4–6.1	80–110

While many ICU patients are benefiting from extensive research, moderate to high levels of hyperglycaemia are still tolerated within the less acute wards, such

as high-dependency (HDU) and post-surgical units. The management of TGC in this area, remains under the influence of ineffective standards characterized by tolerance to moderate hyperglycaemia and reluctance to use insulin intensively. A major roadblock leading to this outcome is the reduced clinical manpower available in these units to implement sometimes intensive protocols [Aragon, 2006; Chase et al., 2008b]. Moreover, not all hospitals have HDU unit, with the numbers of HDU and staffing are generally insufficient [Garfield et al., 2000; Leeson-Payne and Aitkenhead, 1995; Jones et al., 1999]. Therefore patients who were discharged from the ICU often were transferred directly to wards where TGC would even be more difficult to implement. In general wards, the staffing ratio is 1:6, yet a nurse usually may have to care for more [Aiken et al., 2008]. Hence, the use and benefits of insulin protocols within these units (HDU or less critical wards) have not yet been widely addressed in the literature [Whitehorn, 2007].

Based on current evidence from studies in medical and surgical ICUs, it is logical to expect that the maintenance of normoglycaemia within less acute ward patients would limit potential complications associated with elevated blood glucose levels [Chase et al., 2010a]. This assumption is not unreasonable as patients in the ICU and less acute wards share an accelerated catabolic, hyperglycaemic state that also reduces the immune response. Extending tight control to these wards could minimise rebound hyperglycaemia on discharge to the wards [Goldberg et al., 2004b] and minimize the development of (new) infections or further complications, thus improving overall patient care. Furthermore, the workload associated with patients who return to the ICU would be reduced. Studies on factors contributing to ICU rebound or readmission have increased in recent years, evident with more studies being published [Bardell et al., 2003; Utzolino et al., 2009; Rosenberg et al., 2001]. A review on ICU readmisson and rebound can be found from Elliott [2006].

However, to fully implement TGC in less acute wards posed significant challenges. These wards do not have the same nursing resources compared to ICU, making constant monitoring and titration difficult. In addition, patients do not have arterial or (often) intravenous lines for regular blood sampling. IV insulin has the advantages of administering accurate doses and provide a faster response than subcutaneous insulin. Hence, there is a pressing need for insulin delivery protocols that can be successfully implemented with minimal clinical effort, burden and resources. This necessitates an entirely different approach in engineering

a TGC protocol from that which is used in an ICU. More succinctly, while the avenue of providing TGC remains the same in these wards (insulin), the means and resources by which it is implemented will have to be very different.

1.1 Hyperglycaemia in less acute wards

Although it is now becoming an unacceptable practice to allow hyperglycaemia and its associated effects [Preiser and Devos, 2007; Brownlee, 2001; Hirsch and Brownlee, 2005; Egi et al., 2006], moderately elevated blood glucose levels are tolerated or recommended [Moghissi et al., 2009] because of the fear of hypoglycaemia [Egi et al., 2010; Bagshaw et al., 2009a] and higher nursing effort frequently associated with TGC [Mackenzie et al., 2005; Aragon, 2006; Preiser and Devos, 2007; Vanhorebeek et al., 2007; Chase et al., 2008a]. It was hoped that [Finfer and Heritier, 2009] would clear some of these confounding issues about setting appropriate glycaemic targets. This study, better known as the NICE-SUGAR (Normoglycaemia in intensive care evaluation and survival using glucose algorithm regulation) multi-centre study, had statistical power with 6100 patients. However, the control group with target range of 7.7–10.0 mmol/L (140–180 mg/dL) had lower 90 day mortality rate compared to the interventional group with strict lower range target of 4.5–6.0 mmol/L (81–108 mg/dL). More significantly, they failed to separate their cohorts glycaemically, and had other methodological issues [Chase et al., 2010a]. Hence, the study failed to answer these questions, as did the similar Glucontrol study [Preiser et al., 2009].

Table 1.2 lists the established recommended glycaemic targets for patients in non-critical settings. These glycaemic targets were established for patients with Type 1 and Type 2 diabetes on the basis of growing evidence that tight glycaemic control improves outcome [Nathan et al., 2005]. However, many patients in less acute wards still do not meet these glycaemic goals and the glycaemic target has been seen as too stringent, given the lack of study to support general inpatients [Inzucchi and Rosenstock, 2005]. The fear of hypoglycaemia has led to raising glycaemic target bands [Moghissi et al., 2009]. Moreover, with the result of NICE-SUGAR study [Finfer and Heritier, 2009], reconsideration of glycaemic targets in the critically ill meant target range in the less acute patients were reconsidered as well. The American Diabetes Association [2008] and Garber et al. [2004] state

that inpatient hyperglycaemia is common, harmful, and with better blood glucose control, mortality can be decreased along with complications, length of hospital stay and health care costs.

Table 1.2 Glycaemic target in less acute wards. Convert mg/dl to mmol/L; multiply by 0.055.

Resources	Preprandial	Postprandial
American Diabetes Association [2008]	<126 mg/dl	<180-200 mg/dl
American College of Endocrinology [2007]	< 110 mg/dl	<180 mg/dl

Patients in less acute wards, share more similarity in metabolic status to patients recovering from critical illness than to critical care patients in general. In Chase et al. [2008a, 2010a] as critically ill patients recover, their insulin sensitivity rises, but is still low compared to ambulatory individuals with Type 2 diabetes. Consequently, their insulin requirements decrease and the hourly doses are generally more consistent. Hence, it is likely that this patient population would benefit from intensive insulin therapy being transferred from the ICU setting to a less acute ward. However, there are several factors which hampered the effort to apply the same level of control seen in the ICU to less acute wards, namely:

- Fear of hypoglycaemia and method of TGC
- Clinical burden and lack of access for samples
- Lower nursing resources for intensive therapy and monitoring

These issues are very different from the ICU setting and thus necessitates a different approach of tight glycaemic control.

1.1.1 Fear of Hypoglycaemia and TGC Method

Among practitioners, fear of hypoglycaemia is a major limiting factor in implementing tight glycaemic control. Due to higher incidence of hypoglycaemia among patients, two major studies were terminated early [Brunkhorst et al., 2008;

Preiser et al., 2009]. In Brunkhorst et al. [2008], the incidence of severe hypoglycaemia <2.2 mmol/L (<40 mg/dL) was 17% in the intensive therapy group compared to 4.1% in the conventional group. The study [Brunkhorst et al., 2008] was supposed to include 600 septic patients, but was stopped after 488 patients, with the conclusion that septic patients were put at an increased risk of serious events related to hypoglycaemia. The multicentre mixed ICU Glucontrol study of Preiser et al. [2009] had severe hypoglycaemia in 8.7% of the patients receiving insulin therapy compared to 2.7% treated to a higher target. Hypoglycaemia in Van Den Berghe et al. [2006b] is reported to be as high as 18.7% in the medical ICUs. Results from the largest randomized trial to date, [Finfer and Heritier, 2009] also showed much higher incidence of severe hypoglycaemia in intensively treated patients versus the control group, with 6.8% and 0.5% respectively. This study, NICE-SUGAR study [Finfer and Heritier, 2009] also reported an increase in the TGC arm with a lower glycemic target, but was also subject to criticism of its treatment approach, analysis and randomisation methods [Henderson and Finfer, 2009; Myburgh and Chittock, 2009; Preiser, 2009; Van den Berghe et al., 2009]. The meta-analysis that followed the publication of the NICE-SUGAR study showed that most studies failed to achieve a result either way, but also had significantly variable numbers of centres, patients, target cohorts and ICU types [Griesdale et al., 2009]. Thus, overall comparisons are difficult, making it almost impossible to assess which factors are associated with successful TGC.

Due to hypoglycaemia, the neonatal NIRTURE TGC study [Beardsall et al., 2007] was also terminated. Almost all studies report increased hypoglycemia with intensive TGC [Griesdale et al., 2009], excepting SPRINT [Chase et al., 2008c]. One recent study links hypoglycemia in the first 24h of stay, for those patients who stay longer than 24h, as a factor for increased risk of death [Bagshaw et al., 2009b] although this was not the case in SPRINT [Chase et al., 2008c]. Thus, hypoglycemia and hyperglycemia are risk factors, and fear of hypoglycemia in particular has thus driven recent doubts about the role of TGC.

Hypoglycaemia may be described as having blood glucose level lower than 2.2 mmol/L (40 mg/dL)[Van Den Berghe et al., 2001], 3.3 mmol/L (60 mg/dL) [Kagansky et al., 2003] or 3.9 mmol/L (70 mg/dL) [Cryer et al., 2003]. The differences are attributed towards hospital targets and whether it is categorized as mild or severe hypoglycaemia. The symptoms include sweating, dizziness, fatigue, blurred vision, confusion and convulsions [Cryer et al., 2003; Whitehorn, 2007].

These clinical symptoms are often masked by patient's own critical condition and sedation. Seizures, coma, irreversible brain damage and in extreme cases death, are among the major consequences of hypoglycaemia [Cryer et al., 2003; Whitehorn, 2007; Bagshaw et al., 2009a; Egi et al., 2010]. Some physicians are still unsure whether the benefit of tight glycaemic control outweighs the risk of hypoglycaemia, making the issue of tight control still unresolved. However, from an engineering perspective this issue is more about the means by which TGC is implemented [Chase et al., 2010b] to manage patient variability.

Although these results were from the critically ill populations, physicians are still apprehensive to implement tight glycaemic control in less acute wards. This issue is partly due to insufficient studies in the area. To date there has only been 1 randomized controlled trial in the non-critical settings. The RABBIT-2 trial, was a prospective, multicentre, randomized trial conducted in patients admitted to a general medical service with blood glucose values between 7.7 mmol/L and 22.2 mmol/L (140 mg/dL and 400 mg/dL). Patients were randomized to receive Glargine and Glulisine, and sliding-scale insulin. The study did not demonstrate differences in mortality or clinical outcome between both groups. Hypoglycaemia was observed to be low in both groups [Umpierrez et al., 2007]. However, the study has its own significant limitations, where patients with hyperglycaemia without pre-existing diabetes were excluded from the study. This group of patients are thus more likely to benefit from tight glycaemic control and see less hypoglycaemia, which may have skewed the results.

As noted, the mixed results seen imply that best methods of providing TGC have not yet been disseminated. In particular, of 3 successful studies [Van Den Berghe et al., 2001; Krinsley, 2004; Chase et al., 2008c], only the SPRINT protocol by Chase et al. [2008c] reduced hypoglycaemia by 50% versus it's conventional group. This protocol was unique in its approach by controlling both insulin and nutritional inputs to metabolic balance. Uniquely, it was also the only protocol engineered using model-based methods [Lonergan et al., 2006b,a; Chase et al., 2008c, 2010c]. In Lonergan et al. [2006a] and Chase et al. [2008c], these studies showed reductions of 17-42% in mortality for patients whose length of ICU stay was 3-5 days or longer. They were matched by equally impressive reductions in cost per patient treated [Van den Berghe et al., 2006; Krinsley and Jones, 2006], and in reduced clinical incidence of sepsis, polyneuropathy and organ failure [Chase et al., 2010b; Van den Berghe et al., 2003].

Hence, SPRINT's [Chase et al., 2008c] unique design and approach was able to rise above issues of workloads and patient variability to provide a better, more consistent control and outcome than any other study. However, these methods have not yet been used for less acute wards at this time.

In particular, many ICUs and less acute wards use sliding scale methods, that titrates insulin on a simple proportional scale. Golightly et al. [2006]; Arnold and Keller [2009]; Hirsch [2009] and [Schnipper et al., 2006] are among many other studies that revealed outcomes associated with worse glycaemic control using sliding-scale insulin method. Umpierrez et al. [2007] is the only study to date conducted in non-critical settings, and clearly established that sliding-scale insulin failed to provide adequate glycaemic control. Hence, scheduled subcutaneous injection has been found to be better in these settings without the increased risk of hypoglycaemia. Sliding-scale should not be used in management of hospitalized patients with elevated blood glucose level. It is erratic, widely variable, often ineffectual, and prone to deficiencies in monitoring, documentation, and prescribing soundness [Golightly et al., 2006]. There have been suggestions to abolish the use of sliding-scale [Queale et al., 1997; Umpierrez and Maynard, 2006].

Efforts to improve glycaemic control in this population of patients that are less critically ill are thus clearly needed. A serious solution will account for important factors such as patient specific insulin resistance, meals, weight, illness and/or basal requirements [Moghissi, 2008]. Clearly, patients will not have the same insulin sensitivities resulting in blood glucose variability and difficulty in control. Hence, new engineered methods are required that can manage these factors.

1.1.2 Clinical Burden and Lack of Access

When an ICU patient is transferred to a less acute ward, several things change that impact glycaemic control. The most significant change have to do with access lines to blood. This change affects both input infusions and drug delivery, as well as blood samples.

More specifically, only ICU patients have arterial lines. Arterial lines are commonly used in TGC for removing small amounts of blood to measure blood

glucose with a glucometer or blood gas analyser. The alternative is a typical pin-stick glucometer, which causes minor discomfort or a time consuming and invasive venous blood draw via syringe. Neither is an option for measuring more than 4x per day in a less acute ward.

Similarly, intravenous (IV) lines are also typically removed on leaving ICU. Hence, insulin infusions (and other drugs) must be given in long acting doses. For TGC this change necessitates the use of much more variable and difficult to manage subcutaneous (SC) insulins, which increases the difficulty and variability of TGC in these wards.

1.1.3 Nursing Resources and Less Intense Monitoring

Differences in routine, environments and loss of invasive monitoring [Coyle, 2001] are among the factors that make nurses in less acute wards feel that caring for recently discharged patients from the ICU is stressful [Hall-Smith et al., 1997]. Achieving tight glycaemic control is labour intensive [Aragon, 2006; Mackenzie et al., 2005], and some patients who were discharged from ICU still need one-to-one care. However, less acute wards are not well resourced to provide this level of care with demand for ICU increasing annually [Wild and Narath, 2005; Green, 2002; Swenson, 1992].

High workloads often result in patient care being delayed in these situations. However, to provide better glycaemic control care to patients, coordination and timing of blood glucose monitoring, meals, administration of insulin must be be done in timely manner. Missing any of these could result in hypo/hyperglycaemia. Van Den Berghe et al. [2001, 2006a] used extra staff to accommodate the additional work required for intensive therapy in the ICU. In Goldberg et al. [2004b] it is stated that every hour, a nurse should locate a glucose metre, perform a fingerstick, record and properly document the readings and perform the appropriate insulin rate adjustments. This process would take around 5 minutes per patient [Whitehorn, 2007]. For a protocol that optimizes nutritional intake as well as insulin, the process would be even longer. Such monitoring is possible in the ICU but not in less acute wards. Hence, methods for less acute wards must be non-invasive in terms of workload, resuscitation and less monitoring and oversight by stretched nursing resources.

In general, there is lack of concern over good glycaemic control in non-critical settings. The result can include an unwillingness to treat and frequent interruptions to treatment during meal times, medications, examinations and other procedures. All of these issues can prevent a protocol that can maintain a good glycaemic control from achieving success [Moghissi, 2008; Deepak et al., 2003]. Hence, a pervasive feeling still exists that blood glucose control is not important other than preventing hypoglycaemia.

Additionally, clinical data to support tight glycaemia control in this arena is still lacking, and there is little agreement on how tight the control should be. Although the debate on these issues continues, there should be no debate that patients in less acute wards should continue to receive the level of control they received in the ICU. The benefit of TGC should not be limited to the ICU. As a result, patients often move from a clinical setting where glycaemic management is a priority to one where it is ignored or receives less attention. Hence, it is not uncommon to see stabilised patients moving to the less acute wards and then returning in 1-3 days to the ICU with deteriorated condition and renewed high blood glucose levels.

The challenge is to find and implement glycaemic goals with a standardized, safe and effective protocol. There is a need for a system that can maintain good blood glucose control outside of the ICU that can support patients transferring from ICU to less acute wards, while addressing the differences in the environment. Most importantly, the system or protocol must minimize the number of frequent interventions and nursing effort to match the staffing available in these wards, while simultaneously providing a quality care.

1.2 Model-based Glycaemic Control

Clinically validated glucose-insulin models that are clinically applicable and have good predictive performance can eliminate potential for hypoglycaemia [Chase et al., 2006, 2010c]. Interestingly, some TGC studies that reported a mortality reduction also had reduced and relatively low hypoglycaemic rates [Chase et al., 2008c], whereas those reporting no change or higher mortality had excessive hypoglycaemia [Finfer and Heritier, 2009; Brunkhorst et al., 2008]. This latter set of

'point' also effectively divides model-based or model-derived protocols (SPRINT) from all others. More specifically, model-based and model-derived TGC methods have shown significant ability to provide very tight control with little or no hypoglycaemia [Chase et al., 2006, 2007, 2008c; Hovorka et al., 2007; Le Compte et al., 2009].

Many studies have developed glucose-insulin models with varying degrees of complexity for a wide range of uses, primarily in research studies of insulin sensitivity [Chase et al., 2007; Mari and Valerio, 1997; Bergman et al., 1981; Parker and Doyle, 2001; Hovorka et al., 2008, 2004b; Wong et al., 2006b]. These studies were developed primarily on different glucose intolerant but otherwise healthy cohorts and relied on a range of different assumptions. The common and ultimate goal is to develop model-based insulin therapy for tight glycaemic regulation, albeit for different purposes in some cases. More importantly, depending on the context of how the model is to be used, real-time identification of a patient-specific model may or may not be a prerequisite.

TGC methods should directly account for patient-specific insulin sensitivity and its potential to vary hour to hour when determining a given intervention, something only model-based approaches might currently provide [Lin et al., 2008; Le Compte et al., 2009]. Patients are individual and dynamic in their condition. To be patient-specific, a TGC protocol must directly (e.g. model-based) or indirectly (model-derived) account for both intra- and inter- patient variability. Currently, only a very few protocols either directly or indirectly adapt their intervention based on patient insulin sensitivity [Chase et al., 2008c; Wong et al., 2006b; Le Compte et al., 2009]. Most of these are model-based or, in the case of SPRINT, model-derived [Lonergan et al., 2006a; Chase et al., 2007; Lonergan et al., 2006a]. As a result, they are able to explicitly and directly account for variations in the patients metabolic response, as they have greater insight than typical clinically derived protocols without these computations.

Most other reported protocols, do not account for or assess insulin sensitivity in any way [Van Den Berghe et al., 2001; Krinsley, 2004; Van Den Berghe et al., 2006a; Treggiari et al., 2008; De La Rosa et al., 2008; Goldberg et al., 2004b; Inzucchi and Rosenstock, 2005; Goldberg et al., 2004a; Finfer and Heritier, 2009; Brunkhorst et al., 2008; Preiser et al., 2009], including the recent, major RCTs. Other protocols, adjust based on surrogate response to insulin decreases (e.g

resistance increases) [Davidson et al., 2005], but do so in fixed multiples, rather than via an explicit or patient-specific algorithm. None account for the hour to hour variability, or the risks it imposes.

For a model to be successful when used in the delivery of TGC, it needs to reflect observable physiology, as well as known biological mechanisms. In addition, it should be uniquely identifiable in clinical real-time, and thus the type and number of parameters to be identified should reflect the clinically available data. Finally, the most important aspect for a model to be used in model-based TGC is its predictive ability. Most studies provide only fitting error as validation, for example [Hovorka et al., 2007; Parker and Doyle, 2001]. Fitting and prediction error are due to model being able to capture patient's dynamics. How well a model captures a patient's dynamics is related to the fitting error, and if the model is able to predict the future glycaemic changes, that verifies the model parameters used do reflect clinical physiology. Therefore, prediction accuracy is significant as it validates the fitting method used and that the model parameters were not simply molded to fit the collected data.

1.3 Preface

In summary, the problem of critically ill or recovering critically ill patient is summarised as a strong counter-regulatory hormone driven stress response that induces significant insulin resistance and can antagonise insulin production and action. Coupled with unsuppressed endogenous glucose production, EGP and potentially excessive nutritional inputs, high blood glucose is inevitable. Dynamic patients whose condition, and thus insulin resistance, evolves regularly and sometimes acutely, provide a further challenge to providing consistently tight TGC across every individual patient in a cohort. Coupled with clinical burden in measuring frequently, and large swings in blood glucose are inevitable without the ability to adapt. Thus, the overall problem becomes one of managing a highly dynamic cohort, with minimal effort or intervention, which also displays significant variability both between and within patients. Considered generically, this definition is a classic dynamic systems and control problem definition that can be readily addressed if the major driving factors can be accurately modeled and understood.

Hence, the goal of this research is to develop a model-based protocol that is clinically practical and tailored for glycaemic control in the less acute wards. It will provide TGC by controlling insulin delivery in both the subcutaneous and/or intravenous route (if available). Optimizing nutritional requirements intake may also be a (lesser) option in this environment. The protocol design incorporates physiological modeling and engineering techniques and must be able to adapt to individual patient clinical requirements. By doing so, the protocol will produce accurate patient-specific recommendations for each insulin interventions. It will be a comprehensive protocol that follows insulin-resistant patients from ICU to less acute wards, transitioning from intravenous insulin to subcutaneous insulin, while maintaining normo-glycaemia and minimising clinical effort, and thus reducing ICU rebound and cost.

The target would be to provide TGC for each individual patient, as in the study by [Chase et al., 2010a]. Hence, the analysis of TGC from the developed control model protocol besides from cohort analysis, would be on per-patient analysis. A move that is not commonly reported in TGC trials apart from [Chase et al., 2008c; Van den Berghe et al., 2003; Goldberg et al., 2004a].

The goal is pursued by further developing and linking physiological models of each part for the whole system, from glucose regulation and the interaction between glucose and plasma insulin to the absorption kinetics of long acting subcutaneous insulin. All the models are validated before being used for protocol analysis and design. Variability is introduced in the identified Glargine model parameters to account for intra- and inter- patient variability, and simulated via Monte Carlo analysis. The overall thesis preface is outlined:

Chapter 2 reviews previous glucose-insulin models that have been applied for glycaemic control in the critical care settings. As computational capability and access improve, there are avenues of further improvement where better models or methods can be developed. This chapter presents an updated glucose-insulin control model for use in real-time glycaemic control. The developed model, ICING (Intensive Control Insulin-Nutrition Glycaemic Model) is a comprehensive, more physiologically relevant glucose-insulin dynamic system model. The ICING model is an integration and improvement of two clinically validated glucose-insulin physiological models.

Chapter 3 presents the parameter identification method for the critical population parameters in the developed glucose-insulin, ICING model. The updated model with it's fitting and predictive virtual patient validation is also presented in this chapter. The results confirm that the ICING model is suitable for developing model-based insulin therapies, and capable of delivering real-time model-based TGC with a very tight prediction error range.

Chapter 4 presents the development and validation of a detailed pharmacokinetics model of the subcutaneous absorption kinetics of Glargine. Glargine will cover the basal need for patients in the less acute wards. If Glargine can be successfully used for TGC, nursing effort can be greatly reduced as Glargine only needs once or twice injection daily. Hence, in order to use a model-based method, Glargine pharmacokinetics and pharmacodynamics need to be modeled. The fundamental structure of the model is taken from a prior model but new development is made to better capture the physiological aspect. Critical pharmacokinetics measures, maximal plasma insulin concentration, C_{max} and time to maximal plasma insulin concentration, T_{max} were used for validation purposes. A Monte Carlo study was performed on identified model parameters to account for patients variability often seen clinically.

Chapter 5 presents simulated virtual control trials adapting the glucose-insulin pharmacokinetics, ICING model developed in Chapters 2 and 3, as well as the validated subcutaneous Glargine absorption kinetics developed in Chapter 4. Virtual trials were performed to assess the effectiveness of Glargine as basal insulin replacement for TGC in less critical patients. Efficacy of Glargine was evaluated by comparison of glycaemic performance using Glargine in virtual trials against the clinical results from SPRINT protocol. The overall results show an approach to managing the intravenous to subcutaneous insulin transition that occurs as patients leave intensive care for less acute wards during their hospital stay. Safe, effective approaches to this transition will ensure that clinical burden and workload are not increased, while maintaining the benefits of tight glycemic control.

Chapter 6 presents simulated virtual control trials to seek the optimum controller by using Glargine as basal insulin and SPRINT protocol. The goal is to seek a protocol that can aid patient recovery, and seamlessly transition IV insulin in the intensive care unit to subcutaneous insulin that will be

the sole form of TGC input used in less acute wards. A transition protocol would enable a relatively labour intensive intravenous insulin with frequent measurement in the ICU to less intensive, longer acting, subcutaneous insulin in less acute wards with consequently fewer measurements. The optimal protocol, SPRINT-1U+Glargine, has the potential to be effectively employed in a clinical pilot study.

Chapter 7 presents Monte Carlo analysis to quantify the performance and robustness of the SPRINT-1U+Glargine protocol developed in Chapter 6. The protocol is analyzed to assess its robustness towards physiological variability and sensor errors. For clinical implementation, it is crucially important to ensure the protocol is robust towards a wide range of expected variability seen in a clinical setting.

Chapter 8 presents the conclusions of the thesis.

Chapter 9 presents the future avenues for the study with a focus on the pilot clinical trial to be conducted at Christchurch Hospital's ICU and High Dependency Ward.

Chapter 2

Model Development

Metabolic modeling has been a useful tool for the understanding of glucose-insulin dynamics. During the last decade, a wide variety of models have been proposed. These models provide better insight, and serve as a platform to understand a complex physiology with varying degrees of complexity. The primary use of metabolic models has been the development of model-based measures to assess metabolic parameters, with a focus on measuring insulin sensitivity [Docherty et al., 2009; Lotz et al., 2008; Chase et al., 2007; Mari and Valerio, 1997; Bergman et al., 1981; Parker and Doyle, 2001; Hovorka et al., 2008, 2004b; Wong et al., 2006a,b].

Models can be grouped into two classes, simple models and comprehensive models. A simple model has the advantage of having less identifiable parameters, but at the potential expense of being less physiologically accurate or specific. A comprehensive model on the other hand, may represent the true or more exact nature of a system, but can be too complex and generally not identifiable without extensive data that is not readily available in a clinical setting.

According to American Diabetes Association (ADA), among the two kinds of models in healthcare are:

- Biological Modeling
- Clinical Medicine

Clinical glycaemic control modeling is a model that includes both of the above compartments, biological modeling and clinical medicine, and requires a complete

knowledge of the dynamic system. There is a need for physiological accuracy to ensure accurate prediction from a known clinical intervention. However, given the lesser amount of data typically available to fit patient-specific model parameters for predicting outcomes, it may require less physiological resolution. Hence, most clinical model-based control applications look for the simplest physiologically relevant model to be effective.

This chapter examines several forms of existing clinical glycaemic control models. Intensive insulin therapy and TGC, particularly in ICU, are the subjects of increasing and controversial debate in recent years. Model-based TGC has shown potential in delivering safe and tight glycaemic management, all the while limiting hypoglycaemia. A comprehensive, more physiologically relevant Intensive Control Insulin-Nutrition-Glucose (ICING) model is presented and validated using data from critically ill patients. Two existing glucose-insulin models are reviewed and formed the basis for the ICING model. Model limitations are discussed with respect to relevant physiology, pharmacodynamics and TGC practicality. Model identifiability issues are carefully considered for clinical settings.

This chapter also contains significant reference to relevant physiology and clinical literature, as well as some references to the modeling efforts in this field. It then presents a more comprehensive model, ICING (Intensive Control Insulin-Nutrition Glycaemic Model) from this context. ICING is designed specifically for use in glycaemic control, particularly in the ICU and beyond.

2.1 Physiological Basis of Glucose-Insulin System

Metabolic modeling has been used to estimate glucose disappearance and insulin glucose-dynamics for relatively 50 years now. Bolie [1961] is one of the pioneers in modeling the linear glucose disappearance and glucose-insulin dynamics, in the simplest form. This model although may be oversimplified, provided the base for many research on diabetes modeling such as the work by [Ackerman et al., 1964]. With ordinary differential equations to represent the insulin and glucose system, Bolie [1961] proposed the following model:

Glucose disappearance:

$$\dot{G} = -a_1 G(t) - a_2 I(t) + p \tag{2.1}$$

Insulin Kinetics:

$$\dot{I} = -a_3 G(t) - a_4 I(t) \tag{2.2}$$

where G_t represents glucose concentration, I is the insulin, a_1 is rate of liver accumulation of glucose, a_2 is rate of tissue utilisation, a_3 is rate of insulin destruction, a_4 is rate of insulin production, and p is glucose feed.

However, the starting point of glucose-insulin dynamics modeling, and perhaps the best known, is the Minimal Model of Bergman et al. [Bergman et al., 1981]. The equation presented below is not the originally published but the most commonly known. This simple compartment model has two equations for glucose disappearance, and one for insulin kinetics:

Glucose disappearance:

$$\dot{G} = (X - P_1)G(t) + P_1 G_b + P(t) \tag{2.3}$$

$$\dot{X} = -P_2 X(t) + P_3(I(t) - I_b) \tag{2.4}$$

Insulin Kinetics:

$$\dot{I} = -nI(t) + \frac{u(t)}{V} \tag{2.5}$$

where t is the time, $G(t)$ is the total plasma glucose concentration at time t, $X(t)$ is proportional to insulin action in a remote compartment, and $I(t)$ is the plasma insulin concentration. Inputs to the system include $P(t)$, glucose appearance from external glucose sources, and $u(t)$, exogenous insulin. There are two terms that define the steady state or basal plasma glucose and insulin levels under no external influences, G_b and I_b. Three patient-specific parameters, P_1, P_2 and P_3, arise from this model, with the ratio P_3/P_2 being the insulin sensitivity index. Signs of P_1 and P_2 are changed from the original publication in Equations (2.3) and (2.4) to have these parameters numerically positive valued per accepted sign conventions [Carson and Cobelli, 2001]. A graphical representation of this Minimal Model definition is shown in Figure 2.1.

The model is primarily used in clinical studies. In Bergman [2002], it is men-

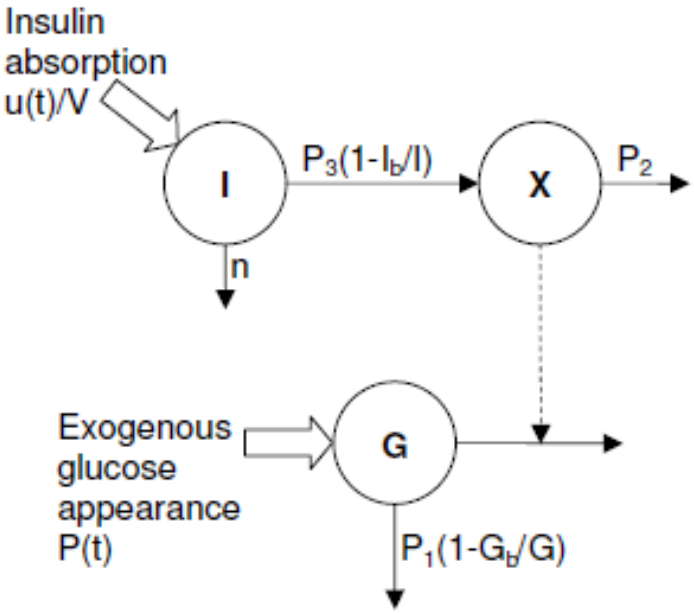


Figure 2.1 Minimal Model of Bergman et al. [1981] as defined by Equations (2.3)–(2.5).

tioned that more than 500 studies can be linked to the Minimal Model [Bergman et al., 1981]. A major contribution from this model is it provides mean of estimating insulin sensitivity, S_I. The model clearly illustrates the three main basic dynamics that must be captured in a glycaemic control problem:

1. Insulin pharmacokinetics and distribution — from exogenous input to action in the periphery
2. Glucose pharmacokinetics and/or appearance, where meal models for $P(t)$ in Equation (2.3) would add compartments
3. Glucose-insulin pharmacodynamics accounting for the insulin-mediated removal of glucose

However, the model does have some drawbacks particularly in regard to be used as a clinical glycaemic control [Doran et al., 2004a,b]. Specifically, it does not account for saturation of glucose removal by insulin [Prigeon et al., 1996; Natali et al., 2000; Rizza et al., 1981], saturation of insulin transport [Thorsteinsson, 1990; Frost et al., 1973; Ellemann et al., 1987; Prigeon et al., 1996], measurable and unmeasurable glucose compartments [Cobelli et al., 1992, 1999; Vicini et al.,

1997; Caumo et al., 1999], or the dynamics of insulin receptors and their mass [Hovorka et al., 2004a], to name a few. All of these issues have been raised in the extensive physiological modelling literature, and several modified versions of this model developed as a result. It is also not identifiable for individuals who are highly insulin resistant when there is assay error or noise, creating significant problems for use at the bedside.

After more than 3 decades, the minimal model analysis continues to evolve and widely studied. Table 2.1 lists several studies that could be linked to Minimal Model [Bergman et al., 1981].

One of these versions is the study by Van Herpe et al. [2007]. It is a fourth order model which retains the fundamental structure of the Minimal Model Bergman et al. [1981]. The model uses an optimized adaptive minimal modeling approach, specifically designed for blood glucose prediction in the critically ill. The equations that govern the model with parameter descriptions below are taken from Van Herpe et al. [2007].

$$\dot{G} = (P_1 - X(t))G(t) - P_1 G_b + \frac{F_G}{V_G} \tag{2.6}$$

$$\dot{X} = P_2 X(t) + P_3(I(t) - I_b) \tag{2.7}$$

$$\dot{I}_1 = \alpha max(0, I_2) - n(I_1(t) - I_b) + \frac{F_1}{V_1} \tag{2.8}$$

$$\dot{I}_2 = \beta\gamma(G(t) - h) - nI_2(t) \tag{2.9}$$

where G is the glucose, I_1 is the insulin concentrations in the blood plasma, X describes the effect of insulin on net glucose disappearance proportional to insulin in the remote compartment. I_b does not have a clinical interpretation but introduced for mathematical reasons-fraction of insulin concentration derived from endogenous insulin secretion. G_b is the basal value of plasma glucose and I_b is the plasma insulin. Inputs to the model are F_1 the exogenous insulin flow and F_G the carbohydrate calories flow, where both are administered intravenously. Glucose distribution space and insulin distribution volume are denoted by V_G and V_I respectively. P_1 represents the glucose effectiveness when insulin remains at the

Table 2.1 Models evolved from the Minimal Model [Bergman et al., 1981].

Reference	Improvement to Minimal Model
Caumo and Cobelli [1993a]	Introduced two glucose compartments.
Derouich and Boutayeb [2002]	Introduced parameters related to physical exercise.
Andersen and Højbjerre [2005]	Adopted a Bayesian graphical model to describe the coupled minimal model that accounts for measurement and process variability.
Wong et al. [2006a,b]	Introduced renal glucose clearance rate.
Chase et al. [2007]	Introduced additional linear terms and a grouped term for insulin sensitivity.

basal level. P_2 and P_3 are the fractional rates of net remote insulin disappearance and insulin-dependent increase, respectively. Endogenous insulin is represented as the insulin flow that is released in proportion (by γ) to the degree by which glycaemia exceeds a glucose threshold level h. Additionally, n denotes the time constant for insulin disappearance. In cases where glycaemia does not surpass the glucose threshold level, h the part that represents endogenous insulin production from the first part of the equation I_1 is equal to 0. Finally, α is the scaling factor for I_2, while β serves to keep the units checked.

To represent typical features of patients seen in the ICU, where intra- and inter- patient variability are high, the model of Van Herpe et al. [2007] is re-estimated at frequent intervals. By frequent re-estimation, the model should better capture the patient's dynamics. In contrast to the original Minimal Model, this model introduces endogenous and exogenous insulin, where exogenous insulin is not presented in the original Minimal Model. In particular, most patients in the ICU do not have prior diabetes, which means their endogenous insulin secretion capability is still functioning. In their case, with increased insulin resistance, exogenous insulin is required. Hence, endogenous and exogenous insulin must be modelled to capture the unique hyperglycaemic and hyperinsulinamic ICU patient case.

The Minimal Model [Bergman et al., 1981] performs well during the intravenous glucose tolerance test (IVGTT) with a single glucose shot. IVGTT is a test in which glucose, is given through an IV to test the response of the body in releasing insulin into blood. This would correspond to how well the body reacts to glucose and in turn, to insulin. The method is used to test for resistance to insulin and ability to reduce insulin. However, in the ICU, this carbohydrate appearance in the Minimal Model [Bergman et al., 1981] is not valid. Hence, the model is developed with a goal for continuous flow of glucose. To portray this dynamic, the endogenous insulin section of the Minimal Model [Bergman et al., 1981] is transformed into two sections, as seen in Equation (2.8– 2.9) in Van Herpe et al. [2007]'s model.

This predictive control model has not been clinically validated, and only tested on a simulation basis using the first 48 hours after admission data for 19 critically ill patients. *In-silico* results, in terms of control behaviour with reference tracking and suppression of unknown disturbance factors show the potential of

the model based control algorithm to be used in the ICU [Van Herpe et al., 2009]. However, its predictive performance in validating the intervention chosen has not been reported.

There have been several other metabolic models used in clinical examination of critical care patients and glycaemic control [Wong et al., 2006a; Chase et al., 2006, 2007, 2008c; Hovorka et al., 2007; Le Compte et al., 2009]. The first model as reviewed by Chase et al. [2006] is of [Chee et al., 2003, 2004], who used an optimized PID (proportional-integral-derivative) and sliding mode control, and focused on applying continuous glucose sensors. Although [Chee et al., 2003, 2004] is a control algorithm and not a physiological model, but the projected glucose is a control model.

The PID control model from Chee et al. [2003, 2004] is defined:

$$\text{Additional Insulin infusion} = \begin{cases} 4\text{U/h, if } \|\bar{W}_{Zone}\| > 4.5 \\ 2\text{U/h, if } 3.6 \leq \|\bar{W}_{Zone}\| \leq 4.5 \\ 2\text{U/h, if } 2.7 \leq \|\bar{W}_{Zone}\| < 3.6 \\ 2\text{U/h, if } \|\bar{W}_{Zone}\| < 2.7 \end{cases} \tag{2.10}$$

where

$$\|\bar{W}_{Zone}\| = \frac{1}{\sum_{i=1}^{24} i} \left(\sum_{n=1}^{24} n W_{Zone}[n] \right) \tag{2.11}$$

and

$$\text{Insulin bolus} = \begin{cases} 6\text{U/h, if } \Delta y_{proj} \geq 2 \text{ mmol/L} \\ 4\text{U/h, if } 1 \leq \Delta y_{proj} < 2 \text{ mmol/L} \\ 0\text{U/h, if } \Delta y_{proj} < 1 \text{ mmol/L} \end{cases} \tag{2.12}$$

where

$$\Delta y_{proj} = \left(\frac{\sum_{i=1}^{6} X_i Y_i}{\sum_{i=1}^{6} {X_i}^2} \right) \Delta x \tag{2.13}$$

$$X_i = x_i - \tilde{x} \tag{2.14}$$

$$Y_i = y_i - \tilde{y} \tag{2.15}$$

$$\tilde{x} = \frac{x_{max} + x_{min}}{2} \tag{2.16}$$

$$\tilde{y} = \frac{y_{max} + y_{min}}{2} \tag{2.17}$$

x_{max} and x_{min} are the maximum and the minimum time values in the 30-min window, and y_{max} and y_{min} are the maximum and the minimum blood glucose levels in the 30-min window.

The integral control Equation (2.10) is implemented when sliding tables do not provide adequate glycemic reduction, and the amount of additional insulin is calculated using Equation (2.11), a normalized weighted average of the blood glucose level (BGL) zones using a 2-hour triangular window. Derivative control is implemented using Equations (2.12)–(2.17). Expert control is implemented by keeping an active sliding table and 'offsetting' the recommended sliding table input according to several conditions, based on Equations (2.10)–(2.12), in order to determine a the control input.

Another model is that of Hovorka et al. [2002] that forms the basis of MPC model. However, it is more of a physiological research, specifically a tracer study on healthy adults. Hence, a better reference of models that have been used for clinical control is of Hovorka et al. [2004a], which was used for controlling Type 1 diabetes.

$$\begin{aligned}\dot{Q}_1(t) = &-\left[\frac{F_{01}^c}{V_G G(t)} + x_1(t)\right] Q_1(t) + k_{12} Q_2(t) \\ &-F_R + U_G(t) + EGP_0[1 - x_3(t)]\end{aligned} \tag{2.18}$$

$$\dot{Q}_2(t) = x_1(t) Q_1(t) - [k_{12} + x_2(t)] Q_2(t) y(t) G(t) = \frac{Q_1(t)}{V_G} \tag{2.19}$$

$$F_{01}^c = \begin{cases} F_{01} & \text{if } G \geq 4.5 \text{ mmol/L} \\ \dfrac{F_{01} G}{4.5} & \text{otherwise} \end{cases} \tag{2.20}$$

$$F_R = \begin{cases} 0.003(G - 9) V_G & \text{if } G \geq 9 \text{ mmol/L} \\ 0 & \text{otherwise} \end{cases} \tag{2.21}$$

$$U_G(t) = \frac{D_G A_G t e^{-t/t_{max,G}}}{t^2} \tag{2.22}$$

$$\dot{S}_1(t) = u(t) - \frac{S_1(t)}{t_{max,I}} \tag{2.23}$$

$$\dot{S}_2(t) = \frac{S_1(t)}{t_{max,I}} - \frac{S_2(t)}{t_{max,I}} \tag{2.24}$$

$$\dot{I}(t) = \frac{U_I(t)}{V_I} - k_e I(t) \tag{2.25}$$

where

$$U_I(t) = \frac{S_2(t)}{t_{max,I}} \tag{2.26}$$

$$\dot{x}_1(t) = -k_{a1} x_1(t) + k_{b1} I(t) \tag{2.27}$$

$$\dot{x}_2(t) = -k_{a2} x_2(t) + k_{b2} I(t) \tag{2.28}$$

$$\dot{x}_3(t) = -k_{a1} x_3(t) + k_{b3} I(t) \tag{2.29}$$

where Q_1 and Q_2 represent masses of glucose in the accessible and inaccessible compartments, k_{12} the transfer rate between the inaccessible and accessible compartments, V_G the distribution volume of the accessible compartment, y and G the measurable glucose concentration, and EGP_0 the endogenous glucose production extrapolated to the zero insulin concentration. F_{01}^c is the total non-insulin-dependent glucose flux corrected for the ambient glucose concentration and F_R is the renal glucose clearance above the glucose threshold of 9 mmol/L. $U_G(t)$ is the gut absorption rate, dependent upon the carbohydrates digested, D_G, carbohydrate bioavailability, A_G, and the time-of-maximum appearance rate of glucose

in the accessible compartment, $t_{max,G}$. The insulin subsystem is described by Equations (2.23)–(2.29). S_1 and S_2 are a two-compartment chain for absorption of subcutaneously administered rapid-acting insulin, $u(t)$ the insulin input (bolus/infusion), and $t_{max,I}$ the time-to-maximum insulin absorption. $I(t)$ is the plasma insulin concentration, k_e is the fractional elimination rate and V_I the distribution volume. The insulin action subsystem consists of three components, endogenous glucose production, transport/distribution and disposal (x_1, x_2 and x_3). Finally, k_{ai} and k_{bi} $(i = 1, \ldots, 3)$ represent the activation and deactivation rate constants of insulin action, respectively. A graphical representation is shown in Figure 2.2.

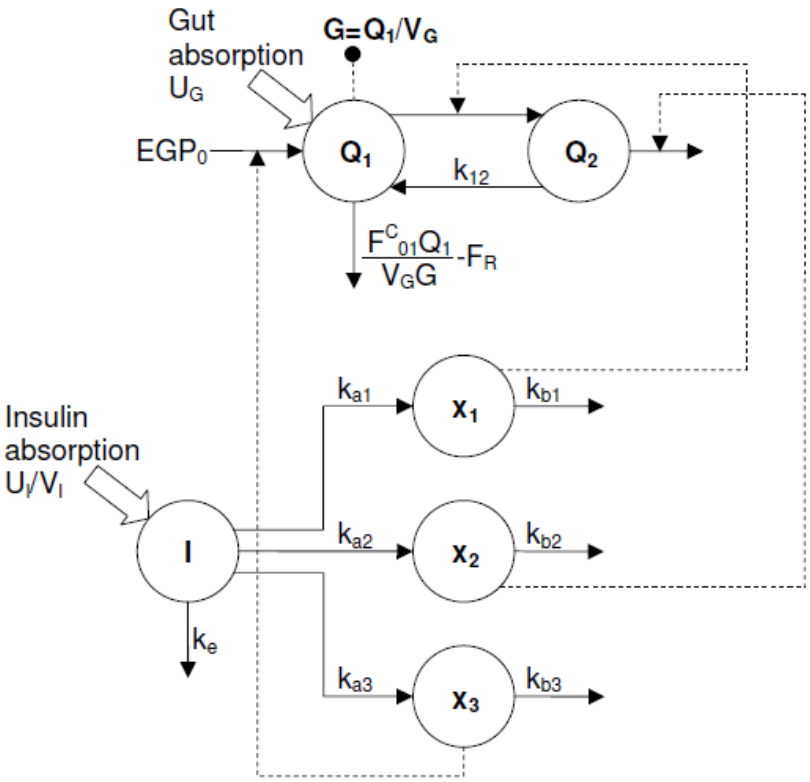


Figure 2.2 Glucose-insulin compartmental model of Hovorka et al. [2004a] as defined by Equations (2.18)–(2.29).

The MPC approach is most suitable for systems with long delays and open-loop characteristics. However, a similar version of this approach is used for ICU patients in the eMPC approach [Plank et al., 2006; Hovorka et al., 2007]. It has been trialled for 48 hours on cardiovascular surgery ICU patients with good results. Again, its predictive ability and validity have not been reported.

2.2 Glucose-Insulin Physiology Model

Two clinically validated glucose-insulin physiology models set the basis for this study. The model from Chase et al. [2007] was developed and validated specifically for glycaemic level management in the ICU. It is very loosely based on the Minimal Model [Bergman et al., 1987] with additional non-linear terms and a grouped term for insulin sensitivity. Unlike the Minimal Model, this model captures the fundamental dynamics seen in critically ill patients, yet has a relatively simple mathematical structure enabling rapid identification of patient-specific parameters [Hann et al., 2005]. This model only requires measurements in blood glucose levels. Therefore, it can be used for identification of 1-2 critical parameters at the bedside for clinical real-time identification and control. This structure has been widely used in clinical TGC studies and other analysis [Wong et al., 2006a; Lonergan et al., 2006a,b; Lin et al., 2006, 2008; Le Compte et al., 2009].

The second model is from Lotz et al. [2008] and was developed for high resolution diagnosis of insulin resistance with minimal clinical intensity and effort. The modeled insulin sensitivity has high correlation to the euglycaemic hyperinsulinemic clamp (EIC) and high repeatability [Lotz et al., 2008, 2006]. This model has more patient-specific parameters, but is not suitable for real-time patient-specific parameter identification because it also requires non-real time plasma insulin and C-peptide assays [Lotz et al., 2009]. The laboratory turnaround time for plasma insulin and C-peptide levels is typically overnight which is not practical for supporting therapy selection. Recent work has sought to eliminate this issue in healthy subjects while using this model, but at a less of model precision [Docherty et al., 2009].

This section quickly reviews both models, and presents a new combined model that is more comprehensive and has a stronger physiological relevance for use in the ICU and less acute wards.

2.2.1 Critical Care Glucose-Insulin Model

Equations (2.30)–(2.34) presents the model used for glycaemic control in intensive care from Chase et al. [2007], hereafter referred to as the “ICU Model”.

ICU Model

$$\dot{G} = -p_G G(t) - S_I(G(t)+G_E)\frac{Q(t)}{1+\alpha_G Q(t)} + \frac{P(t)}{V_G} \quad (2.30)$$

$$\dot{Q} = -kQ(t) + kI(t) \quad (2.31)$$

$$\dot{I} = -\frac{nI(t)}{1+\alpha_I I(t)} + \frac{u_{ex}(t)}{V_I} \quad (2.32)$$

$$P(t_i < t < t_{i+1}) = \bar{P}_{i+1} + (P(t_i) - \bar{P}_{i+1})e^{-k_{pd}(t-t_i)} \quad \text{where } \bar{P}_{i+1} < P(t_i) \quad (2.33)$$

$$P(t_i < t < t_{i+1}) = \bar{P}_{i+1} + (P(t_i) - \bar{P}_{i+1})e^{-k_{pr}(t-t_i)} \quad \text{where } \bar{P}_{i+1} > P(t_i) \quad (2.34)$$

A schematic of the model is shown in Figure 2.3. The symbols G [mmol/L] denotes the glucose above an equilibrium level, G_E [mmol/L]. Plasma insulin is I [mU/L] and exogenous insulin input is $u_{ex}(t)$. The effect of previously infused insulin being utilized over time in the interstitium is represented by Q [mU/L], with k [1/min] accounting for the effective life of insulin in the system. Patient endogenous glucose removal and insulin sensitivity are p_G [1/min] and S_I [L/mU/min] respectively. The parameter V_I [L] is the insulin distribution volume and n [1/min] is the constant first order decay rate for insulin from plasma. External nutrition is $P(t)$ [mmol/min]. In Equations (2.33)–(2.34), k_{pr} [1/min] and k_{pd} [1/min] are the rise and decay rates of exogenous (enteral) plasma glucose appearance, and $\bar{P}_i$ and $\bar{P}_{i+1}$ are the stepwise consecutive enteral glucose feed rates used to model dextrose control. The glucose distribution volume is V_G [L]. Michaelis-Menten functions are used to portray saturations, with parameter α_I [L/mU] used for saturation of plasma insulin disappearance, and α_G [L/mU] for saturation of insulin-stimulated glucose removal.

This model was developed explicitly for critical care glycaemic control [Chase et al., 2007; Wong et al., 2006b; Chase et al., 2005; Lin et al., 2008], and its fundamental structure was validated on clinical data from critically ill patients [Chase et al., 2008c, 2010c; Suhaimi et al., 2010]. All the compartmental transport and utilisation rates are treated as constants except insulin sensitivity, S_I. Insulin sensitivity S_I is the critical dynamic parameter, and is typically fitted to patient data hourly [Hann et al., 2005], producing a step-wise hourly varying profile. The SPRINT glycaemic control protocol [Chase et al., 2008c; Lonergan et al.,

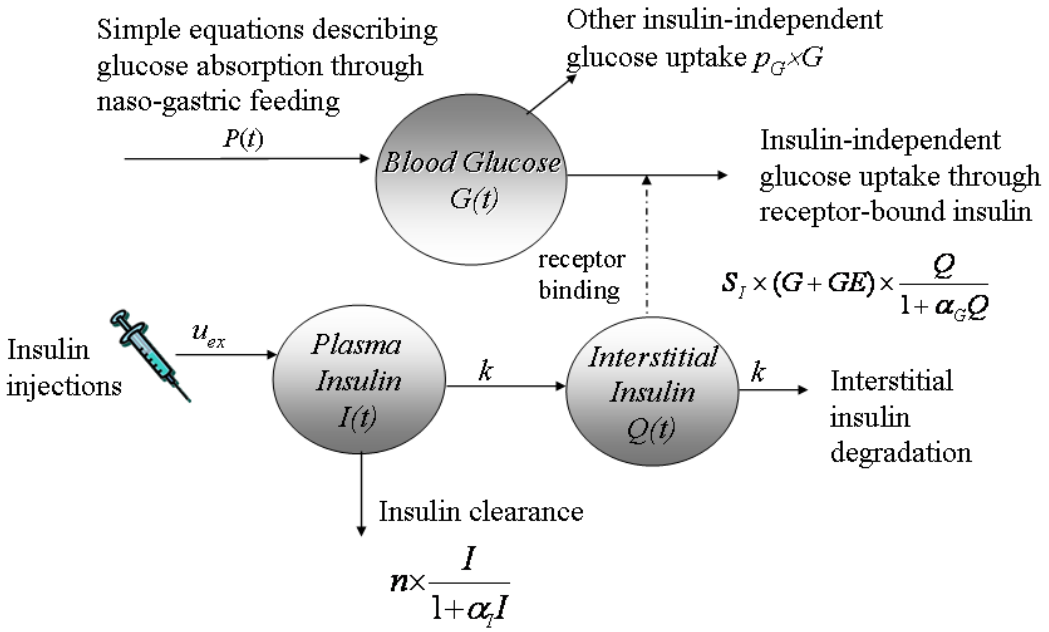


Figure 2.3 Schematic of Critical Care Glucose-Insulin Model defined in Equations (2.30)–(2.34). The model is adopted from Chase et al. [2007] and referred to as the "ICU Model".

2006a,b] was developed using this model. Importantly, the pre-trial virtual trial simulation of SPRINT gave very similar results to the subsequent actual clinical implementation results [Chase et al., 2007], providing a further measure of model validation.

However, this model does not describe the gastric uptake of glucose in a completely realistic way. Equations (2.33) and (2.34) express simple exponential rises and decays of glucose absorption, which eventually reach the steady state equals to the feeding rate. This simple expression works well in critical care, where nasogastric feeding rate is not adjusted frequently. If the feeding rate is changed more frequently than once every hour, Equations (2.33) and (2.34) fail to describe the gastric absorption correctly. In particular, the amount of glucose fed does not equate the area under the glucose appearance curve. Figure 2.4 demonstrates this issue graphically.

This model also uses an "equilibrium blood glucose level" term, G_E, which is usually set to the patient's blood glucose level at the start of insulin therapy or a long moving average. This term effectively addresses the endogenous balance of glucose and insulin. Hence, this model does not explicitly express endogenous insulin production. Thus, when there is a significant shift in this balance in a patient, for any number of reasons [Chase et al., 2005; Wong et al., 2006b; Doran et al., 2004a], G_E often needs to be adjusted to capture the patient's (then) current clinical glucose-insulin dynamics. Hence, the term is non-physiological, unidentifiable and ignored in later versions of this model [Chase et al., 2007; Le Compte et al., 2009; Lin et al., 2008; Blakemore et al., 2008; Suhaimi et al., 2010]. These latter models also includes endogenous insulin terms in the same form.

This model also has relatively simple insulin kinetics compared to other more extensive models [Thorsteinsson, 1990; Ferrannini and Cobelli, 1987a,b; Toffolo et al., 2006]. It does not explicitly express different routes of insulin clearance and transport from plasma. Instead, the lumped out-flux from plasma is expressed by a saturable term $-nI/(1+\alpha_I I)$. In addition, as only kI appears as an input to interstitial insulin Q, the difference between n and k, (n-k) is implicitly the insulin clearance by liver and kidneys, which was clinically validated in Lotz et al. [Lotz et al., 2006]. The insulin flux between plasma and interstitial is also only one way in this model, ignoring the diffusion from interstitium back to plasma, as it was designed for IV TGC using bolus delivery. Therefore, the insulin concentration

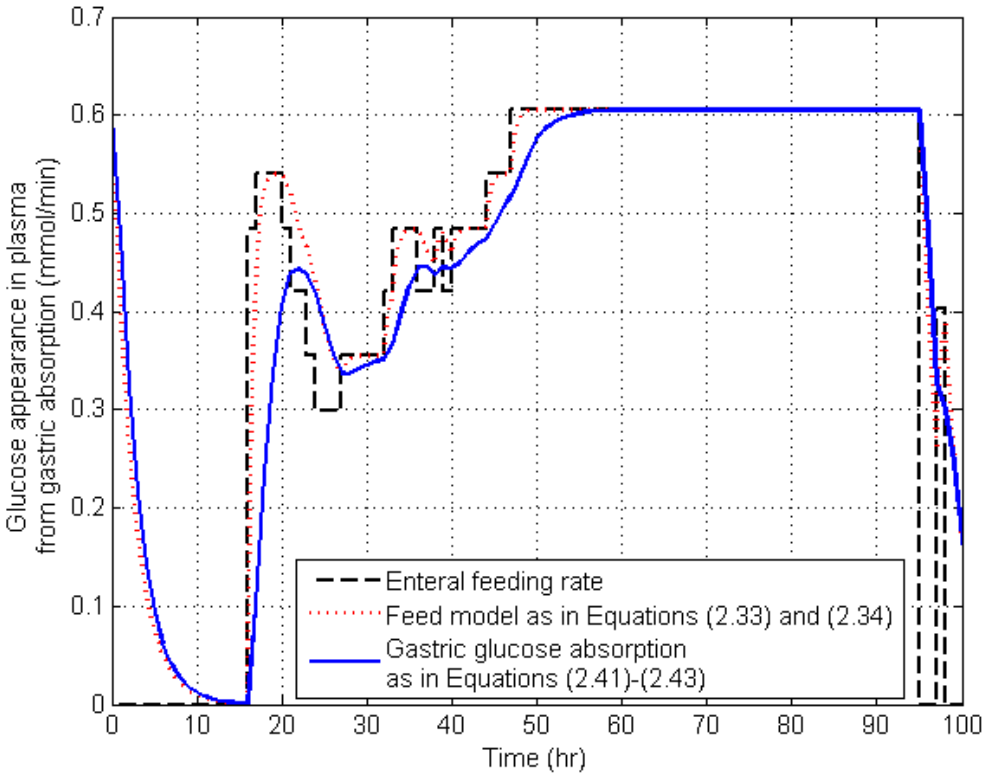


Figure 2.4 Gastric glucose absorption issues with the Critical Care Glucose-Insulin model of Equations 2.33 and 2.34 depicted in red dots, $(\cdots)$. The model does not realistically describe the gastric uptake of glucose, portraying simple exponential rises and decays of glucose absorption. This model works well in the ICU where feed, $P(t)$ is not adjusted frequently. The solid blue line, (–) shows the ICING feed model of Equations (2.41)–(2.43). This model is suitable for modeling meal ingestion over a short period of time as it conserves ingested glucose.

gradient between plasma and the interstitium using bolus delivery is always large enough that diffusion back to plasma is negligible. However, this case and mode of insulin delivery is less typical in the ICU in general and will introduce error no matter the delivery mode.

2.2.2 Glucose-Insulin Model for Insulin Sensitivity Test

Equations (2.35)–(2.37) presents the model used for insulin sensitivity testing from Lotz et al. [2008], hereafter referred to as the "S_I Test Model".

S_I Test Model

$$\dot{G} = -p_G G(t) - S_I(G(t)+G_E)\frac{Q(t)}{1+\alpha_G Q(t)} + \frac{P(t)}{V_G} + EGP(t) \quad (2.35)$$

$$\dot{Q} = \frac{n_I}{V_Q}(I(t)-Q(t)) - n_C Q(t) \quad (2.36)$$

$$\dot{I} = -n_K I(t) - \frac{n_L I(t)}{1+\alpha_I I(t)} - \frac{n_I}{V_P}(I(t)-Q(t)) + \frac{u_{ex}(t)}{V_P} + (1-x_L)\frac{u_{en}(t)}{V_P} \quad (2.37)$$

where the nomenclature for this model is largely the same as that for the critical care model from Chase et al. [2007] in Section 2.2.1 and Equations (2.30)–(2.34). This model has more parameters and more extensive insulin kinetics. It includes the endogenous glucose production rate EGP [mmol/min], as well as the endogenous insulin production u_{en} [mU/min]. The endogenous insulin production can be calculated from C-peptide measurements using a well validated insulin-C-peptide kinetics model [Van Cauter et al., 1992]. Endogenous insulin goes through first pass hepatic extraction, where x_L is the fraction of extraction. This model also has more physiologically specific insulin transport parameters compared to Chase et al. [Chase et al., 2007], where n_K is the kidney clearance rate of insulin from plasma [1/min], n_L is the liver clearance rate of insulin from plasma [1/min], n_I is the diffusion constant of insulin between compartments [L/min], and n_C is the cellular insulin clearance rate from interstitium [1/min]. Finally, it also

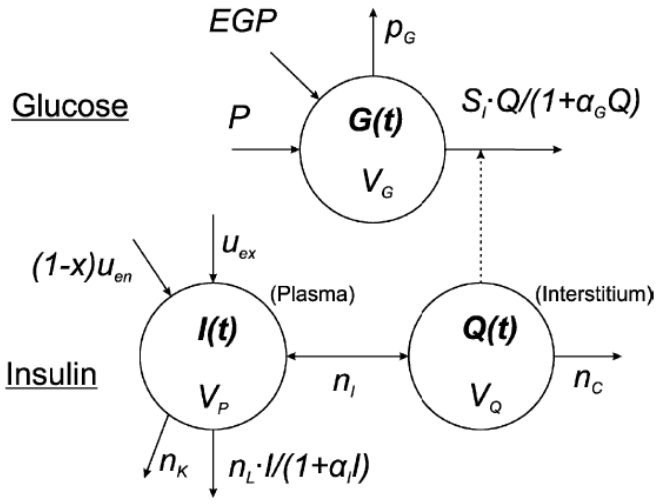


Figure 2.5 A schematic of glucose-insulin sensitivity test as defined in the Equations (2.35)–(2.37). The schematic and its pharmacodynamic interaction is adopted from Lotz et al. [2008]. In this study, the model is referred to as the "S_I Test Model".

uses different volumes for each compartment, where V_P is the plasma volume (+Fast exchanging tissues) [L] and V_Q is the interstitial fluid volume [L]. The experimental V_P and V_Q are however very close [Lotz et al., 2008].

In [Lotz et al., 2008; Van Cauter et al., 1992], measurements from insulin and C-peptide are used to identify n_L and x_L for each person. S_I and V_G are then calculated for each person using blood glucose measurements. All other parameters are treated as population constants. The insulin sensitivity S_I identified using this model correlates highly to EIC results [Lotz et al., 2008, 2006]. Therefore, this model is effective as a diagnostic tool for insulin resistance, but considered too complex for use in TGC for ICU patients.

2.2.3 Intensive Control Insulin-Nutrition Glycaemic Model-ICING

The new and more physiologically comprehensive model developed from the best aspects of both models [Chase et al., 2007; Lotz et al., 2008] is defined:

$$\dot{G} = -p_G G(t) - S_I G(t)\frac{Q(t)}{1+\alpha_G Q(t)} + \frac{P(t) + EGP_b - CNS}{V_G} \quad (2.38)$$

$$\dot{Q} = n_I(I(t) - Q(t)) - n_C\frac{Q(t)}{1+\alpha_G Q(t)} \quad (2.39)$$

$$\dot{I} = -n_K I(t) - \frac{n_L I(t)}{1+\alpha_I I(t)} - n_I(I(t) - Q(t)) + \frac{u_{ex}(t)}{V_I} + (1-x_L)\frac{u_{en}}{V_I} \quad (2.40)$$

$$\dot{P}1 = -d_1 P1 + D(t) \quad (2.41)$$

$$\dot{P}2 = -min(d_2 P2, P_{max}) + d_1 P1 \quad (2.42)$$

$$P(t) = min(d_2 P2, P_{max}) \quad (2.43)$$

$$u_{en}(t) = k_1 e^{\frac{I(t)^{k2}}{k_3}} \quad (2.44)$$

A schematic of the model is shown in Figure 2.6. The nomenclature for this model is largely the same as defined in Sections 2.2.1 and 2.2.2. However, this model does not use "equilibrium blood glucose level" G_E anymore, and G(t) is now the absolute (total) blood glucose level, per more recent works [Wong et al., 2008c; Suhaimi et al., 2010; Blakemore et al., 2008; Le Compte et al., 2009]. This model has an additional insulin independent [Hasselbalch et al., 1999] central nervous system glucose uptake, CNS, as well, with value between 0.29–0.38 mmol/min [Hasselbalch et al., 1996, 1998, 1999; Baron et al., 1988; Takeshita et al., 1972; Cohen et al., 1967; Strauss et al., 2003; Hattori et al., 2003; Bingham et al., 2002]. Finally, the model also has a constant "basal" endogenous glucose production term EGP_b, for the theoretical maximum endogenous glucose production for a patient with no exogenous glucose or insulin.

This EGP_b term is the theoretical endogenous glucose production for a patient under no presence of exogenous glucose or insulin. Endogenous glucose production is difficult to obtain in clinical setting without extensive clinical testing. The testing involves euglycaemic clamp for insulin sensitivity measure, and radioactively labelled glucose is given intravenously 120-180 mins before clamp begins. Multiple samples are drawn at baseline (before clamp) and after steady state is achieved, to measure specific plasma glucose activity. The testing is labo-

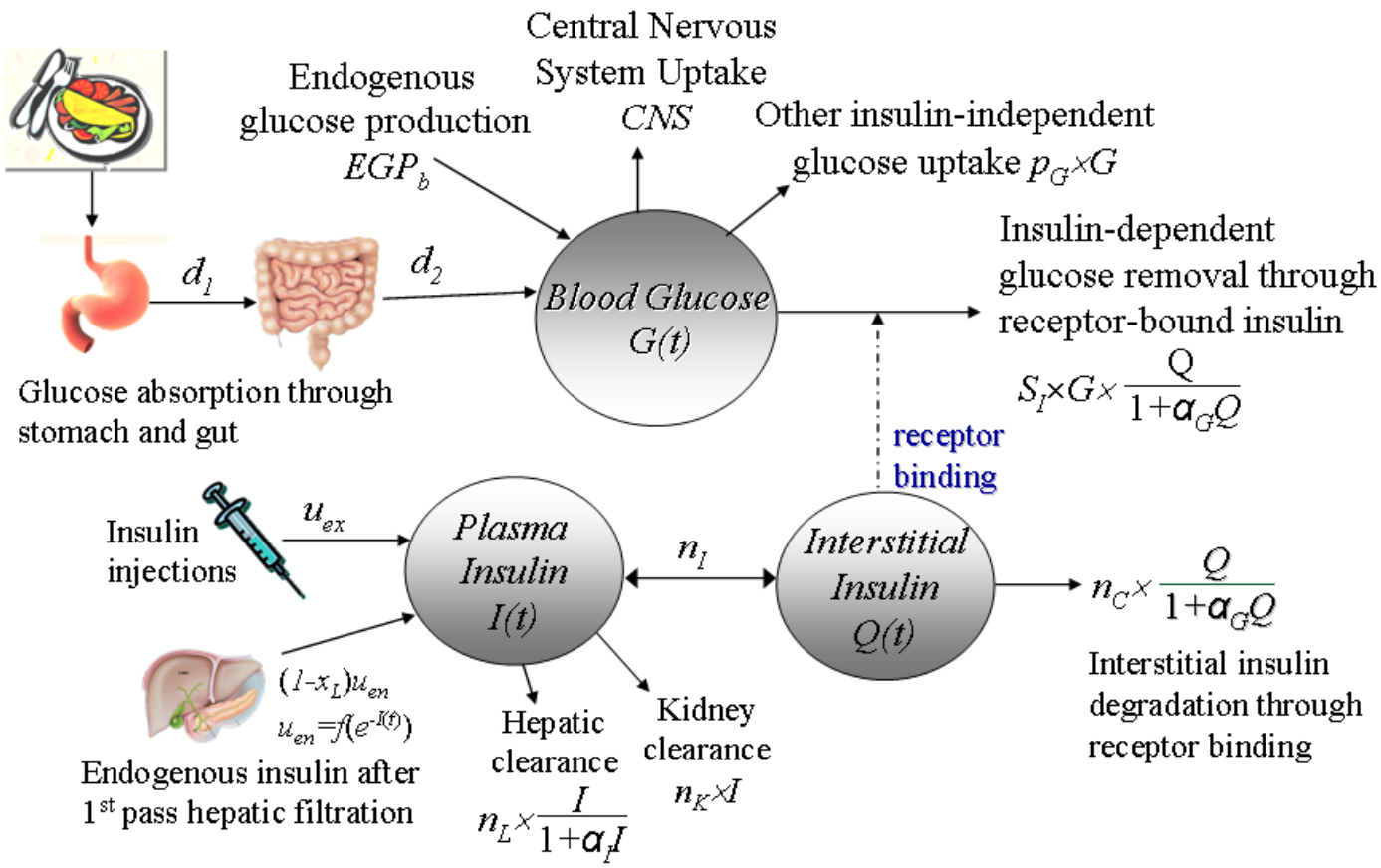


Figure 2.6 Intensive Control Insulin-Nutrition Glycaemic Model, or referred to as the ICING model in this study as defined in Equations (2.38)–(2.44). ICING model is an integration and improvement of two previous models, the "S_I Test Model" described in Section 2.2.2 and the "ICU Model" in Section 2.2.1.

rious and time-consuming thus the value of EGP_b can't be obtained in real-time. Moreover, the actual value of clinical testing can be affected since radioactively labeled glucose is lost in metabolic pathways. The actual quantification of the endogenous glucose production is beyond the scope of this thesis but it is described extensively in Radziuk [1987].

Therefore, the term EGP_b is a constant in this model, whereas the EGP in Lotz et al. [2008] is a function of time. Experimentally, endogenous glucose production (i.e., time-varying measurements) would be suppressed in normal individuals with increasing blood glucose level $G(t)$ and increasing insulin in the interstitial space $Q(t)$ [DeFronzo and Ferrannini, 1991]. However, as noted in Chapter 1, one feature of the ICU patients studied is unsuppressed EGP can increase with $G(t)$ instead of decrease. In this case, EGP_b is taken as a constant and modulated by glucose using the p_G term of Equation (2.38). Any variation in the actual value of EGP_b would be described by the combining effect of EGP_b, p_G and S_I. These three parameters represent the whole body insulin sensitivity of the patient. For instance, if EGP is high, this would be reflected with lower values of S_I, which in turn would mean a higher value of glucose. The decision to keep EGP_b as a constant and within a physiological range is justified, since at any instant the term is undermodeled, it will be reflected in p_G and S_I.

As in Equation (2.38), insulin independent glucose removal, excluding central nervous system uptake CNS and the suppression of endogenous glucose production from EGP_b with respect to $G(t)$ are represented by p_G. Insulin mediated glucose removal and the suppression of EGP from EGP_b is represented by S_I. S_I, thus effectively represents the whole-body insulin sensitivity, which includes tissue insulin sensitivity and the action of Glucose Transporter-4 (GLUT-4). The action of GLUT-4 is associated with the compounding effect of receptor-binding insulin and blood glucose, and its signaling cascade is also dependent on metabolic condition and can be affected by medication [McCarthy and Elmendorf, 2007; Foster and Klip, 2000; Bryant et al., 2002; Andersen et al., 2004]. Therefore, S_I is time varying and can reflect evolving patient condition. Its variation through time can be significant, particularly for critically ill patients whose metabolism is extreme and highly dynamic [Lin et al., 2006, 2008].

Equations (2.39) and (2.40) define the insulin pharmacokinetics similarly to Lotz et al. [2008] and Equations (2.36)–(2.37). Insulin flux from plasma is sat-

urable, as its degradation after binding in the interstitium [Duckworth et al., 1998]. The receptor-bound insulin $Q/(1 + \alpha_G Q)$ is also the insulin effective for glucose removal to cells. Hence this term also appears in Equation (2.38) for glucose dynamics. Note that n_I in Equations (2.39) and (2.40) has unit [1/min] rather than [L/min] as in Equations (2.36) and (2.37). This is because the new model in Equations (2.38)–(2.44) does not use different volumes for plasma and interstitial insulin distribution, since the experimental values are very similar in Lotz et al. [2008]; Lotz [2007]. To compare and convert n_I from Lotz el al., its value needs to be divided by V_P from Lotz et al., to obtain the same units.

These two equations are largely similar to that of Lotz et al. [2008]. The insulin degradation from interstitial space is saturable in this model. It was found that insulin degradation from interstitial space is by interaction with insulin degrading enzyme after receptor binding [Duckworth et al., 1998]. Therefore, it is the receptor bound insulin that is degraded from interstitium. Since insulin binding is a saturable process due to limited number of receptor available, the amount of bound insulin is expressed by $Q/(1 + \alpha_G Q)$. It is also this receptor bound portion of insulin that is capable of mobilizing GLUT-4 and remove glucose from plasma. Hence, this term is the part responsible for insulin-mediated glucose removal in Equation (2.38).

Equations (2.41)–(2.43) present the gastric absorption of glucose-a model that describes compartments of stomach, gut and the rate of glucose appearance. Specifically, $P1$ [mmol] represents the glucose in the stomach while $P2$ [mmol] represents the gut. The complex process of digestion is assumed to be linear and presented by linear transport rates between the compartments, d_1 [1/min] and d_2 [1/min]. Amount of dextrose from enteral feeding is $D(t)$ [mmol/min]. Glucose appearance, $P(t)$ [mmol/min] from enteral food intake $D(t)$, is the glucose flux out of the gut $P2$. This flux is saturable, and the maximal out flux is $P_{max} = 6.11$ [mmol/min]. The addition of this saturable gut absorption rate, P_{max} effectively makes the gut absorption a non-linear process, hence more physiologically true. Typically, for ICU patients on enteral feeding, P_{max} is not reached. Any additional parenteral dextrose is represented by $PN(t)$. This dextrose absorption model conserves ingested glucose, and therefore is also suitable for modeling meal ingestion over a short period of time in contrast to the simpler model of Equations (2.33) and (2.34). The previous feed model describe by Equations (2.33) and (2.34) is only a simple mathematical approximation suitable for model-

ing relatively constant enteral feeding. This meal model which describes the main compartments of digestion with respect to patients who are either on enteral feed or TPN, is sufficient. However, once patients start to eat a more extensive model is required.

Equation (2.44) is a generic representation of endogenous insulin production when C-peptide data is not available from the patient for specific identification of its production. Endogenous insulin production, with the base rate being k_1 [mU/min], is suppressed with elevated plasma insulin levels. The exponential suppression is described by generic constants k_2 and k_3. Model parameters associated with endogenous insulin production, eventhough are not identifiable in real-time, can be kept at population constants which is within justifiable physiological range. To ensure its robustness, sensitivity test must be performed. Therefore, eventhough the model of Lotz et al. [2008] required non-real time plasma-insulin and C-peptide data, it will not affect the efficacy of the Intensive Control Insulin-Nutrition Glycaemic Model, as the endogenous insulin production for critical and less critical patients will be suppressed with exogenous insulin.

The major difference between this model and the models of Chase et al. [2007] and Lotz et al. [2008] is the elimination of G_E. The concept of "equilibrium blood glucose level" is ambiguous and hard to determine in a dynamic situation. For the experimental setting in Lotz et al. [2008], patients are subjected to overnight fast before insulin sensitivity testing. Therefore G_E can be assumed and obtained as the first blood glucose measurement in insulin sensitivity test. However, it is not possible to determine G_E correctly for a patient just admitted to the ICU needing insulin therapy as they are under an extreme metabolic state. This model eliminates G_E but uses a constant EGP_b. This allows the model to adapt to the patient's dynamic through p_G and S_I, which represent insulin-independent and insulin-dependent glucose removal respectively. Because of this change, p_G, S_I and EGP_b need to be identified for this model. Parameter identification method is discuss in detail in the following chapter.

2.3 Summary

Focusing on concept and development of a model, a comprehensive, more physiologically relevant glucose-insulin dynamic system model, ICING (Intensive Control Insulin-Nutrition Glycaemic Model) is developed in this chapter. The ICING model is an integration and improvement of two clinically validated glucose-insulin physiological models. The new model has more explicit physiological relevance. Glucose utilisation and its endogenous production in particular, are more distinctly expressed. A more realistic model for gastric glucose absorption accounting for the stomach, gut and saturable glucose appearance is also introduced. Finally, the model also includes explicit pathways of insulin clearance and transport from plasma, which reflects biological mechanisms.

Chapter 3

Parameter Identification and Dynamic System Model Validation

This chapter presents the parameter identification method used to identify critical constant population parameters in the developed ICING model of the previous chapter. The methodology (rigorous) on finalising model parameter values and thus, which dynamics are important is discussed in this chapter. The validation outcome goals on prediction and fitting error are part of the methodology. Identification of critical constant population parameters was performed in two stages, thus addressing model identifiability issues. It is a critical aspect of this modeling approach to ensure clinical utility.

Model predictive performance is the primary factor for optimizing population parameter values. The use of population values are necessary due to the limited clinical data available at the bedside in the clinical control scenario [Hann et al., 2005; Lotz et al., 2008]. To validate these choices, a sensitivity study to confirm the validity of limiting time-varying parameters to hourly identified insulin sensitivity, S_I is also presented. Insulin sensitivity, S_I, the only dynamic, time-varying parameter, is identified hourly for each individual. All population parameters are justified physiologically and with respect to values reported in the clinical literature. The parameter sensitivity study confirms the validity of limiting time-varying parameters to S_I only, as well as the choices for the population parameters.

The ICING model is validated against clinical data from critically ill patients. It is assessed for both its fitting and, more critically for model-based tight glycaemic control, its predictive performance. The outcome goal is a next generation TGC control method suitable for developing model-based insulin therapies, and

capable of delivering real-time model-based TGC with a very tight prediction error range.

3.1 Validation Cohort

The total number of patients that were on SPRINT glycaemic control protocol study [Chase et al., 2008c], is 394 patients. SPRINT is a model-derived protocol implemented at the Christchurch Hospital Department of Intensive Care. From these 394 patient records, patients who stayed less than 72 hours in the ICU, were excluded from model validation. It has been identified that patients with length of stay greater than 3 days were to benefit more from intensive insulin therapy than short-stay patients [Van Den Berghe et al., 2006a]. Moreover, for model parameter identification sufficient data measurements are needed for model parameter evaluation. Patient with a short stay would not fit in this criteria. Hence, this cohort ($>$ 3 days) is of a greater interest for validating the glucose-insulin pharmacodynamics models for glycaemic control.

Model validation was thus performed on data from 173 patients (42,941 total hours) that were on the SPRINT TGC protocol for 3 or more days, from August 2005 to September 2007 [Chase et al., 2008c]. Validation is performed on data of critically ill patients instead of patients in a high-dependency unit as Christchurch Hospital does not until recently have patients in the step down unit. Data was collected for all BG measurements, insulin administered and nutrition given. Insulin used was Actrapid while Resource Diabetics Norvatis or Glucerna was used for nutrition. This cohort had statistically significant hospital mortality reductions of 25–40% depending on length of ICU stay, as well as significant reductions in the rate and severity of organ failure [Chase et al., 2010b]. These patients had long enough stays to exhibit periods of both dynamic evolution and metabolic stability. Hence, they usually reached a more stable condition and were responding to the glycaemic control protocol used in the Christchurch Hospital ICU, New Zealand.

Partition of test and validation were not performed since the method works well with modest or small data sets, where few patients may dominate results one way or another. With more than 42,000 hours worth of data, any outliers

would not be significant. Thus, performing data partitioning would only add complexity and unnecessary in this context.

To evaluate the severity of patient's disease and for comparison of cohort, particularly to assess the efficacy of different protocols with different settings, an APACHE II (Acute Physiology And Chronic Health Evaluation) ICU scoring system is used. Patient is more severe and at a higher risk of death with higher scores. The median APACHE II score for this cohort is 19 [IQR:16, 25] and the median age is 64 [IQR:49, 73] years old. The percentage of operative patients is 33%. This cohort broadly represents the cross-section of patients often seen in the ICU. Table 3.1 shows the cohort characteristics covering medical condition, sex, APACHE II score and age.

Table 3.1 Model Validation Cohort Summary

N	173
Age (median [IQR])	64 [49,73]
Percentage of Males	63.58%
APACHE II Score (median [IQR])	19 [16,25]
Total Length of SPRINT (hours)	42941
Operative	
Cardiovascular	10.40%
Respiratory	1.73%
Gastrointestinal	13.87%
Neurological	1.73 %
Sepsis	0
Trauma	4.04%
Other(Renal,metabolic,orthopaedic)	1.15%
Non-Operative	
Cardiovascular	6.93%
Respiratory	24.27%
Gastrointestinal	7.51%
Neurological	5.78 %
Sepsis	8.67%
Trauma	9.82%
Other(Renal,metabolic,orthopaedic)	4.04%

3.2 Parameter Identification

The introduction of EGP_b and its implied relationship with p_G and S_I in the new ICING Model in Chapter 2.2.3 compared to the ICU Model in Chapter 2.2.1, requires EGP_b, p_G and S_I to be identified. Apart from p_G and EGP_b, model parameters associated with insulin kinetics, primarily n_K, n_L, n_C and n_I also need to be evaluated for validation and use with ICU patient data. Since ICU patient data only contains blood glucose levels, feed rates (via enteral nasogastric or parenteral routes) and insulin inputs (infusion and/or bolus), the parameter identification and model validation in this study were performed in two stages to avoid identifiability issues.

The first stage focuses on glucose dynamics and substitutes the glucose equation in the ICU model Equations (2.30), (2.33) and (2.34) with Equations (2.38) and (2.41)–(2.43). Identification of p_G and EGP_b as model constants in Equation (2.38) is performed in this stage. The model used in this stage, (Equations (2.31), (2.32), (2.38) and (2.41)–(2.43)) is referred to as the 'Intermediate Model'. The second stage focuses on insulin kinetics and transforms the model into its final form defined by Equations (2.38)–(2.44). Identification of insulin kinetics parameters is performed in this stage.

Insulin sensitivity, S_I, the critical dynamic parameter, is identified hourly using an integral based method for a grid of p_G and EGP_b values [Hann et al., 2005]. Optimal parameter values for p_G, EGP_b and insulin kinetics are chosen according to the model's goodness of fit and, more importantly, the one hour forward prediction accuracy. The goodness of fit is simply the error between the clinical blood glucose measurements and the identified model generated blood glucose levels. The predictive ability looks at how accurately the model can forecast clinical blood glucose levels for known interventions one hour ahead. The prediction is made by assuming the current fitted hourly S_I for the next hour, and calculating the model predicted blood glucose level for the next hour using Equation (2.38) and the clinical records of insulin and feed. Importantly, better predictive performance implies better model-based clinical glycaemic control performance. Therefore, predictive performance is the primary criterion, with goodness of fit second, in determining the best parameter values. Finally, a sensitivity study is performed on the other parameters treated as population constants. This verifies

the validity of using population constants for these parameters.

Intra- and inter- patient variabilities are examined by looking at the data on a *by-cohort* or *per-patient* basis. *By-cohort* analysis looks at the statistics on all the available hourly fitting and prediction errors (weighting each hour equally), whereas *per-patient* analysis looks at the statistics on each individual patient (weighting each patient equally).

Essentially the model improvements from the ICU model to the ICING model are made in two stages: firstly on the glucose compartment, secondly on the insulin pharmacokinetics. During each stage, the important population constant parameters are optimised using grid-search methods. The grid-search approach is robust to measurement noise and can provide an assessment of parameter sensitivity. Moreover, if the decision space or range to be set up is known and sufficiently covers the physiological range, then grid-search approach is the best method. Furthermore, since the cost function being minimized is multi-variable (fit, predict, median and 90% interval) the variable space may be non-convex. Thus, grid-search will ensure all minima is located and the best value would be chosen. The only drawback is the computational burden, as each grid point will be evaluated.

During the first stage of improvements on the glucose compartment, EGP_b and p_G are optimised as a pair. The insulin pharmacodynamics are kept as in Equations (2.31) and (2.32) during this stage-as the constant parameters in Equations. (2.39) and 2.40 are yet to be optimised. In the second stage of model improvement, the ICING model takes its complete form and the constant insulin pharmacokinetics parameters are optimised. Finally a re-assessment of p_G and EGP_b, as well as a parameter sensitivity using the completed ICING model is performed.

The following section describes in detail the parametric grid identification of p_G, EGP_b and the insulin kinetics parameters. The cost function being minimized is effectively the median and 90% interval of fitting error, as well as median and 90% of prediction error where prediction precedes fitting error. The goal is to find the best population parameters. The overall parameter identification process and the stages of model transformation are shown as a flowchart in Figure 3.1. Note that the second stage has three components, which thus include the validation

of Stage 1 values after the Stage 2 to ensure the overall integrity of the resulting model.

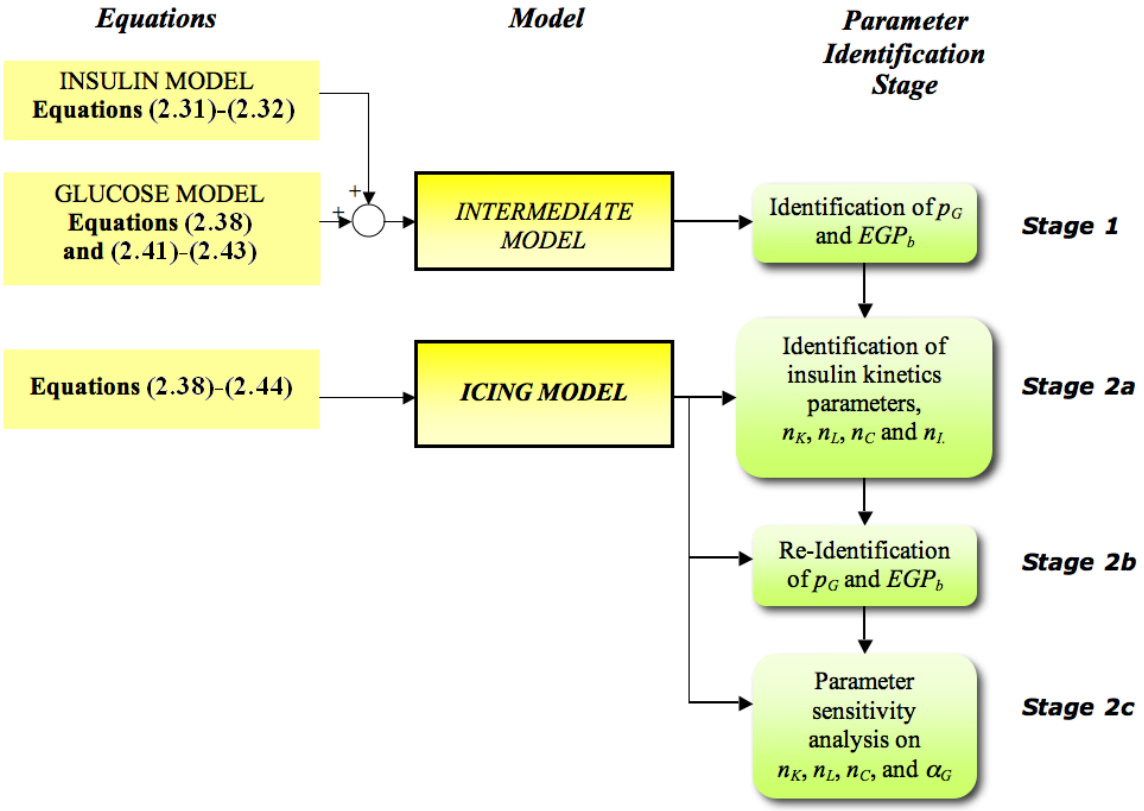


Figure 3.1 Flowchart of the parameter identification process for the ICING model development.

3.2.1 Identification of p_G and EGP_b – Stage 1

In the first stage of model improvement, p_G and EGP_b are optimised as a pair. Constant parameter values used in this stage of parameter identification can be seen in Table 3.2. These constant parameters are consistent with values found in surveys of population studies [Wong et al., 2006b; Lin et al., 2008; Wong et al., 2008c]. These values have been verified for their suitability of being set to population constants in a previous parameter sensitivity study [Hann et al., 2005], as well as in clinical glycaemic control and analysis studies [Le Compte et al., 2009; Wong et al., 2006b; Chase et al., 2005; Blakemore et al., 2008].

The same integral fitting method used for S_I cannot be applied to either p_G

Table 3.2 Models and constant parameter values and/or ranges.

Constant Parameters	*ICU Model* Chase et al. [2007]	*S_I Test Model* Lotz et al. [2008]	*Stage 1 Model*	*ICING Model (Final)*
G_E [mmol/L]	starting BG*	starting BG*	-	-
CNS [mmol/min]	-	-	0.3	0.3
α_G [L/mU]	0.0154	0	0.0154	0.0154
V_G [L]	13.3	10.00–15.75	13.3	13.3
α_I [L/mU]	0.0017	0.0017	0.0017	0.0017
n [1/min]	0.16	-	0.16	-
k [1/min]	0.0198	-	0.0198	-
p_G [1/min]	0.01	0.01	*to be identified*	*from Stage 1 Model*
$EGP_b[mmol/min]$	-	-	*to be identified*	*from Stage 1 Model*
n_I	-	0.21–0.36 [L/min]	-	*to be identified* [1/min]
n_C [1/min]	-	0.032–0.033	-	$= n_I$
n_L [1/min]	-	0.10–0.21	-	0.1578
n_K [1/min]	-	0.053–0.064	-	0.0542
x_L	-	0.50–0.95	-	0.67
V_I [L]	3.15	-	3.15	3.15
V_Q [L]	-	4.44–7.47	-	-
V_P [L]	-	3.90-5.96	-	-
k_{pr} [1/min]	0.0347	-	-	-
k_{pd} [1/min]	0.0069	-	-	-
d_1 [1/min]	-	-	0.0347	0.0347
d_2 [1/min]	-	-	0.0069	0.0069
P_{max} [mmol/min]	-	-	6.11	6.11
k_1 [mU/min]	-	-	-	45.7
k_2	-	-	-	1.5
k_3	-	-	-	1000

or EGP_b. In particular, p_G and S_I are both coupled to the first order solution of $G(t)$. Consequently, a unique solution cannot be identified. In addition, p_G trades off with EGP_b. Therefore, a grid analysis of p_G and EGP_b is used to find the most suitable combination of parameter values.

More specifically, patient blood glucose data are fitted by integral identification of S_I, while holding p_G and EGP_b constant at a selected grid coordinate. The grid covers $p_G = 0.001 \rightarrow 0.1$ [1/min] with increments of 0.001, and $EGP_b = 0.0 \rightarrow 3.5$ [mmol/min] with increments of 0.1. These values more than span the clinically relevant range. The resulting fitting and prediction error are calculated for each patient at each p_G, EGP_b coordinate. The resulting errors are than analysed across all 173 patients at each grid coordinate to find an optimal combination.

3.2.2 Identification of Insulin PK Parameters – Stage 2

Model improvements on insulin pharmacokinetics (PK) are made in the second stage, and the model takes its final form as defined in Equations (2.38)–(2.44). Parameters associated with insulin kinetics are identified in this stage. Lotz et al. [2008] uses measurements from insulin and C-peptide to identify patient-specific liver clearance n_L, and first pass endogenous insulin hepatic uptake, x_L, in Equations (2.36)–(2.37). In particular, the value for kidney clearance, n_K, was taken from a well validated population model of C-peptide kinetics, and the transcapillary diffusion rate, n_I, was calculated by a method proposed by the same authors [Van Cauter et al., 1992].

For this study, ICU patient data does not contain the insulin measurements to allow for unique identification of n_L and x_L. However, the transition from Equations (2.31) and (2.32) to Equations (2.39) and (2.40) makes n_I the critical parameter to be investigated.

The interstitial insulin transfer rate, k, in Equation (2.31) was calculated to correspond to the active interstitial insulin half-life [Chase et al., 2005]. Effectively, Equation (2.31) thus represents a delay compartment for insulin action in

the interstitium, and can be re-written:

$$Q(t) = k \int_0^t I(\tau) e^{-k(t-\tau)} d\tau \tag{3.1}$$

On the other hand, the analytical solution of Q in Equation (2.39) is:

$$Q(t) = n_I \int_0^t I(\tau) e^{-(n_I+n_C)(t-\tau)} d\tau \tag{3.2}$$

Therefore, the decay rate of interstitial insulin is $n_I + n_C$ in Equation (2.39), and this rate should be comparable to k in Equation (2.31).

Studies indicated that the steady state interstitial to plasma insulin ratio is between $0.4 - 0.6$ [Gudbjörnsdóttir et al., 2003; Sjöstrand et al., 1999; Sjostrand et al., 2000]. Lotz et al. [2008] uses a population value of 0.5 for this ratio. Therefore $n_I = n_C$ can be assumed from the steady state calculation using Equation (2.39) provided the steady state Q is low so that $Q/(1 + \alpha_G Q) \approx Q$.

In this study, a grid search of n_I is used to obtain a suitable model value. Again, integral fitting is used to identify hourly S_I. The grid covers $n_I = n_C = 10^{-4} \rightarrow 0.02$ [1/min]. The fitting and prediction error are calculated at each grid point for each patient. Other constant parameter values are listed in Table 3.2. The value for n_K is taken from Van Cauter et al. [1992] and n_L is the mean fitted value found in Lotz et al. [2008] and Lotz [2007]. First pass hepatic insulin uptake, x_L, was also a fitted parameter in Lotz et al. [2008], and is coupled with liver clearance n_L. In this study, x_L is assumed to be 0.67, which is within the range reported by Lotz et al. [2008] and Lotz [2007]. More specifically, x_L has a relatively insignificant role in this study compared to Lotz et al. [2008] and Lotz [2007], as patients on intensive insulin therapy can be assumed to have their endogenous insulin production suppressed due to elevated plasma insulin levels [Chiasson et al., 1980; Insel et al., 1975]. The other constant parameters are kept the same as in the identification of p_G and EGP_b.

3.2.3 Re-assessment of p_G and EGP_b–Stage 2b

Following the Stage 2 identification of n_I, a re-assessment of the population constant values of p_G and EGP_b from Stage 1 is performed using the complete ICING model. The grid analysis covers $p_G = 0.005 \rightarrow 0.025$ [1/min] and EGP_b= $0.5 \rightarrow 2.5$ [mmol/min] with an increment step of 0.0033 and 0.33 respectively. The analysis is performed as before with prediction and fitting error assessed. The goal is to ensure the values used in Stage 2a are still justified. Note that, if necessary, Stage 2a and 2b can be iterated to convergence.

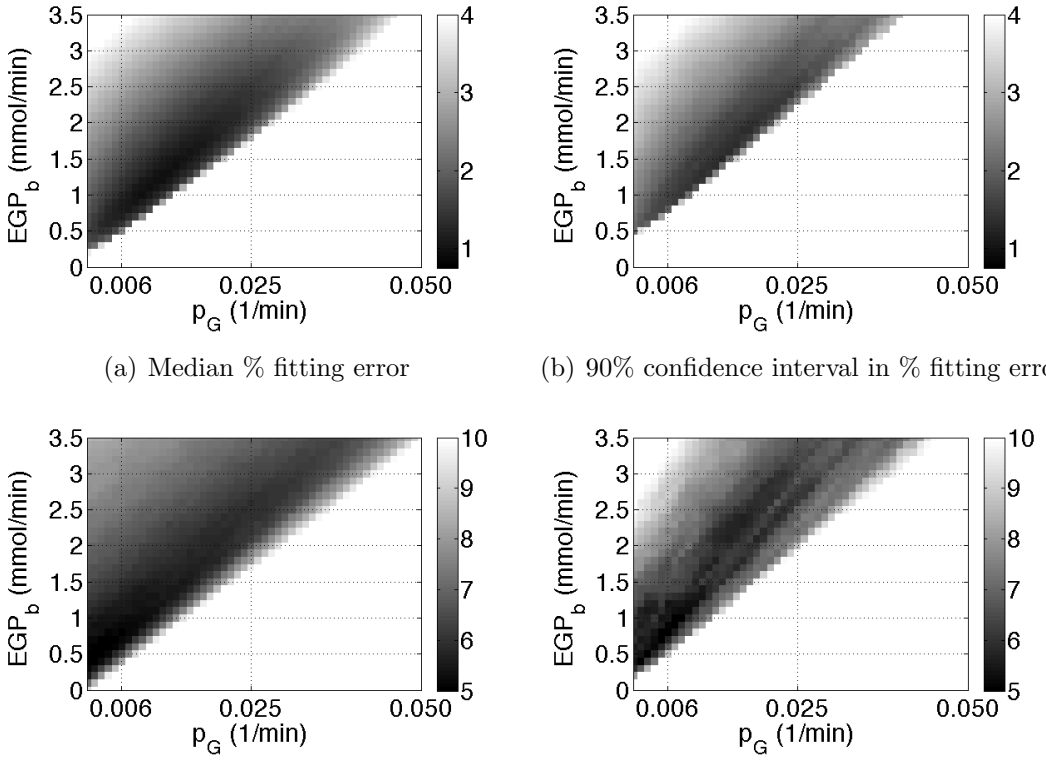
3.2.4 Parameter sensitivity analysis–2c

Finally, the robustness of model population parameters n_L, n_K, n_C and α_G on the model fit and predictive performance of the ICING model are tested by modifying individual model values (summarized in Table 3.2) by $\pm$50%. While one parameter is being altered, the rest of the parameters are kept at their original values in Table 3.2. Changes in model performance can indicate the suitability of their assumed values, and whether or not they should be used as population constants. This last stage is the final model validation to ensure robustness of the optimised parameters.

3.3 Results

3.3.1 p_G and EGP_b – Stage 1

The *per-patient* median fitting and prediction errors over the ranges $p_G = 0.001 \rightarrow 0.1$ [min^{-1}] and $EGP_b = 0 \rightarrow 3.5$ [mmol/min] are shown in Figure 3.2. Sub-figures 3.2(a) and 3.2(c) show the median of all median hourly % errors for each patient. Sub-figures 3.2(b) and 3.2(d) show the median range of the 90% confidence interval in hourly % error for each patient. Smaller (tighter) ranges mean a tighter distribution with less outliers. In general, lower fitting and prediction errors and error ranges are produced in the lower p_G and lower EGP_b regions, where the plot is darkest.



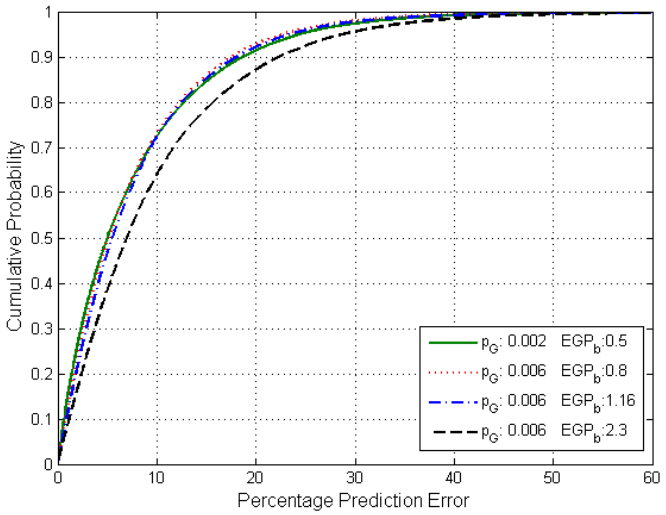
(a) Median % fitting error

(b) 90% confidence interval in % fitting error

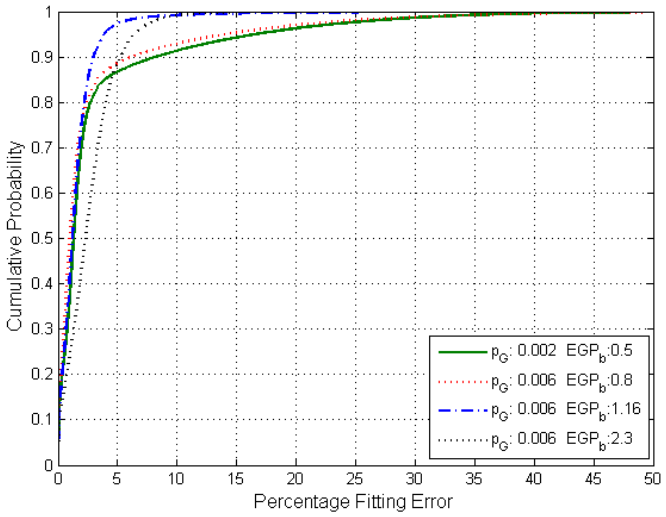
(c) Median % prediction error

(d) 90% confidence interval in % prediction error

Figure 3.2 *Per-patient* percentage fitting and prediction error with respect to p_G and EGP_b. Each coordinate plots the median of the results from individual patients. 3.2(a) and 3.2(c) show the median of the median hourly % error for each patient. 3.2(b) and 3.2(d) show the median range of the 90% confidence interval in hourly % error for each patient. Smaller (tighter) range means tighter distribution with less outliers.



(a) By cohort: Prediction error (%)



(b) By cohort: Fitting error (%)

Figure 3.3 Cumulative distribution functions (cdf) of *by-cohort* prediction and fitting errors with different combinations of p_G and EGP_b. The following values of p_G and EGP_b were tested; [p_G, EGP_b] = [0.002, 0.5], [0.006, 0.8], [0.006, 1.16] and [0.006, 2.3] Every hourly error contributes to the cdf. The performances are quite similar for all combinations excepting p_G and EGP_b= [0.006, 2.3], which were tested as a supra-physiological value across the cohort.

Figure 3.3(a) shows the cumulative distribution function of the prediction error over all available hourly data for the selected p_G and EGP_b combinations. The performance is very similar for [p_G, EGP_b] = [0.002, 0.5], [0.006, 0.8] and [0.006, 1.16]. However, the predictive performance is significantly worse for EGP_b = 2.3 mmol/min, where this value is tested to demonstrate the impact of applying

an extreme, supra-physiological value across the entire cohort. In contrast, Figure 3.3(b) shows the cumulative distribution function of the fitting error for the same combinations of p_G and EGP_b values. The model clearly delivers the best fitting error with $[p_G, EGP_b] = [0.006, 1.16]$.

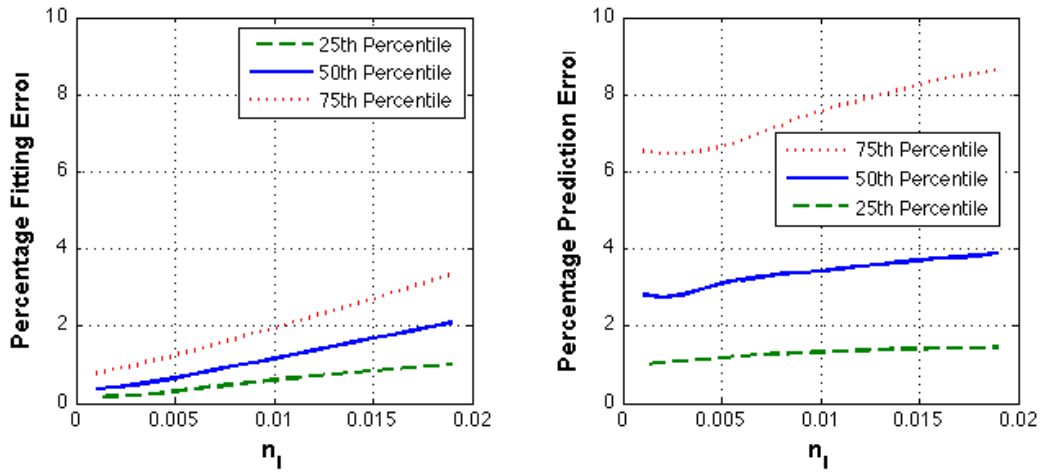
From the figures of percentage prediction and fitting error generated, it can be observed that the best balance between fitting and prediction is achieved by the combination $[p_G, EGP_b] = [0.006, 1.16]$. Glucose metabolism studies reported EGP values range from $0.91 \rightarrow 1.4$ [mmol/min] [Blakemore et al., 2008; Tappy et al., 1999; Chambrier et al., 2000]. The value for EGP_b identified in this study is therefore physiologically valid. Reported values for p_G from studies have been shown to range between $0.004 \rightarrow 0.047$ min^{-1} [Bergman et al., 1981; Cobelli et al., 1999; McDonald et al., 2000; Pillonetto et al., 2002]. Therefore, the identified p_G = 0.006 [1/min] is also physiologically valid.

3.3.2 Insulin Kinetics Parameters – Stage 2a

The median of the 25^{th}, 50^{th} and 75^{th} percentile fitting and prediction errors for each patient across $n_I = 10^{-4} \rightarrow 0.02$ min^{-1} in the full ICING model are shown in Figure 3.4. It can be seen that $n_I = 0.003$ min^{-1} provides the best predictive performance while fitting error is low through the entire range.

The value for n_I identified for the new model is very low compared to that of [Lotz et al., 2008; Lotz, 2007] (0.003 v.s. $\sim$0.0476 min^{-1}). Lotz et al. [2008] and Lotz [2007] used a method to calculate n_I adopted from Van Cauter et al. [1992]. This method estimates n_I from an individual's age, sex, weight, BSA, BMI and diagnosis of type 2 diabetes, developed using a model for C-peptide and its measurements. However, the n_I population value calculated using this method fails to capture long term blood glucose-insulin dynamics. The interstitial insulin peaks and decays a lot faster and does not accumulate over a few hours compared to having n_I at its newly identified value, as shown in Figure 3.5.

Specifically, insulin "pooling" and delayed utilization effects have been observed in critically ill patients by [Doran et al., 2004a]. With n_I at such a high value, these features are lost from the model because the modeled insulin degradation is too fast. Note that given $n_I = n_C = 0.0476$ min^{-1}, the interstitial



(a) Fitting Error (%) (b) Prediction Error (%)

Figure 3.4 Fitting and prediction errors from the n_I grid search, showing the median of the 25^{th}, 50^{th} and 75^{th} percentile for each patient (N=173) across $n_I = 10^{-4} \rightarrow 0.02$ min^{-1} in the full ICING model. The green-dashed line (- -) depicts the 25^{th} percentile, the solid blue line (–) represent the 50^{th} percentile while the 75^{th} percentile is represented by the dotted-red line ($\cdots$). $n_I = 0.003$ min^{-1} provides the best predictive performance while fitting error is low through the entire range.

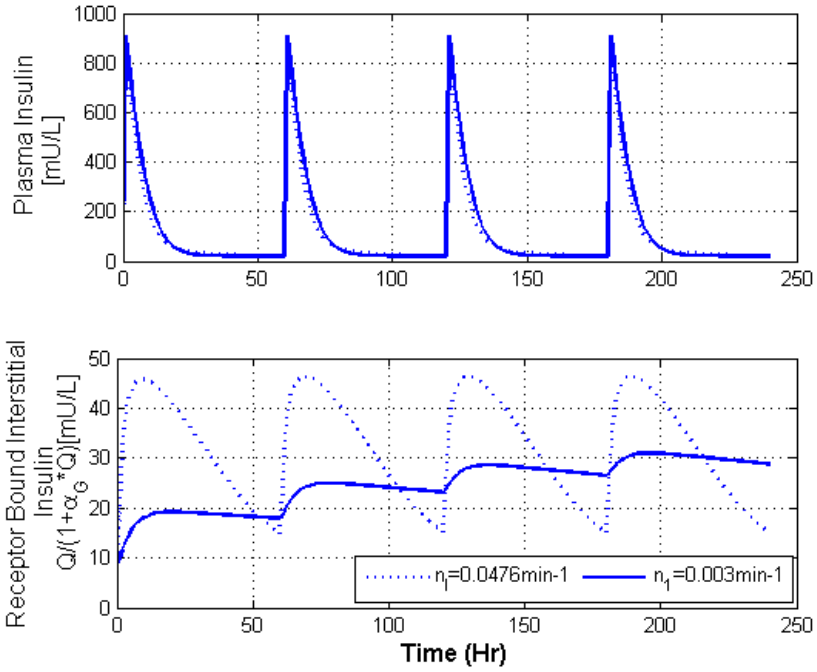


Figure 3.5 Dose response curves of plasma insulin and receptor bound interstitial insulin from an insulin injection of 3U at the beginning of each hour.

half life of insulin from Lotz et al. [2008] is more than 3 times shorter than the shortest reported time [Natali et al., 2000].

"Effective" insulin half lives have been reported to be between 25–130 mins (k in Equation (3.1) or $n_I + n_C$ in Equation (3.2) to be between 0.0277–0.0053 min^{-1}) [Mari and Valerio, 1997; Natali et al., 2000; Turnheim and Waldhausl, 1988]. The value for k in the Critical Care Model of Equation (2.30)–(2.34) was 0.0198 min^{-1}, which corresponds to a interstitial half life of 35 mins based on the same references. The value for $n_I + n_C$ in the ICING model is 0.006 since $n_I = n_C = 0.003$ min^{-1}, and corresponds to a half life of 115.5 mins. The half lives from both models, although both within the reported ranges, were on the opposite ends of the spectrum. However, when k was chosen for the Critical Care Model, clinical data were limited for its optimization [Chase et al., 2007; Wong et al., 2006b; Chase et al., 2005]. The grid search on n_I performed in this study clearly optimized this value for model performance using currently available data.

Patient 5004 is shown in Figure 3.6 as an example of typical model fit using the fully identified ICING model. The results show the model is capable of capturing the patient's highly variable dynamics during critical illness, particularly from the 50^{th} hour to the end of the patient's stay, where the insulin requirement varied significantly from hour to hour.

In Figure 3.6, only the *end-of-hour* insulin levels in plasma, I and interstitial insulin, Q are plotted for readability. Plasma insulin is depicted in the second panel while interstitial and effective interstitial insulin, Q are in the third panel. The response curves from insulin injections plotted *by the minute* can be seen in Figure 3.5. The impact of n_I on modeled insulin can be seen with two different values used. The receptor bound insulin using $n_I = 0.0476$ min^{-1} from Lotz et al. [2008] peaks and decays a lot faster than having the smaller $n_I = 0.003$ min^{-1} found in grid search. More importantly, the large n_I value does not allow receptor-bound insulin levels to accumulate over time. In addition, it also means there is a lot of unbound insulin that is diffused back to plasma. Hence, the slower decay in plasma concentrations. Applying this large n_I value, the model fails to capture a patient's long term glucose-insulin response. The per-patient fitting error also increases to 5.32 [IQR: 0.98, 9.70]% from 2.80 [IQR: 1.18, 6.41]%. More specifically, over 25% of the hourly modeled BG fails to capture clinical measurements, which typically have a minimum measurement error of 7% based

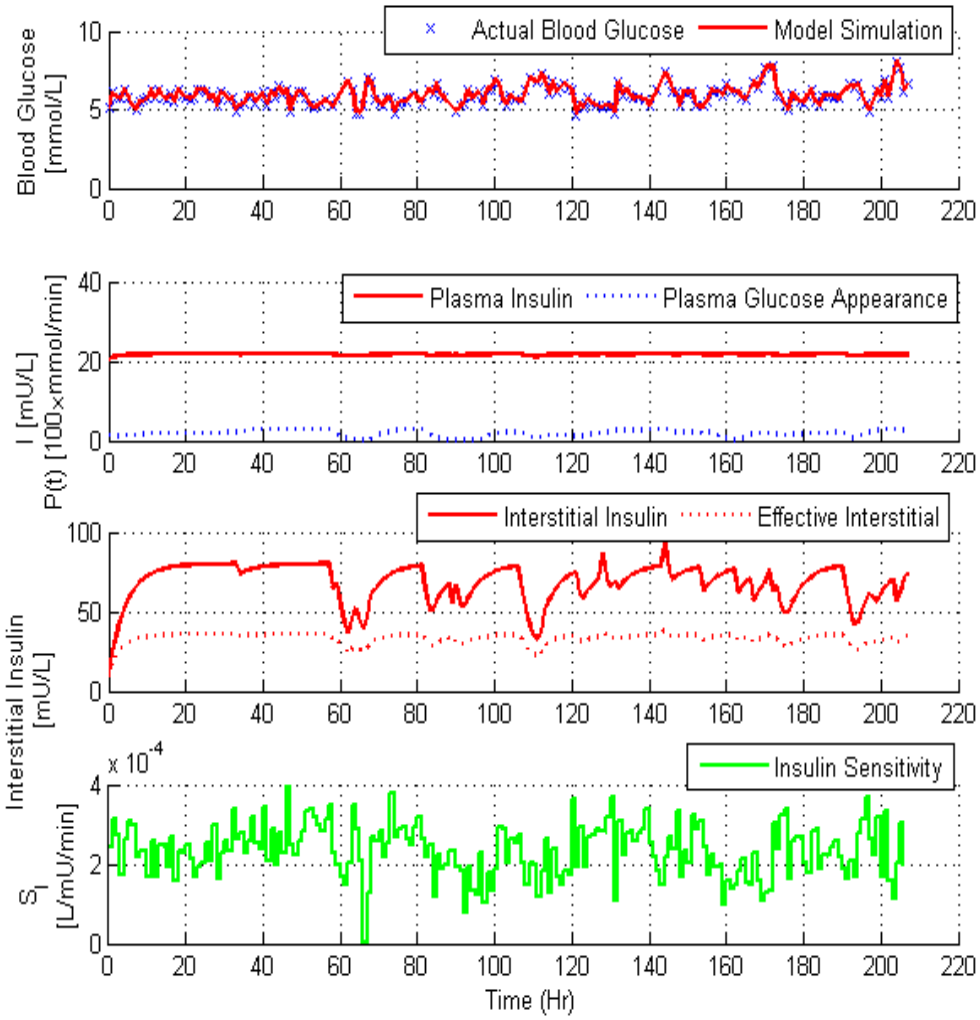


Figure 3.6 Model simulation results on Patient 5004 using the parameters identified for the ICING model. Only *end-of hour* data are plotted for readability. In the top panel, the solid line (–) illustrates the blood glucose model simulation while crosses (×) represents the actual blood glucose measurements. The second panel demonstrates the plasma insulin appearance (–) and plasma glucose appearance (· · ·). The third panel shows the interstitial insulin (–) and the effective (receptor-bound) interstitial insulin (· · ·). Model fitted insulin sensitivity is displayed in the bottom panel.

on the glucometres used in the SPRINT [Chase et al., 2008c] study [Arkray, 2001].

Figure 3.7 shows the model fit on Patient 5004 using $n_I = 0.0476$ min^{-1} in the ICING model. Values for n_K and n_L are the same, but n_I is 0.0476 min^{-1} instead of the value of 0.003 min^{-1} used in Figure 3.6. The model clearly failed to capture the patient's glucose-insulin dynamics as can be observed with the poor blood glucose fit in the top panel. The fitted insulin sensitivity, S_I profile in the bottom panel also contains unphysiological spikes.

Figure 3.8 shows the effect of ignoring receptor binding saturation on insulin degradation on Patient 5004. The term $Q/(1 + \alpha_G Q)$ was taken out of Equation (2.39) to produce this figure by setting α_G=0, with all other parameters as before. The quality of fit for the blood glucose measurements is similar to Figure 3.6 when saturation is included in insulin degradation from interstitium. However, noticeably lower insulin concentrations in plasma are achieved and are likely not physiologically realistic given the dosing given and reported insulin half lives in the literature. Hence, there is a need for saturable receptor binding degradation. With the introduction of receptor binding saturation in the ICING model, there is a limit for receptor bound insulin degradation. In return, the plasma insulin level would be higher as noticeable in the third panel of Figure 3.6, since insulin that do not bind with receptors would diffuse back into plasma.

The improvements in model performance from the ICU model of Equations (2.30)–(2.34), through improvements in glucose compartment of Equations (2.38) and (2.41)–(2.44) (Stage 1), and finally the ICING model in Equations (2.38)–(2.44) are shown in Table 3.3. The table shows the median and IQR for absolute percentage model fit and predictive error for the total 42,941 hours of clinical data from 173 patients. Results are shown on both *per-patient* and *by cohort* basis to highlight any inter- and intra- patient variability in model performance.

The final model achieved improvements in performance compared to the ICU model in Equations (2.30)–(2.34). The predictive ability of the ICING model improved significantly with much lower median prediction errors. More importantly, the spread of error is tighter, evident by a much lower upper quartile (75^{th} percentile) error, which is now within measurement error for both *by-cohort* and *per-patient* results. The main reduction is in the upper quartile cohort predic-

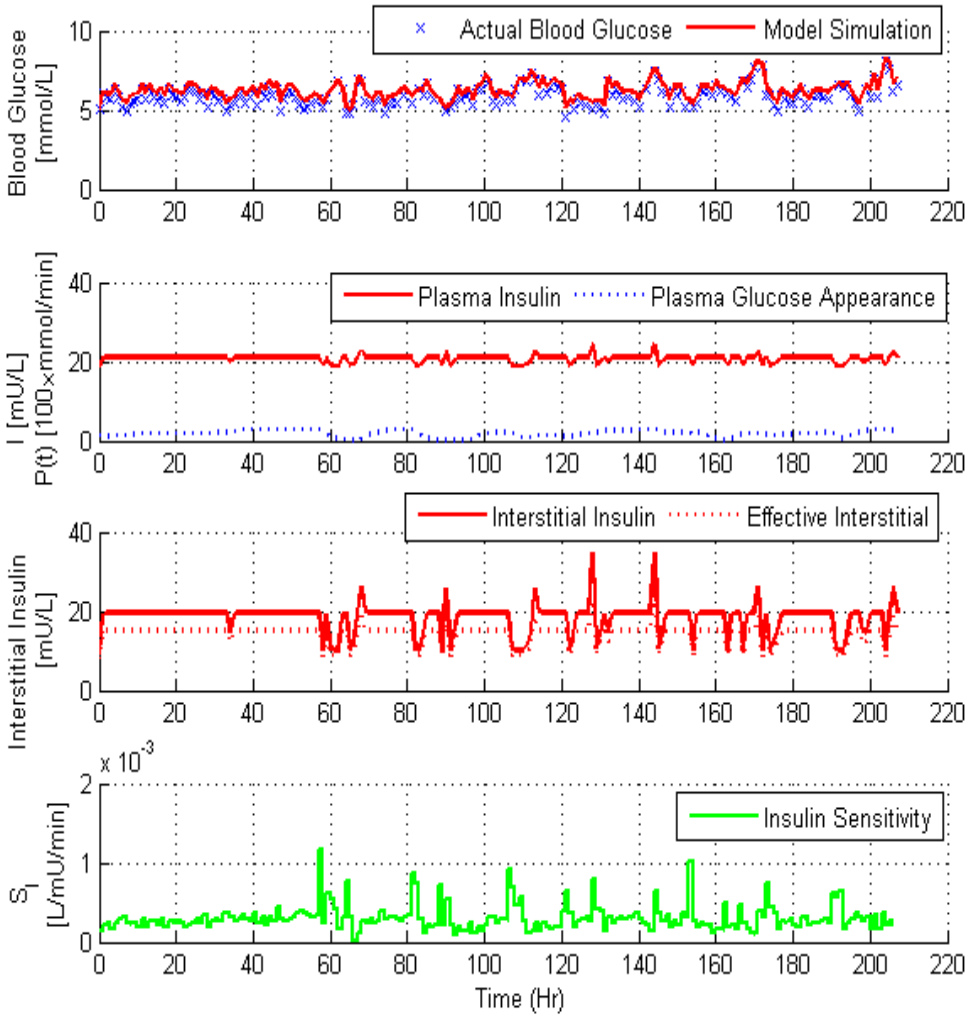


Figure 3.7 Model simulation results on Patient 5004 using insulin kinetics parameters values from Lotz et al. Lotz et al. [2008]. In the top panel, the solid line (-) illustrates the blood glucose model simulation while crosses (×) represents the actual blood glucose measurements. The second panel demonstrates the plasma insulin appearance (-) and plasma glucose appearance (···). The third panel shows the interstitial insulin (-) and the effective (saturated) interstitial insulin (···). Model fitted insulin sensitivity is displayed in the bottom panel.

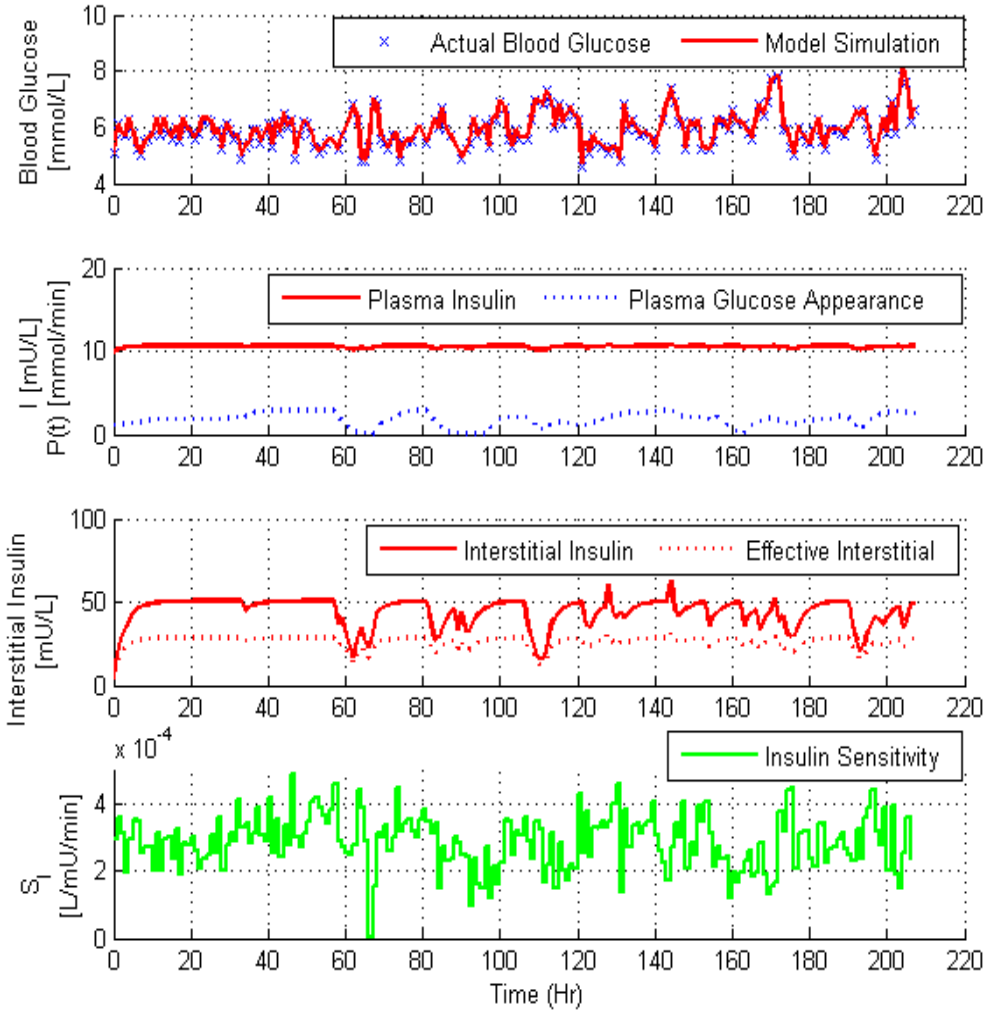


Figure 3.8 Model simulation results on Patient 5004 using the Intensive Control Insulin-Nutrition Glycaemic Model but without saturation in insulin degradation from interstitium. In the top panel, the solid line (-) illustrates the blood glucose model simulation while crosses ($\times$) represents the actual blood glucose measurements. The second panel demonstrates the plasma insulin appearance (-) and plasma glucose appearance ($\cdots$). The third panel shows the interstitial insulin (-) and the effective (saturated) interstitial insulin ($\cdots$). Model fitted insulin sensitivity is displayed in the bottom panel.

tion error, which is reduced to 6.47% from 10.64%, indicating significantly better management of inter-patient variability in the final model.

The main results in Table 3.3 show:

1. Improvement in glucose compartment reduces **intra- patient** variability with lower *per-patient* upper quartile prediction.
2. Finalised ICING model reduces **inter- patient** variability with lower upper quartile *by-cohort* prediction errors.

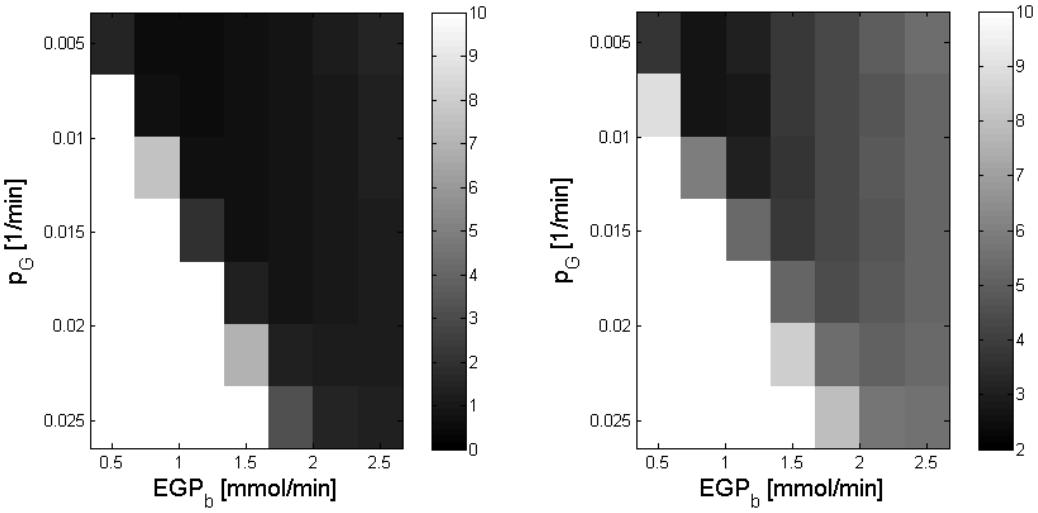
Table 3.3 Comparison of median and IQR for prediction and fitting error

Prediction Error (%) median [IQR]			
	Original ICU Model	*Improved Glucose Compartment*	*ICING Model*
Per-Patient[#]	5.90 [4.75,7.51]	5.23 [4.20,6.36]	**2.80 [1.18,6.41]**
By Cohort[+]	5.59 [2.46,10.64]	5.02 [2.11,10.34]	**2.81 [1.08,6.47]**
Fitting Error (%) median [IQR]			
Per-Patient[#]	1.11 [0.84,1.63]	0.86 [0.58,1.18]	**0.50 [0.21,0.99]**
By Cohort[+]	1.02 [0.41,1.94]	0.71 [0.23,1.44]	**0.47 [0.20,0.97]**
S_I (10^{-3} L/mU/min) median [IQR]			
Per-Patient[#]	0.25 [0.11,0.45]	0.21 [0.13,0.41]	**0.31 [0.23,0.40]**
By Cohort[+]	0.24 [0.14,0.40]	0.21 [0.14,0.32]	**0.31 [0.20,0.48]**

[#] Per-patient analysis weights each patient equally, indicating *inter-patient* variability.
[+] By-cohort analysis weights each hour of data equally, indicating *intra-patient* variability.

3.3.3 Re-Identification of p_G and EGP_b–2b

Results for the re-identification process of p_G and EGP_b by grid analysis covering p_G= 0.005 → 0.025 [1/min] and EGP_b= 0.5 → 2.5 [mmol/min] with an increment step of 0.0033 and 0.33 respectively, are shown in Figure 3.9. The result, in terms of *per patient* median percentage fitting and prediction error conveys that the initial coordinate selection of p_G and EGP_b as identified in Section 3.3.1 is justified and is therefore left unchanged. The combination of p_G= 0.006 [1/min] and EGP_b= 1.16 [mmol/min] by employing the model described in Equations (2.38)–(2.43) produces a result that is within the same range of fitting and prediction error as obtained in Section 3.3.1. Hence, no adjustments to the model are required after this added validation stage.



(a) Median (%) Fitting Error

(b) Median (%) Prediction Error

Figure 3.9 Per-Patient Median Percentage Fitting and Prediction Error with respect to p_G and EGP_b in the final ICING model.

3.3.4 *EGP* in Other Models

Many models have tried to include an estimated time-varying function for endogenous glucose production, *EGP* typically for use in experimental tracer studies [Dalla Man et al., 2004; Avogaro et al., 1996; Caumo and Cobelli, 1993b; Mari et al., 1994]. Others developed functions based on study data [Hovorka et al., 2008; Araujo-Vilar et al., 1998; Picchini et al., 2005; Ruiz-Velázquez et al., 2004; Silber et al., 2007]. Many other models simply assume total suppression of endogenous glucose production by either exogenous insulin, exogenous glucose, or both [Chase et al., 2005; Bergman et al., 1987; Wong et al., 2008b], based on research studies in Type 1 and Type 2 diabetes [Mittelman et al., 1997; Ader and Bergman, 1990; Shah et al., 2000; Thomaseth et al., 2008; Cherrington et al., 1998].

In reality, tracer studies require different assumptions depending on experimental settings. The results are thus highly variable between individuals and influenced by different conditions [Chambrier et al., 2000; Cherrington et al., 1998; Mevorach et al., 1998; Monzillo and Hamdy, 2003; Cherrington, 1999; Elahi et al., 1989]. Models focusing on a particular group of patients typically choose to treat endogenous glucose production as a constant, particularly in considering diabetic

individuals [Jauslin et al., 2007; Hovorka et al., 2002; Wong et al., 2008b].

Parameters for endogenous glucose removal, p_G, and basal endogenous glucose production, EGP_b, in the ICING model, trade off with each other. Therefore, it is important that they are identified as a pair as was done in Stage 1. The definition for EGP_b implies this parameter stays constant for any given patient. Hence, this study uses a basal endogenous glucose production EGP_b as a constant in the mathematical model. This choice allows the variation in actual endogenous glucose production be described by combining EGP_b, variable suppression via p_G and G, and also S_I and I. More importantly, the approach allows S_I be uniquely identified given the available data is limited to 1-2 hourly BG measurements.

The value for p_G found in this study is somewhat at the lower end of the range found in other studies [Bergman et al., 1981; Cobelli et al., 1999; McDonald et al., 2000; Pillonetto et al., 2002]. It is suspected for hyperglycaemic ICU patients that the suppression of EGP by plasma glucose levels is minimized compared to otherwise healthy subjects, which has been reported elsewhere due to high levels of circulating catecholamines, thus reducing the suppression of EGP from elevated G and I [Bistrian, 2001; McCowen et al., 2000; Mizock, 2001; Thorell et al., 2004; Dungan et al., 2009]. Hence, this lower value appears justified on physiological grounds.

The decision to keep p_G as a constant in this study is based on its relatively constant behaviour in ICU patients in prior analysis [Hann et al., 2005]. Grid analysis for the identification of p_G and EGP_b as constants population parameters found the most suitable combination of parameter values in reported physiological ranges [Bergman et al., 1981; Blakemore et al., 2008; Tappy et al., 1999; Cobelli et al., 1999]. Hence, this choice is left since no new evidence arose from this analysis to contradict this choice.

3.3.5 Parameter Sensitivity–2c

The parameter sensitivity study results for n_K, n_L, n_C and α_G are shown in Table 3.4. Changes of $\pm 50\%$ from their final parameter values for the ICING model in Table 3.2 have no clinically (as opposed to statistically) significant effect on simulation results in terms of prediction error, fitting error and identified insulin sen-

Table 3.4 Sensitivity analysis on prediction error, fitting error and S_I

	Baseline	n_K		n_L	
		+50%	−50%	+50%	−50%
Prediction Error (%)	2.81	2.82	2.78	2.88	2.73
median [IQR]	[1.08,6.47]	[1.09,6.49]	[1.05,6.46]	[1.12,6.51]	[1.03,6.43]
Fitting Error (%)	0.47	0.51	0.43	0.54	0.39
median [IQR]	[0.20,0.97]	[0.22,1.02]	[0.18,0.90]	[0.24,1.08]	[0.17,0.84]
S_I (10^{-3}L/mU/min)	0.31	0.35	0.28	0.37	0.26
median [IQR]	[0.20,0.48]	[0.22,0.53]	[0.18,0.43]	[0.24,0.58]	[0.17,0.38]

	n_C		α_G	
	+50%	−50%	+50%	−50%
Prediction Error (%)	2.93	2.75	2.74	3.02
median [IQR]	[1.13,6.52]	[1.04,6.46]	[1.03,6.40]	[1.17,6.55]
Fitting Error (%)	0.54	0.42	0.41	0.62
median [IQR]	[0.24,1.08]	[0.18,0.88]	[0.17,0.87]	[0.28,1.17]
S_I (10^{-3}L/mU/min)	0.35	0.29	0.39	0.25
median [IQR]	[0.22, 0.54]	[0.19,0.42]	[0.26,0.57]	[0.16,0.40]

*Baseline is the model performance when no change is made to the constant parameters, and is the same as shown in Table 3.3 for the ICING model. Each time a parameter is studied, the other parameters are kept at the original constant values for the ICING model shown in Table 3.2.

sitivity, S_I. The values for p_G, EGP_b and n_I are 0.006 [1/min], 1.16 [mmol/min] and 0.003 [1/min] respectively. These sensitivity study results suggest n_K, n_L, n_C and α_G can be fixed at their current population values without over simplifying the model. However, α_G does produce a notable shift in insulin sensitivity, S_I as expected, given their trade-off relationship mathematically. A previous study showed changes in α_G produce a magnification in insulin sensitivity S_I without compromising model performance, unless it approaches non-physiological levels Chase et al. [2004].

3.4 Model Limitations and Justification

This model would benefit from further investigation into some parameters. The critical parameters are those that influence the shape of $Q/(1 + \alpha_G Q)$, as this level is the ultimate unknown (being unmeasurable) and the critical link between insulin and BG response. These parameters are effectively n_I and α_G, as the parameters that only appear in the plasma insulin equation (Equation (2.40)) can be more readily identified given insulin and C-peptide measurements. α_G in this model is assumed to be 1/65, which is the highest saturation level. The reason is purely for safety, as to avoid excessive insulin from being administered. Hence, it is more of a conservative choice. Simulation studies had been carried out to investigate the impact of these parameters, namely "effective" insulin half life and insulin-stimulated glucose removal saturation [Chase et al., 2005, 2004]. Both variables have direct impact on S_I. However, given that both parameters are kept in reported range of physiological levels, their variation simply creates a shift or magnification in the identified S_I profiles and do not compromise model fitting or prediction performance. Ultimately, it is the control, or prediction performance, that is the most critical for a model designed for model-based therapeutics. However, further studies where plasma insulin and C-peptide was measured would provide unique raw data on these parameters and their variation in the critically ill patient.

The discrepancy between n_I found in this study and Lotz et al. [2008] may have several explanations. These explanations include inherently different plasma-interstitium diffusion rates under critical illness and insulin diffusion across barrier being a saturable process. The latter possibility arises because the experimen-

tal diffusion rates 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 will not be reflective of insulin.

In addition, the plasma concentration achieved in critically ill patients is very different to that in EIC experiments or otherwise healthy diabetic individuals. The relatively low value of n_I identified in this study may indicate a significantly impaired transcapillary transport for patients who are critically ill, which is a unique result. In particular, sepsis causes a dysfunction in micro-circulation as well as cell metabolism, which is a condition prevalent in critical care. Patients in [Lotz, 2007] were subjected to an overnight fast. Hence, their plasma concentrations are relatively low and diffusion rates are faster for the short, very low insulin dose tests used in that research. In contrast, critically ill patients are often hyperinsulinaemic and infused with large amount of insulin. Therefore, it is expected that the value of n_I for patients in less critical ward would increase. These ideas need to be further investigated with more insulin and C-peptide studies.

Glucose uptake is strongly correlated with interstitial insulin [Poulin et al., 1994]. However, interstitial insulin concentrations and dynamics are difficult or impossible to measure experimentally. This study attempted to find a realistic description of interstitial insulin by linking plasma insulin and BG response through known biological mechanisms and parameter identification. The diffusion rate between plasma and the interstitial space n_I, was identified as the critical parameter, and its population value is chosen using grid search. The identified optimal parameter value provided low fitting and prediction error in BG and particularly reduced inter-patient variability in prediction error. Hence, the established shape of interstitial insulin can be concluded as realistic, bridging the link between plasma insulin and blood glucose response.

Any attempt to improve the shape of interstitial insulin should be continued once additional data from C-peptide and plasma insulin are available, justifying a clinical study. For now, the model is more than satisfactory since the percentage of fitting and prediction errors are predominantly below the measurement error of 7–12%. The data used for the development of the model covers a broad cohort

of what is typically seen in ICU patients, both highly dynamic and stable.

3.5 Model Identifiability

A further important issue addressed throughout this study is model identifiability. Given the limited data available, it is crucial to maintain a model that is uniquely identifiable with relatively infrequent (hourly at most frequent) bedside blood glucose measurements. Although the model presented in this study requires many population assumptions, and resulted in a much simpler structure compared to many others [Sorensen, 1985; Parker and Doyle, 2001; Hovorka et al., 2008, 2004b; Parker et al., 2001], it is able to accurately capture the highly dynamic response in critical illness. With limited data in a noisy and highly variable environment, such as critical care, a model that requires the minimal number of parameters to be identified will potentially cope most successfully both mathematically and clinically. All the parameters kept as population constants have been carefully studied and their sensitivity analysed.

Eventhough the model parameters were fitted and validated using data of patients in the ICU, this would not be an issue. Data of patients from step down unit weren't used simply because it is not available. However, patients in the intensive care and step-down unit do share similarities in metabolic status. Sensitivity analysis up to 50% was performed on model parameters to ensure the robustness. In Le Compte et al. [2009], the model used for glycaemic control of neonates in ICU was developed from the model of Chase et al. [2007]. Most of the model parameters for neonates were kept at same values as in Chase et al. [2007], and to ensure the validity, a 20% sensitivity analysis was performed. Hence, for this study, sensitivity analysis of up to 50% should be more than sufficient as it is not expected that the model parameters for the critically ill and less critically ill patients, would vary much more than 50%.

The study thus presents a clinically applicable yet comprehensive glucose-insulin model that is uniquely identifiable for each patient at any given time. Eventhough data of 173 patients (translates to 42 000 hours of data) may seem to be limited, but the patients cover a broad cohort of what is typically seen in the ICU. Virtual simulation is the best method to assess clinical control protocol-

saves time, cost and a number of protocols can be tested. Therefore, having a large amount of data is appreciated, a clear benefit for in-silico trials. However, as for now assessing future protocol performance and controller's adaptability would work well on these 173 patients. Long stay patient (> 3 days) may exhibit both periods of dynamic evolution and metabolic stability. The low, and more importantly tightly distributed, prediction errors of the model, where few fail to be within the clinical measurement error of 7-12% [Chase et al., 2008c, 2007], indicates the model is well suited for use in real-time, patient-specific TGC.

3.6 Summary

The new ICING model presented and validated in this study chapter is an integration and improvement of two clinically validated glucose-insulin physiological models [Chase et al., 2007; Lotz et al., 2008]. This new model has more explicit physiological relevance without increasing the number of patient-specific parameters to be identified. In particular, the insulin kinetics is expressed with distinctive routes for insulin clearance and transport from plasma, which reflects biological mechanisms. A more realistic model for gastric glucose absorption accounting for the stomach, gut and saturable glucose appearance is also introduced.

The model is capable of accurately capturing long term dynamics and evolution of a critically ill patient's glucose-insulin response. Insulin sensitivity S_I is the only parameter that is identified hourly for each individual. Its identification is guaranteed to be unique given the integral fitting method used in this study. Population constant parameters p_G, EGP_b and n_I have been identified in steps to avoid model identifiability issues. Parameter sensitivity analysis further confirms the validity of limiting time-varying parameters to S_I only. The model achieved low fitting and, most importantly, low prediction error when fitted to blood glucose data from critically ill patients. Fitting errors and the 75^{th} percentile prediction errors were all well below measurement error for 173 patients and 42,941 hours of data. The new model outperforms its critical care predecessors, and has greater physiological relevance and more detailed insulin kinetics.

It is also, unlike almost all other similar models in the literature, predictively validated against a very large range of clinical data, which is critical for a model

to be used in designing or applying real-time TGC at the bedside. This model therefore offers a platform to develop robust insulin therapies for tight glycaemic control.

Chapter 4

Glargine Model Development

This chapter presents the development and validation of a detailed pharmacokinetics model of the subcutaneous absorption kinetics of Glargine. Model parameters associated with Glargine-specific precipitate decomposition and transport were identified using 6 sets of plasma insulin time-course absorption curves from 4 Glargine studies found in a larger literature review [Scholtz et al., 2005; Heinemann et al., 2000; Lepore et al., 2000; Owens et al., 2000]. Four additional, independent studies [Klein et al., 2007; Danne et al., 2003; Becker et al., 2008; Heise et al., 2004], were used as independent validation test to show the validity of the model and parameters found. The identified model is validated by comparison to reported values for maximum plasma insulin concentration, C_{max}, and time to maximum plasma insulin, T_{max}.

Absorption kinetics often show significant intra- and inter- individual variability. To add this variability to the pharmacokinetics model of Glargine, ranges of variation for the identified Glargine model parameters were introduced into 1000 Monte Carlo simulations. This assessment and analysis portray the likely intra-individual and inter- individual variability that could be expected clinically. The Monte Carlo analysis thus defines a range and distribution of identified and validated model parameter variations to consider in designing a glycaemic control protocol using Glargine.

4.1 Introduction

Basal insulin therapy, has gained renewed interest since the introduction of Glargine [Campbell et al., 2001]. Glargine, a human insulin analogue is prepared by recombinant DNA technology in which the amino acid asparagine at position A21 is replaced by glycine and two arginines are added to the C-terminus of the B-chain at position B31 and B32 [Lantus, 2001]. It is these 3 amino acids that make Glargine different from the human insulin. The addition of two molecules at the B-chain shifts the isoelectric point from 5.4 to 7.4 which makes Glargine a soluble insulin at a slightly acidic pH and less soluble at physiological pH levels [Heinemann et al., 2000; Campbell et al., 2001; Dunn et al., 2003]. The positively charged amino acids ionizes the insulin analogue, hence allowing it to remain soluble at acidic pH of the injection medium and less soluble at the physiologic pH [Campbell et al., 2001; Wang et al., 2003]. Figure 4.1 shows the structural formula of Glargine, and how it differs from the human insulin:

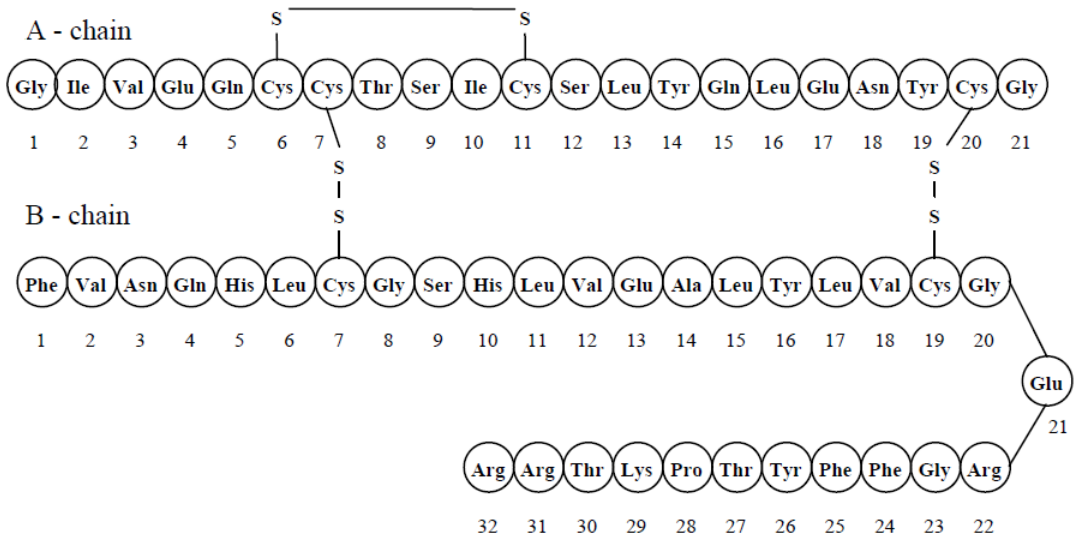


Figure 4.1 Glargine structural formula from [Lantus, 2001]. Asparagine has been replaced by glycine at position A21. At the end of C-terminus of the insulin B-chain, 2 arginine molecules are added. This modification shifts the isoelectric point from pH 5.4 to 7.4. This makes Glargine more soluble at slightly acidic pH and less soluble at physiologic pH [Heinemann et al., 2000; Campbell et al., 2001; Dunn et al., 2003; Wang et al., 2003].

Most conventional basal insulin types have pharmacodynamic (PD) profiles that poorly approximate the flat, basal insulin secretion of a non-diabetic, healthy

individual. Figure 4.2 shows the plasma insulin profile of several rapid, regular and long acting insulins taken from [Hirsch, 2005]. NPH and ultralente are such insulins that are used as basal insulin therapy despite having pharmacokinetics that do not match the endogenous insulin secretion [Scholtz et al., 2005]. Ultralente, for example has a large day to day absorption variability [Binder, 1969] that will caused large swings or fluctuations in blood glucose level. Ideally, basal insulin should mimic the basal insulin secretion of a healthy pancreas, with no distinct peak, a continuous effect over 24 hours, and an absorption pattern that is slow, constant, predictable and reproducible [Campbell et al., 2001]. Glargine, a recombinant insulin analogue appears to mimic this behaviour with its relatively flat time-action profile and more predictable effects [Rosenstock et al., 2001]. This unique property allows Glargine to be given once daily. Thus, this is what makes Glargine the insulin of choice in this thesis.

Other therapy such as CSII (continuous subcutaneous insulin infusion), an insulin pump therapy is not considered as few obstacles are commonly associated with CSII [Wesorick et al., 2008]. Mainly, there is a constant need for pump management which most hospitals lack in expertise. The issue is lack of exposure on CSII among nurses. CSII also involves patient participation, and thus it is limited by patient's level of consciousness. Plus, a physician order must be placed each time insulin dosage is adjusted, and this does not go along with the target of this thesis to develop a nurse-driven protocol. Furthermore, cost is also a big obstacle to CSII therapy and it is the most expensive option for insulin pump [Bruttomesso et al., 2009].

Owens et al. [2000]; Heinemann et al. [2000]; Lepore et al. [2000]; Scholtz et al. [2005] and Luzio et al. [2003] are few literatures that studied the pharmacokinetics and pharmacodynamics of Glargine, comparing it to NPH or ultralente insulin. To find the absorption rate of Glargine from the subcutaneous site, the studies used either euglycaemic glucose clamp technique or external gamma-counting. The time to disappearance of 25% from the administered radioactivity, after subcutaneous injection and residual radioactivity 24 hours after radiolabelled injection, is then measured.

In [Scholtz et al., 2005], the day to day variability in the time-concentration and time-action profiles of Glargine were compared to NPH and ultralente. The result of the study showed that Glargine is associated with low variability and

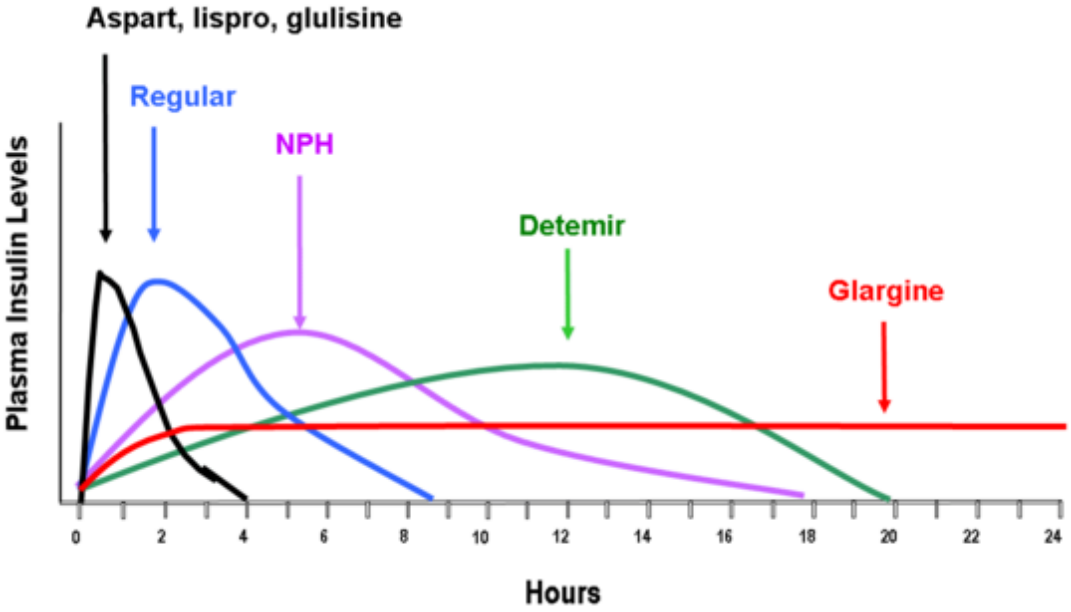


Figure 4.2 Ideal insulin time-action profiles of several insulins reproduced from [Hirsch, 2005].

reproducible activity. NPH on the other hand, had a definite early peak exposure while ultralente with no pronounced peak is highly variable in terms of glucose lowering effect among subjects. Meanwhile, Lepore et al. [2000] found that both NPH and ultralente had a peak concentration and action. Intersubject variability is found to be greater in ultralente compared to Glargine and NPH. A study by Heinemann et al. [2000], also compared the pharmacodynamic properties of Glargine to NPH with the result confirming a smoother metabolic effect in Glargine in comparison to NPH. Lastly, Owens et al. [2000] found that the subcutaneous absorption of Glargine is delayed compared to NPH.

However, limited research has been done in terms of modelling the absorption process of Glargine, since its introduction in 2000. Pharmacokinetics and pharmacodynamics modeling analysis have been used to support licensing dose of drugs. The FDA (US Food and Drug Administration) states that PK/PD might be the supporting evidence of clinical trial efficacy [Rolan and Molnar, 2006]. Hence, there is a definite importance of PK/PD modeling with the widespread confidence. To date, only Tarín et al. [2005] and Wong et al. [2008a,b] reported comprehensive pharmacokinetic models. Mosekilde et al. [1989] proposed an absorption kinetics model for subcutaneous injected insulin. It was the first mechanism based model utilising chemical relationships between insulin polymers to explain

the absorption kinetics. This model was refined and simplified by Trajanoski et al. [1993]. Tarín et al. [2005] later extended the model to cover Glargine's peakless time action profile. Finally, Wong et al. [2008a,b] constructed an extensive physiologically consistent ten-compartment model for the pharmacokinetics of several rapid acting, regular and long acting insulins including Glargine.

Critical reviews of other available studies with general models of subcutaneously injected insulin are reported in Nucci and Cobelli [2000].

Using such deterministic models to determine the pharmacokinetics of insulin, physicians and nurses can better overcome barriers to effective glucose management. The use of model-based methods in Type 1 and Type 2 diabetes has shown the potential for developing successful therapeutic methods for effective glycaemic control [Wong et al., 2008a,b,c; Hovorka et al., 2007; Lehmann, 2001; Tudor et al., 1998]. However, models can not give meaningful prediction or portray the underlying physiology unless their parameters are determined and justified with clinical data. In addition, significant intra- and inter- patient variability in the PK and PD of insulin offer further barriers to model-based control.

To capture the dynamics of Glargine's absorption kinetics, this chapter presents a more comprehensive physiological compartmental model specifically developed for this insulin class. As insulin action is a saturable process, there is a need to model the saturation in Glargine's pharmacokinetics which was not accounted for in the prior model of Wong et al. [2008a,b]. The model structure of Wong et al. [2008a,b] is re-analyzed and re-identified with new parameters, with the addition of Michaelis-Menten saturation thus better capturing the physiological aspects. The model is further validated with several independent studies, thus providing external validation aspect to confirm the validity of the developed model. In particular, intra- or inter- individual variation in insulin absorption can range from 35%-50% [Heinemann et al., 2000]. Thus, a robust model that can capture these variations is equally important. Hence, the model developed in this study accounts for variability seen clinically among patients under Glargine therapy. By having a robust model, it will give sufficient time for intervention and adjustment of insulin before glucose concentrations drift from desired ranges. As a result, hypo/hyperglycaemia can be better avoided. It is intended that this subcutaneous absorption model development would eventually offer a safe means to develop and compare control algorithms using Glargine prior to clinical testing.

4.2 Glargine Compartmental Model

Upon subcutaneous injection, Glargine forms a depot from which absorption into the systemic circulation occurs. The unique pharmacology of Glargine due to the isoelectric shift that alters the association properties stated earlier, makes it precipitate into stable hexamers within the physiologically pH-neutral environment [Guerci and Sauvanet, 2005]. Hexameric dynamics are one of the main processes in a model that determines the onset time and action curve of different insulin preparations [Lehmann et al., 2009]. The addition of zinc as hexamer-stabilizing agent improves the time-action profile [Campbell et al., 2001; Wang et al., 2003]. Insulin hexamers dissociate further over time into dimers or monomers, which are the forms easily absorbed into the bloodstream. It is this unique dissociation process, and the unique very flat and long acting profile of Glargine that it creates, which determines the onset time and action curve [Campbell et al., 2001]. Figure 4.3 describes the disassociation process from hexamer to dimers and monomers.

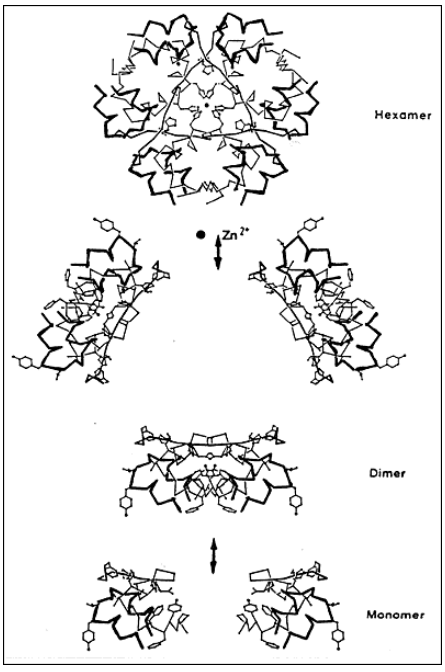


Figure 4.3 The pathway describing the process of insulin hexamers, dimers and monomers. Image sourced from www.endotext.org.

A four compartment description of subcutaneous insulin kinetics is presented, where Glargine is modelled to appear in its precipitate, hexameric, dimeric / monomeric, and (local) insterstitium states. The underlying structure of this

pharmacokinetics model is adopted from Wong et al. [2008a,b]. The model describes the pharmacokinetics processes following subcutaneous administration of Glargine:

Precipitate State:

$$\dot{p_{gla}}(t) = \frac{-k_{prep,gla}p_{gla}(t)}{1+\frac{k_{prep,gla}}{r_{dis,max}}p_{gla}(t)} + u_{p,gla}(t) \tag{4.1}$$

$$u_{p,gla}(t) = \alpha_{gla}u_{total,gla}(t) \tag{4.2}$$

Hexameric State:

$$\begin{aligned}\dot{x_{h,gla}}(t) &= -(k_{1,gla}+k_d)x_{h,gla}(t) + \frac{k_{prep,gla}p_{gla}(t)}{1+\frac{k_{prep,gla}}{r_{dis,max}}p_{gla}(t)} \\ &\quad + u_{h,gla}(t)\end{aligned} \tag{4.3}$$

$$u_{h,gla}(t) = u_{total,gla}(t)(1-\alpha_{gla}) - u_{m,gla}(t) \tag{4.4}$$

Dimeric/Monomeric State:

$$\dot{x_{dm}}(t) = -(k_2+k_d)x_{dm}(t) + k_{1,gla}x_{h,gla}(t) + u_{m,gla}(t) \tag{4.5}$$

Interstitium:

$$\dot{x_i}(t) = -(k_3+k_{di})x_i(t) + k_2x_{dm}(t) \tag{4.6}$$

where all variables in Equations (4.1)–(4.6) are defined in Table 4.1 and the model is shown schematically in Figure 4.4:

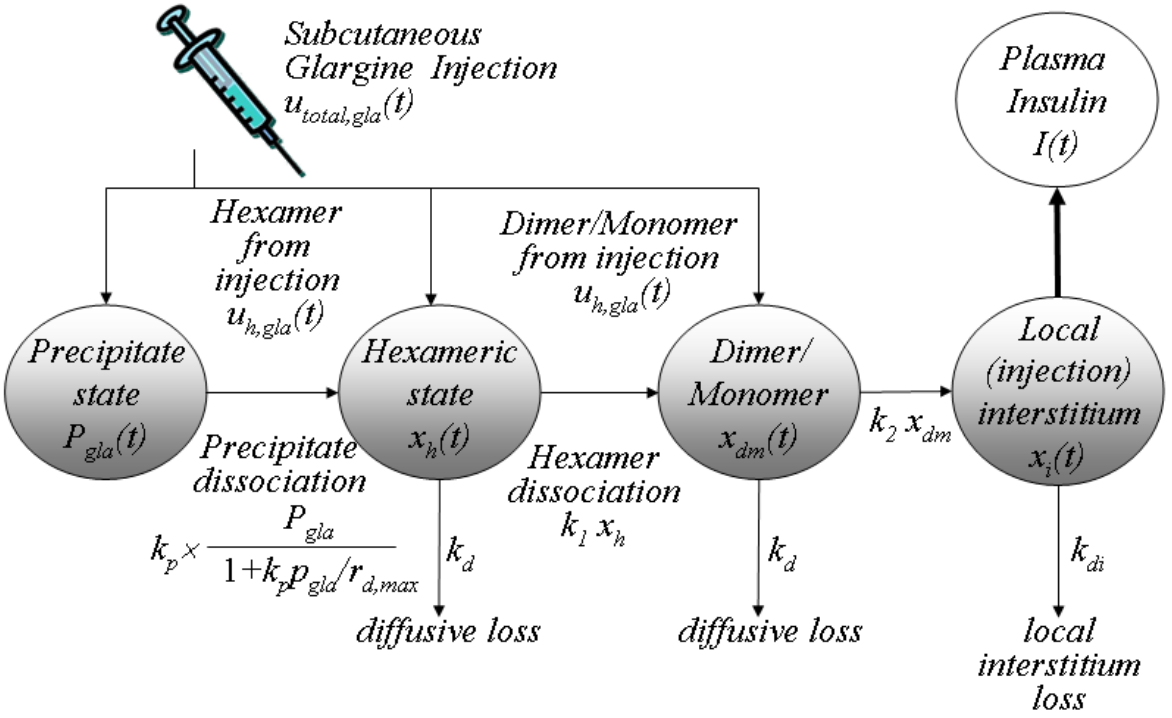


Figure 4.4 Structure of Glargine absorption kinetics model, beginning from subcutaneous Glargine injection, to precipitate compartment, $p_{gla}(t)$, hexameric compartment $x_{h,gla}(t)$, dimeric/monomeric compartment, $x_{dm}(t)$, interstitium, $x_i(t)$ and finally to the plasma insulin compartment, $I(t)$.

Table 4.1 Description of Glargine compartmental parameters.

Parameters	Description
$x_{h,gla}(t)$	Mass in glargine hexameric compt. [mU]
$p_{gla}(t)$	Mass in glargine precipitate compt. [mU]
$x_{dm}(t)$	Mass in dimer/monomer compartment [mU]
$x_i(t)$	Mass in the interstitium compartment [mU]
$r_{dis,max}(t)$	Max glargine precip. dissolution rate [mU/min]
$u_{total,gla}(t)$	Insulin glargine input [mU/min]
$u_{p,gla}(t)$	Glargine precipitate state insulin input [mU/min]
$u_{h,gla}(t)$	Glargine hexamer state insulin input [mU/min]
$u_{m,gla}(t)$	Glargine dimer/monomer state insulin input
$k_{prep,gla}$	Glargine precipitate dissolution rate [min-1]
k_1	Hexamer dissociation rate [min-1]
$k_{1,gla}$	Glargine hexamer dissociation rate [min-1]
k_2	Dimeric/monomeric insulin transport rate into interstitium [min-1]
k_3	Interstitium transport rate into plasma [min-1]
k_{di}	Rate of loss from interstitium [min-1]
k_d	Rate of diffusive loss from hexameric and dimeric/monomeric state compartments [min-1]
α_{gla}	Fraction of glargine as precipitate

Equations (4.1) and (4.3) differ from the original non-linear model in Wong et al. [2008a,b] with the introduction of the Michaelis-Menten saturation terms in these equations. The rate of Glargine precipitate dissolution, $k_{prep,gla}$, is a saturable process and is slower with the introduction of the Michaelis-Menten saturation function. There is a need to model this saturation as the solubility of the Glargine precipitate is limited due to the shifted pH of Glargine molecules [Tarín et al., 2005]. Glargine injection is completely soluble at a pH of 4.0, and once injected in a neutral subcutaneous state with pH 7.4, Glargine is neutralized and formed microprecipitates [Campbell et al., 2001]. Specifically, this model adds a non-linear transport saturation based on the impact of Glargine molecule's own pH on the surrounding depot pH, which limits and extends the process to give Glargine its characteristically flatter profile. Hence, the model development with Michealis-Menten saturation has a greater physiological relevance.

Subcutaneous absorption kinetics are predominantly concentration and volume dependent [Søeborg et al., 2009]. To account for the volume effects of injected insulin volume, the rate of diffusive loss from the hexameric and dimeric/monomeric state, k_d, represents this physiology of the injection site as:

$$k_d = \frac{3D}{r^2} \tag{4.7}$$

$$r = (\frac{3}{4}\frac{V_{inj}}{\pi})^{\frac{1}{3}} \tag{4.8}$$

k_d is the rate of diffusive loss from hexameric and dimeric /monomeric compartments [min-1], D is the diffusion constant [cm^2/min], r is the radius of the subcutaneous depot [cm], and V_{inj} is the dose injection volume [ml or cm^3].

4.2.1 Glargine Sub-model structure

Once Glargine precipitates, it is slowly released from this form to hexamerics. The Glargine sub-model structure is used to model the maximum dissolution rate, $r_{dis,max}$ of the precipitate $p_{gla}(t)$, into a hexameric form in Equations (4.1) and (4.3), $x_{h,gla}(t)$, which is unique to Glargine compared to other insulin [Tarín et al., 2005; Dunn et al., 2003]. This process is defined:

$$r_{dis,max}(t) = Br_{dis,max}(\alpha_{gla}u_{total,gla} < U_{tres}) + \frac{Br_{dis,max}\alpha_{gla}u_{total,gla}}{U_{tres}(\alpha_{gla}u_{total,gla} >= U_{tres})}; \tag{4.9}$$

where $Br_{dis,max}$ is the baseline value of $r_{dis,max}$ for a given dose and U_{tres} is the dose threshold value. Thus, this term in Equations (4.1) and (4.3) limits the precipitate to hexameric change, and is unique to this model.

4.2.2 Plasma Insulin Model Structure

To portray insulin absorption into the overall plasma and interstitium, the ICING glucose-insulin model in Chapter 2.2.3 is used. From the interstitium, exogenous insulin which is from the administration of Glargine will appear in Equation 4.11 as u_{ex} after multiplication with k_3, the interstium transport rate into plasma. The action of insulin, as developed before in Chapter 2 is described:

$$\dot{Q} = n_I(I(t) - Q(t)) - n_C \frac{Q(t)}{1 + \alpha_G Q(t)} \tag{4.10}$$

$$\dot{I} = -n_K I(t) - \frac{n_L I(t)}{1 + \alpha_I I(t)} - n_I(I(t) - Q(t)) + \frac{u_{ex}(t)}{V_I} + (1 - x_L)\frac{u_{en}}{V_I} \tag{4.11}$$

$$u_{en}(t) = k_1 e^{-\frac{I(t)^{k_2}}{k_3}} \quad \text{when C-peptide data are not available} \tag{4.12}$$

where all variables in Equation (4.10)–(4.12) are defined in Chapter 2: Model Development.

4.3 Model Identification and Analysis Method

4.3.1 Model Parameter Identification

The parameters for the Glargine Compartmental Model in Section 4.2 are identified a priori from clinical results in the literature except for $k_{prep,gla}$, $k_{1,gla}$, $Br_{dis,max}$ and U_{tres}, the latter 2 of which define $r_{dis,max}$ in Equation (4.9). For the plasma insulin model structure of the ICING model, the complete parameters can be referred to in Chapter 3: Parameter Identification and Model Validation.

Overall, the model in Wong et al. [2008a,b] has been converted from a non-linear function of hexameric and precipitate compartments into a saturated, linear differential form in Equations (4.1) and (4.3). This change means that the

Glargine precipitation model parameters must be re-identified and re-validated. The model parameters associated with this process are the Glargine precipitate dissolution rate [min^{-1}], $k_{prep,gla}$ and Glargine hexamer dissociation rate [min^{-1}], $k_{1,gla}$. Since $r_{dis,max}$ is the maximum dissolution rate of the precipitate into the hexameric form unique to Glargine, this parameter also needs to be identified and validated for this study.

The constant parameters defined in Wong et al. [2008a,b] are given in Table 4.2. The parameters are kept because they are common to, and validated for, to multiple insulin types in the overall model for multiple insulin types in [Wong et al., 2008a,b]. Hence, this study examines only those model parameters specific to Glargine, thus maintaining the physiological consistency of the combined model if this version of the Glargine model were used.

The remaining parameters associated with the Glargine Compartmental Model, $k_{prep,gla}$, $k_{1,gla}$, $Br_{dis,max}$ and, U_{tres} were identified using 6 sets of plasma insulin time-course absorption curves from Glargine studies found in a larger literature review [Heinemann et al., 2000; Scholtz et al., 2005; Owens et al., 2000; Lepore et al., 2000]. The corresponding pharmacokinetic parameters are calculated from each study and the final population values were taken as the average of all studies. This method is typical of conventional pharmacokinetic study [Rolan and Molnar, 2006]. The Glargine parameters are identified using a standard non-linear recursive least squares (NRLS) fitting method.

NRLS requires initial search values for the optimisation since the method is starting point dependent, which were taken or estimated from those used in [Wong et al., 2008a,b]. In Wong et al. [2008a,b], the parameter values used as starting point for optimisation were obtained from [Shimoda et al., 1997].

The ability of the NRLS method to effectively identify Glargine model parameters, is highly dependent on the initial selection of parameter values. This posed as a limitation in the beginning when the initial selection from Wong et al. [2008a] was not sufficient to give a good data fitting. The method became time-consuming as a unique identifiability is essential for model identification. However, the NRLS managed to converge to an area of 'true parameters' after a few sets of initial parameter values.

Model parameter values resulting in the closest fit to the plasma insulin time-course data in the literature in terms of sum squares of error (SSE) are regarded as the best Glargine model parameters. The SSE function relative to time-course absorption curves data is defined [Wong et al., 2008a,b]:

$$SSE_j = \sum_{i=1}^{N_j} (I_{j,i} - I_j(t_{j,i}))^2 \tag{4.13}$$

where N_j is the number of plasma insulin data points in the j_{th} data set, $I_{j,i}$ is the i_{th} plasma insulin concentration data point in the j_{th} data set, and $I_{j(t,j)}$ is the modeled plasma insulin concentration for the j_{th} data set at $t_{j,i}$, the time at the i_{th} plasma insulin concentration data point.

Table 4.2 Glargine constant population parameters [Wong et al., 2008a,b]

Parameters	Values
k_2	0.0106 [min-1]
k_3	0.0618 [min-1]
k_{dI}	0.0029 [min-1]
α_{gla}	0.9462
D	0.00009 [cm^2/min]

4.3.2 Independent Pharmacokinetics Validation

The model with identified parameter values is validated by simple pharmacokinetic measures. Specifically, the time to maximal concentration, T_{max}, and maximal concentration reached, C_{max} as shown in Figure 4.5. In this example, C_{max} is equivalent to 4.8 mU/L while T_{max} occurs at 762.9 minutes. A validation comparison was made to equivalent C_{max} and T_{max} from reported data where available. In cases where C_{max} and T_{max} are not reported, an estimate is made from best model fit (SSE) alone. To further improve the validity of the model, four further independent published studies were utilized for validation [Klein et al., 2007; Danne et al., 2003; Becker et al., 2008; Heise et al., 2004]. Validation with these additional independent studies provides a broader cohort, as seen in Table 4.3, and illustrates the robustness and the validity of the model to be used for a wider

population. In particular, the independent study by [Danne et al., 2003] provides data for children and adolescents as compared to adults. Hence, this data set provides a direct comparison on the behaviour of Glargine pharmacokinetics profile between three different age groups.

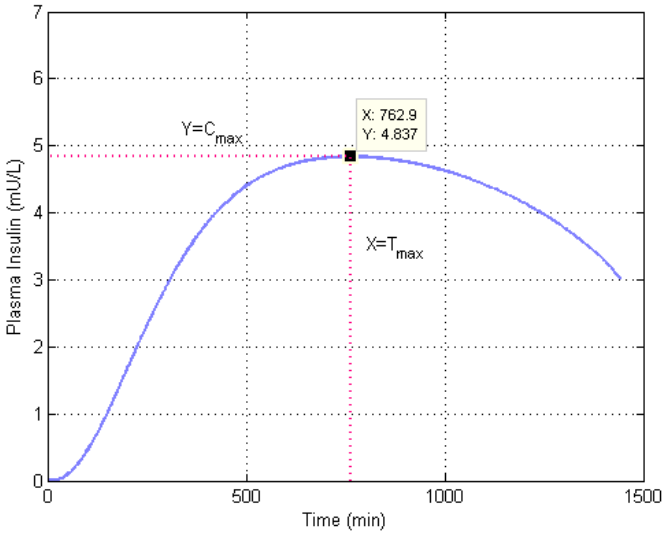


Figure 4.5 An individual model fit example of [Owens et al., 2000] to show the plasma insulin curve with T_{max} and C_{max}, the important criteria used as a model validation. The solid blue line (–) is the plasma curve of Owens et al. [2000] model fit while the dotted red line ($\cdots$) corresponds to each maximal plasma insulin, C_{max}, and time to reach maximal plasma insulin, T_{max}.

4.3.3 Monte Carlo Study

Subcutaneous insulin absorption varies from one person to another, and can also be influenced by temperature, exercise, depth of injection, and many other insulin-dependent/independent factors [Berger et al., 1982; Binder et al., 1984]. Clinical experience has shown that under comparable patient conditions, the same injected subcutaneous dose often does not produce the same metabolic effect [Heise et al., 2004]. Studies on variability of insulin absorption after a subcutaneous administration began several decades earlier [Moore et al., 1959; Binder, 1969]. However, our knowledge on this topic is still limited [Heinemann, 2002].

To model Glargine absorption variability in this study, lognormal distributions in several critical parameters are combined to produce variability matching

Table 4.3 Literature Study Population Details

Study	Condition	Participants (N)	Age (year)	BMI (kg/m^2)	Dose (U/kg)
[Heinemann et al., 2000]	Healthy	15	27±4	22.2±1.8	0.4
[Scholtz et al., 2005]	Healthy	12	23 [18-23]	22.8 [20-25.8]	0.4
[Owens et al., 2000]	Healthy	12	18-44	18-30	0.15
[Lepore et al., 2000]	Type 1	20	32±2	22.2±0.4	0.3
[Klein et al., 2007]	Type 2	27	53±9	31±2.8	0.4
[Danne et al., 2003]	Type 1	30	13 [8-17]	21.4 [16.1-28.16]	0.4
[Becker et al., 2008]	Healthy	24	18-50	18-27	0.4
[Heise et al., 2004]	Type 1	44	34±8	24.5±2	0.4

reported ranges in Glargine dose-response studies. Lognormal distributions are used because the varied model parameters must be positive, which using a normal distribution does not guarantee.

The lognormal propability density function is given:

$$p(x|\mu,\sigma) = \frac{1}{x\sigma\sqrt{2\pi}}\exp\left[\frac{-(ln(x)-\mu)^2}{2\sigma^2}\right] \tag{4.14}$$

where μ and σ are the mean and standard deviation of the variable's natural logarithms.

A lognormal distribution is defined with reference to a normal distribution. To determine μ and σ we need to use this relationship. If X is lognormally distributed, the following describes the algebraic relationship:

Mean [X]:

$$= e^{\mu+0.5\sigma^2} \tag{4.15}$$

Standard Deviation [X]:

$$= e^{\mu+0.5\sigma^2}\sqrt{e^{\sigma^2}-1} \tag{4.16}$$

Parameters $k_{prep,gla}$, $k_{1,gla}$ and α_{gla} are the critical parameters given lognormal distribution in this study, producing variations in C_{max} matching published data. These parameters are critical as they partly define the hexameric compartment. As mentioned previously, hexameric dynamics are one of the main processes that determines the onset time and action curve. Figure 4.6 shows the effect on plasma-insulin curve of Glargine with different tested values for $k_{prep,gla}$, $k_{1,gla}$

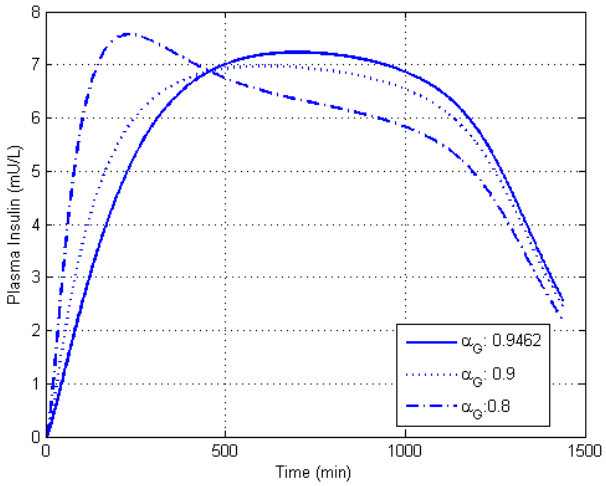
and α_{gla}. Final parameters chosen were those that produced the closest variations up to one standard deviation to reported C_{max}. The other parameters are kept constant in the Monte Carlo simulations at their a priori values. The Glargine pharmacokinetic responses are computed for 1000 Monte Carlo simulations to produce the expected variability distribution.

4.4 Results

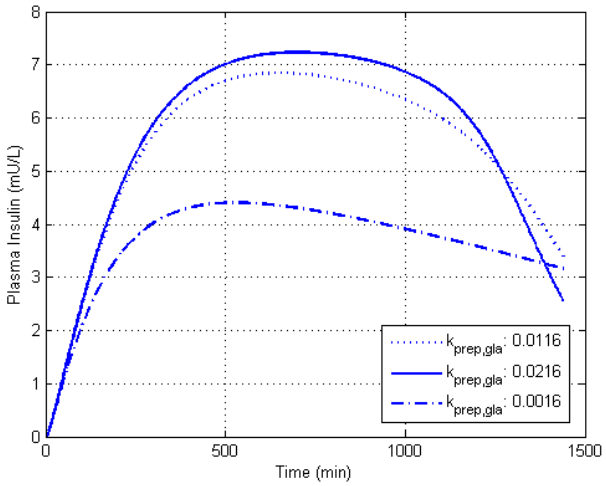
4.4.1 Glargine Model Parameters

The identified model parameters for the Glargine subcutaneous absorption model, $k_{prep,gla}$, $k_{1,gla}$ and $r_{d,max}$ function, $Br_{dis,max}$ and U_{tres} are shown in Table 4.4. Final values are chosen as the mean of each parameter identified individually for each of the 6 studies used [Heinemann et al., 2000; Scholtz et al., 2005; Owens et al., 2000; Lepore et al., 2000]. Figure 4.7 depicts the individual model fit from Scholtz et al. [2005] and Lepore et al. [2000] using fitted parameter values from Table 4.4, along with the reported experimental data.

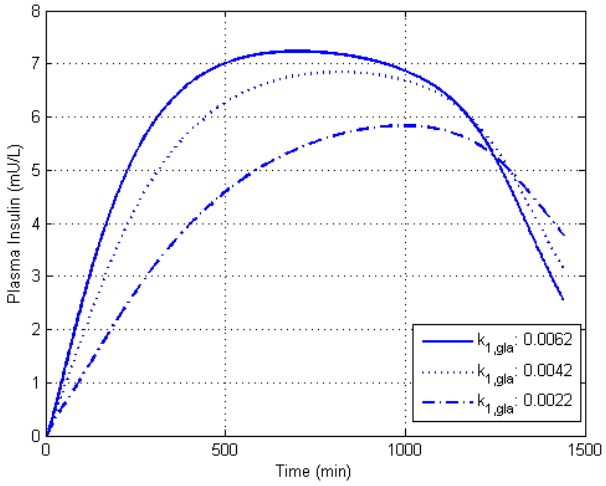
Aside from minimizing error between model fit and data, the estimation of model parameters needs to consider the elimination of experimental noise. Experimental noise, as can be seen in Figure 4.7(b) is defined here as the variation between data points in each data set, which can influence the identified model parameters. This is apparent around minutes 200, where there are 2 plasma insulin concentration points at 8 mmol/L. These data points are inaccurate in respect to the subcutaneous Glargine concentration due to the presence of a significant rate of IV insulin infusion for the first 3 hours. A specific assay for measurement of Glargine at this first 3 hours is not available in the study [Lepore et al., 2000]. A portion of data from 820-1170 minutes, were missed in the model. However, it is not significant as the model approximates the supposed plateau concentration as expected from subcutaneous Glargine. The time from 820-1170 minutes were thus treated as a smooth plateau. The final identified pharmacokinetics model parameters, averaged over the 6 studies used in this study, show good agreement with the data. Good agreement is quantified with SSE and can be referred in Table 4.4. Model parameters that produced model with lowest SSE are selected.



(a) Effect of different α_{gla}



(b) Effect of different $k_{prep,gla}$

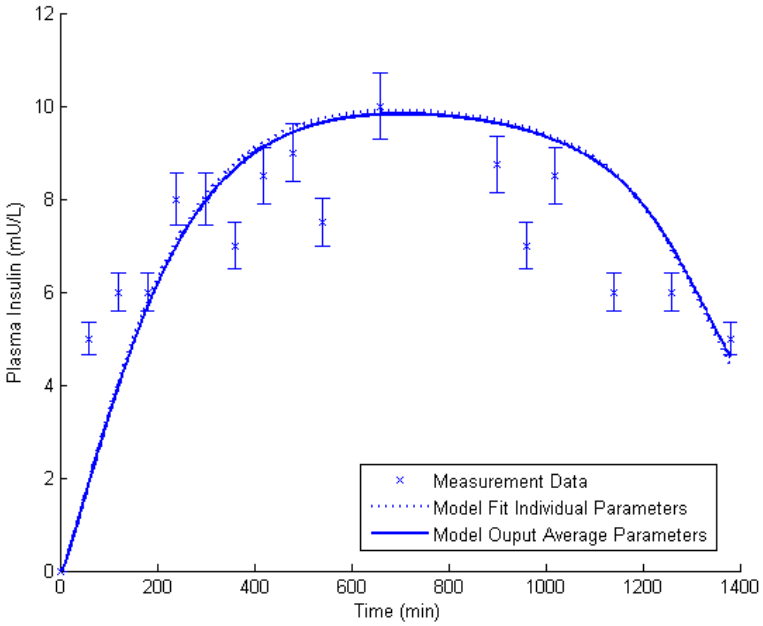


(c) Effect of different $k_{1,gla}$

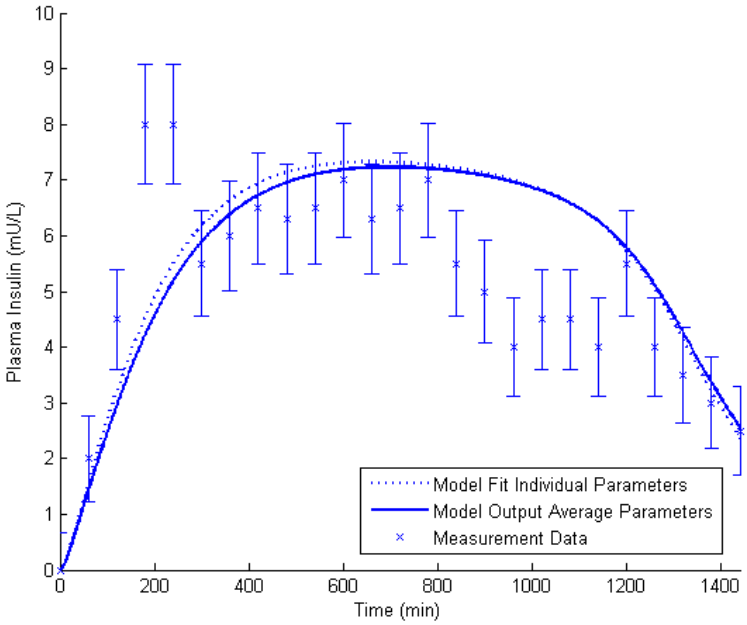
Figure 4.6 The effect of different tested values for α_{gla}, $k_{prep,gla}$, and $k_{1,gla}$.

Table 4.4 Identified Glargine parameter estimates

	Fitted Values						
Model Parameters	Heinemann et al. [2000]	Scholtz et al. [2005]		Owens et al. [2000]		Lepore et al. [2000]	
	Heinemann	*Clamp 1*	*Clamp 2*	*15ug/ml*	*80ug/mL*	*Lepore*	*Mean Parameter*
$k_{prep,gla}$ [min-1]	0.023	0.023	0.019	0.021	0.039	0.005	0.0216
$k_{1,gla}$ [min-1]	0.0064	0.0064	0.007	0.007	0.006	0.0049	0.0062
$B_{rd,max}$	2.314	2.314	2.314	2.314	2.314	2.314	2.314
U_{tres}	2380	2380	2380	2380	2380	2380	2380
SSE Fit	1.42	1.51	1.72	0.92	1.21	1.34	



(a) Model Fit and Model Output of a 32U injection.



(b) Model Fit and Model Output of a 24U injection.

Figure 4.7 Glargine model response of plasma insulin with injection amount of 32U and 24U incorporating the average parameter values fitted to Scholtz et al. [2005] and Lepore et al. [2000]. Solid line (-) corresponds to the model generated output while model fit to experimental data is represented by $(\cdots)$. Crosses (x) present the measured experimental data from Scholtz et al. [2005] and Lepore et al. [2000].

4.4.2 Independent Pharmacokinetics Validation

The subcutaneous Glargine absorption model with the identified mean parameters is validated against external experimental data presented by Klein et al. [2007]; Danne et al. [2003]; Becker et al. [2008] and Heise et al. [2004]. These independent, additional studies provide a measure of external validation as their data was not used for model parameter identification. Table 4.5 shows that the reported C_{max} and T_{max} from the model generated curves are within one standard deviation of C_{max} and T_{max} from the published data of [Klein et al., 2007; Danne et al., 2003; Becker et al., 2008; Heise et al., 2004].

By covering several studies in cohort difference, the quality of mean parameter estimates for Glargine model parameters will increase. The study by [Danne et al., 2003] provides data for group of patients belonging to different age groups. Hence, it is interesting to see if this population would give a different behaviour in comparison to adults population. Validation of the Glargine pharmacokinetic profile in this younger patients conform with Lantus [2001] that there is no difference in the Glargine profile between children, adolescents and adults with Type 1 diabetes. The model is validated by computing T_{max} and C_{max}, the critical clinical parameters modeled to those published in the literature.

To see the performance of the identified model parameters, the dynamics of the model in simulating different Glargine doses of 10U, 20U, 30U, 40U and 50U are shown in Figure 4.8. The clinically flat insulin concentration profile of Glargine with no pronounced peak can be observed. Lepore et al. [2000] reported a duration of action of 20-24 hours after a single dose and 24 to 25.6 hours at steady state. As can be observed, all model curves in Figure 4.8 conform to these existing reports [Lepore et al., 2000; Campbell et al., 2001; Dunn et al., 2003] and maintained the delayed onset of action and a prolongation of action with no pronounced peak, as expected from the pharmacokinetics of Glargine. Note that it is this lack of specific peak that also yields the large variability in C_{max} and T_{max} in Table 4.5.

Table 4.5 Summary measures for Glargine model curve compared to independent studies.

Parameters		Reference			
		Becker et al. [2008]	Heise et al. [2004]	Klein et al. [2007]	Danne et al. [2003]
		Becker	*Heise*	*Type 2*	*Type 1*
T_{max}	Model	750	720	705	702
	Literature	750	500[e]	512± 234	540 ± 240
C_{max}	Model	9	9	9.2	5.4
	Literature	12[c]	14.3±4.8	12.7 ± 8.4	4.9

[c] Corrected for endogenous insulin production and estimated from plotted data. [e] Quoted as maximal time of GIR or glucose infusion rates instead of maximal time to maximum plasma insulin concentration, T_{max}.

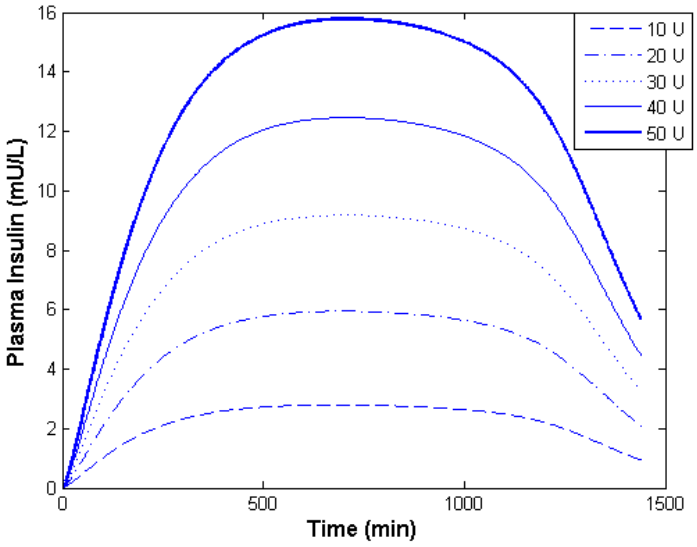


Figure 4.8 Glargine dose responses from model generated output. The slopes over the first 60 mins are different (different rate of absorption). As expected from the time-action profile of Glargine, there is a flat basal period with no pronounced peak. At this basal part, the rate of absorption is the same. The dashed line (–) is for the injection amount of 10U. Dot-dashed line (· · · -) portrays the dose response with injection amount of 20U. The dotted line (· · ·) represents injection amount of 30U. The solid line (-) represents injection amount of 40U. Finally, the weighted solid line (-) is Glargine dose response with the injection amount of 50U.

Table 4.6 Specifications of lognormal distribution for Glargine model parameters

Glargine Model Parameters	Lognormal Distribution Specifications	
	μ	σ
$k_{prep,gla}$	-3.49	0.3
$k_{1,gla}$	-5.1855	0.8330
$alpha_{gla}$	-0.081	0.019

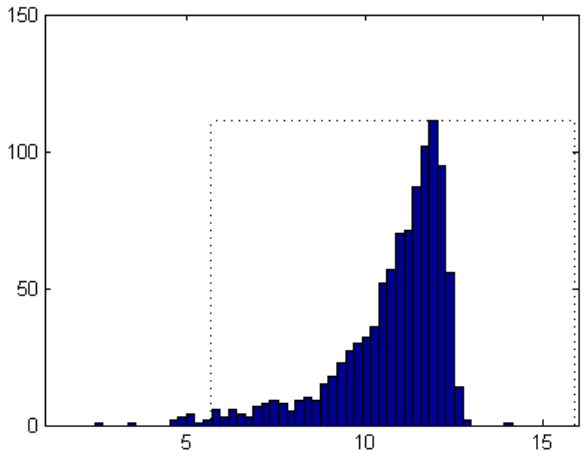
4.4.3 Monte Carlo Analysis and Variability

Table 4.6 shows the assumed μ and σ in Equations (4.14)–(4.16). These values specify the lognormal distribution of Glargine pharmacokinetics parameters, $k_{prep,gla}$, $k_{1,gla}$, and α_{gla}. The decision to adopt a lognormal distribution automatically limits variations in model parameters to be non-negative values as seen in the Figure 4.10. Figure 4.10 shows the randomly selected model parameter variability of the Glargine pharmacokinetics parameters $k_{prep,gla}$, $k_{1,gla}$, and α_{gla} for 1000 Monte Carlo simulations. The theoretical lognormal functions from which they were sampled are also shown in Figure 4.10.

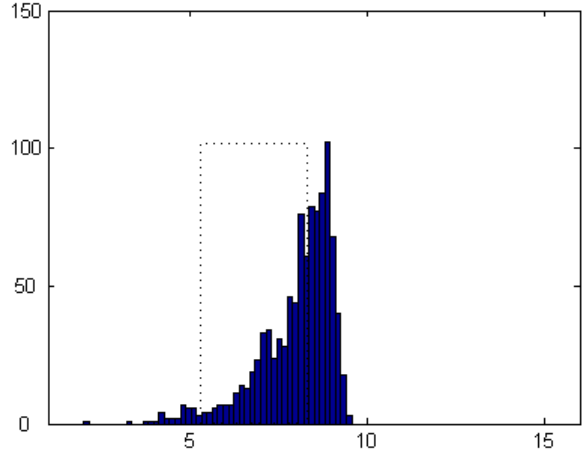
The results in Figure 4.9 illustrate how Glargine pharmacokinetics parameter variability yields expected variability in maximal plasma insulin, C_{max}. The range produced in Figure 4.9 is the best achieved to replicate the reported values by studies in the literature for similar injection doses [Heinemann et al., 2000; Scholtz et al., 2005; Owens et al., 2000; Lepore et al., 2000]. The published values of C_{max} is shown in Table 4.7. For example, a 24U of subcutaneous Glargine as reported by [Lepore et al., 2000], has variations of C_{max} from 7$\pm$1.3 mU/L, and this is presented by the boxed area in Figure 7.1(b). The range of C_{max} produced covers the reported area.

The plot of C_{max} is expressed as a log normal distribution. This distribution maximizes the likelihood of accounting for variability among patients receiving the subcutaneous injection. As absorption rate is dose dependent, where a small dose is absorbed faster than a larger dose [Søeborg et al., 2009], variability of C_{max} as portrayed in Figure 4.9 increases at higher volume of Glargine injection, as expected.

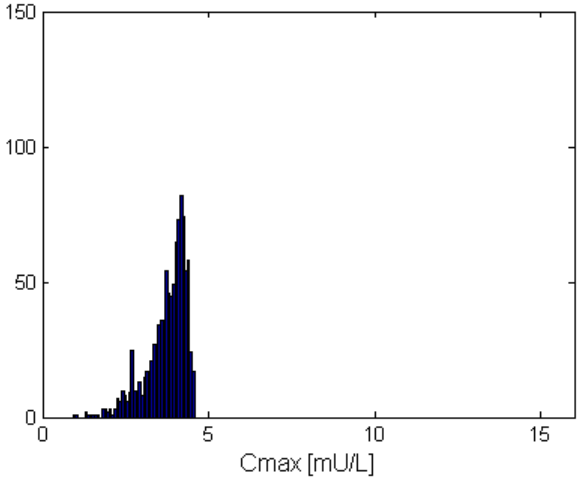
Figure 4.10 shows the randomly selected model parameter variability of the Glargine pharmacokinetics parameters, $k_{prep,gla}$, $k_{1,gla}$, and α_{gla} for 1000 Monte Carlo simulations. The theoretical lognormal functions are also shown in Figure 4.10.



(a) 32U Injection of Glargine

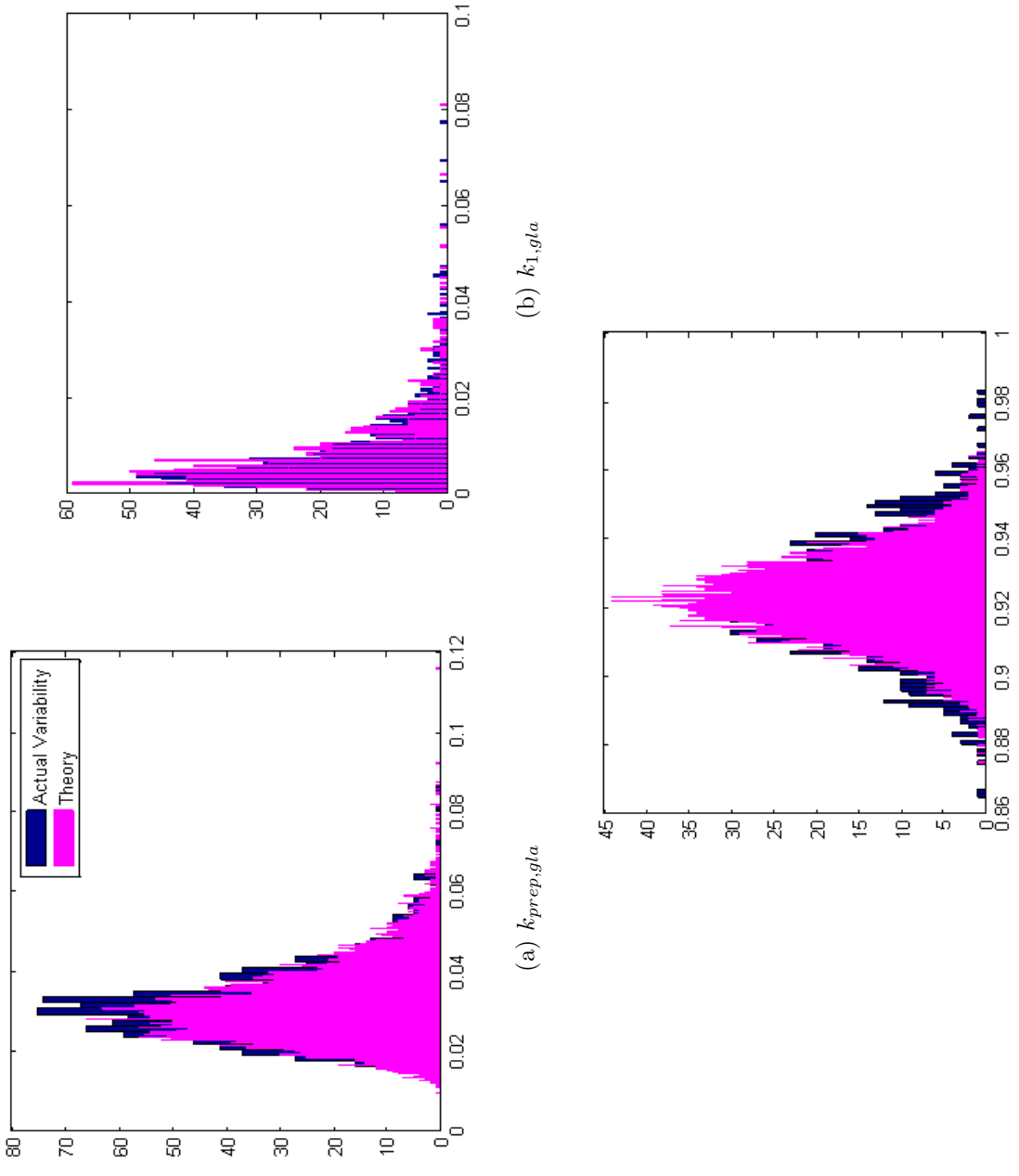


(b) 24U Injection of Glargine



(c) 12U Injection of Glargine

Figure 4.9 Distribution of maximal plasma insulin concentration, C_{max}, computed 1000 Monte Carlo runs with variability in $k_{prep,gla}$, $k_{1,gla}$, and α_{gla}. 7.1(a) a 32U dose, boxed area refers to range quoted in [Scholtz et al., 2005]. 7.1(b) a 24U dose, boxed area refer to range quoted in [Lepore et al., 2000] and 7.1(c) a 12U dose. No quoted range [Owens et al., 2000].



(a) $k_{prep,gla}$ (b) $k_{1,gla}$ (c) α_{gla}

Figure 4.10 Variability of Glargine pharmacokinetics parameters, $k_{prep,gla}$, $k_{1,gla}$, and α_{gla} computed with 1000 Monte Carlo runs as seen in 4.10(a), 4.10(b) and 4.10(c). The blue histogram shows the actual variability while the pink histogram is the theoretical distribution of a lognormal distribution.

Table 4.7 C_{max} from published values. [Scholtz et al., 2005; Owens et al., 2000; Lepore et al., 2000; Heinemann et al., 2000]

Parameters		Reference					
		Clamp1	*Clamp2*	*15ug/ml*	*80ug/ml*	*Lepore*	*Hein.*
C_{max}	Literature	12.1±5.7	10.0±2.5	4.8*	5.5*	7±1.3	13.1±4.3[q]

where Clamp1 + Clamp2, 15ug/ml + 80ug/ml, Lepore and Hein. refers to Scholtz et al. [2005]; Owens et al. [2000]; Lepore et al. [2000] and Heinemann et al. [2000] respectively. * Estimated from plotted data as value is not quoted in study. [q] Summary measures quoted by study not identical to plotted data due to differences in calculation method.

4.5 Discussion

In this study, an extended compartmental model for the absorption kinetics of Glargine is presented. The model is developed from Wong et al. [2008a] with new physiologically based Michaelis-Menten saturation terms introduced in the precipitate and hexameric compartment, replacing empirical non-linear functions. The model paramaters associated with Glargine at the two mentioned states were identified and validated, while maintaning the overall model's physiological consistency with other insulin types, as in the original work Wong et al. [2008a,b]. Hence, this new, more complete and physiological model is consistent with other insulin models of Wong et al. [2008a], and could be used directly within that framework.

The ability of the NRLS method to effectively identify Glargine model parameters, is highly dependent on the initial selection of parameter values. This choice posed a significant limitation in the beginning when the initial selection from [Wong et al., 2008a] was insufficient and yielded poor results. The method also became extremely time-consuming, as unique identifiability is essential for model identification. However, the NRLS managed to converge to an area of 'true parameters' after a few sets of initial parameter values were (empirically) tried.

Identification of the model parameters were based upon 4 main literature studies, Heinemann et al. [2000]; Scholtz et al. [2005]; Owens et al. [2000] and Lepore et al. [2000] which provided 6 sets of data. In previous chapter, the ICING model was developed from data of ICU patients. The reason that literature review of Glargine model development is not from ICU patients as well, is due to unavailable data. However, individuals with Type 1 and Type 2 diabetes may be the closest to represent patients with stress hyperglycaemia in the ICU. Average values over each of these studies are used as a final model parameter value. To best assess the validity of the identified model parameters, data from 4 further different, independent studies, Klein et al. [2007]; Danne et al. [2003]; Becker et al. [2008] and Heise et al. [2004], were utilised. By covering several studies with different cohorts, the validation set provides a significant challenge.

In particular, the study by [Danne et al., 2003] provides data for group of patients belonging to different age groups. Hence, it was interesting to see if this population would give a different behaviour in comparison to adult populations.

Validation of the Glargine pharmacokinetic model profile for these younger patients conforms with Lantus [2001]. Specifically, it showed that, as reported there is no significant difference in the Glargine profile between children, adolescents and adults with Type 1 diabetes. Thus, the model was validated by providing T_{max} and C_{max} values within 1 standard deviation of a range of reported values, in these independent published studies. Glargine is known to be reproducible, constant and predictable. Hence, eventhough different data was used for ICING and Glargine model, it is expected that the same Glargine PK profile would be seen for less critically ill patients.

An equally important outcome/result of this study is the assessment and analysis of parameter variability on the pharmacokinetics model outputs. Clinical experience has found that subcutaneous administration of insulin does not result in highly reproducible metabolic effects, even when the same dose is administered Heise et al. [2004]. Thus, designing any protocol (clinical or model-based) for efficient subcutaneous insulin dosing in an attempt to achieve good blood glucose control has always been a challenge. The major limitation is in the pharmacokinetics profile of subcutaneous insulin and its intra- subject variability. Variable absorption and day to day variability are major factors that contribute to the instability of resulting intra-subject glycaemic levels. Glargine, in comparison to other long acting basal analogues, like NPH and Ultralente, has the lowest reported intrasubject variability [Campbell et al., 2001]. However, its variability is still considered a significant aspect in insulin treatment, affecting glycaemic control and the risk of developing hypoglycaemia Klein et al. [2007].

A reliable system for insulin dosing should thus be able to consider all sources of variation. The decision to vary only three model parameters, $k_{prep,gla}$, $k_{1,gla}$, and α_{gla} is deemed sufficient, as these parameters most influence the modelled variability of Glargine absorption kinetics. In addition, they are Glargine-specific parameters and their variability is thus independent, in this model, of other insulin types, which may have a different variability for the same subjects. Physiologically and clinically, the rate of dissolution and absorption of Glargine can be affected by the state of Glargine forming an amarphous microprecipitate at the injection site. The resulting observed and considerable variability of insulin action is considered here with a Monte Carlo analysis.

The outcome of the Monte Carlo analysis portrays the likely intra- individual

and inter- individual variability that could be expected clinically. Thus, the result of the Monte Carlo analysis defines a range of distribution of variation to consider in designing a glycaemic control protocol using Glargine. These ranges are seen to (broadly) capture those reported in the literature, further validating the overall model and approach. Hence, the main target is to develop control protocol that would be feasible to all the variations often see among patients.

Models used for insulin therapy deal with non-linearities, multiple inputs, and are thus often quite complex. Dealing directly with a patient's outcome, model-based therapies require rigorous analysis and validation. One of the main criteria in model validation is the basic validation associated with variations seen in model parameters [Dartois et al., 2007]. Inter- or intra- individual variability, represented as random effects from model parameters, are often modeled as being normally distributed [Lemenuel-diot et al., 2007]. However, this choice does not accurately represent the actual variations seen in clinical patients. By opting for random effects as a lognormal distribution, instead of being normally distributed, this step immediately constraints the variability of model parameters to be physiologically realistic, non-negative values. Furthermore, as mentioned in Thomaseth et al. [2006], model robustness is improved as a lognormal distribution can designate heavier tails than normal distributions, thus better capturing observed behaviours. Hence, there would be higher probabilities of very large deviations from the mean parameters, which would also be more easily limited in modeling only to physiologically realistic and reported variations from clinical studies.

Specifically, by defining what might be expected, the overall glycaemic control system model can be adapted to the observed insulin variability encountered clinically among patients. More importantly, such validated model variations may also be used to aid therapy selection and decision support [Lin et al., 2008]. The ability to predict subcutaneous insulin absorption using these results based on glycaemic response at the bedside would thus allow further patient-specific optimization of insulin treatment, with the potential to reduce or better manage the patient-specific outcome glycaemic variability.

4.6 Conclusions

A detailed pharmacokinetics model of the subcutaneous absorption of Glargine is developed with variability introduced to the identified model parameters. The model is more physiologically valid compared to a prior model used as fundamental structure with the introduction of Michalis-Menten saturation. External evaluation further confirms the validity of the model with independent data sets. The impact of variability assessed with Monte Carlo increases the potential of the subcutaneous absorption model to be used effectively in a Glycaemic control protocol. The resulting Glargine absorption time-action with expected variability seen intra- and inter- individually would help in designing dosage regimens. Understanding the pharmacokinetic properties of insulin is one of the major source in dosage designs. It is intended that this model development with introduced parameter variability would eventually offer a safe means to develop and compare control algorithms for the less critically ill patients, prior to a clinical testing.

Chapter 5

Virtual Trials

5.1 Introduction

Virtual trial methods have played a substantial part in TGC by providing safe means to develop and analyze glycaemic control protocols prior to clinical validation in pilot trials [Chase et al., 2010c, 2007]. With validated virtual patient simulations, a patient's immediate response towards a known intervention, either from insulin administration alone or combination of insulin and nutrition, can be assessed. Virtual methods and simulations are also able to account for physiological variability, clinical compliance and/or sensor errors, thus offering a close view of behaviour seen typically in clinical settings. Hence, protocols may be optimised virtually to save time, save money and, most important of all, yield a better patient outcome in clinical implementation.

In [Chase et al., 2007], any glycaemic control protocol must reduce elevated blood glucose levels in a controlled, predictable manner, and hold them in a tight range in the presence of any pertubations. It must be adaptive, and/or able to identify changes in patient metabolic status, particularly with respect to insulin sensitivity [Lin et al., 2011, 2008]. More importantly, the protocol needs to be simple enough to be easily implemented and effective enough to be essentially automated to minimise the consumption of clinical time and expertise.

This chapter presents the application of the developed Glargine compartmental model in Chapter 4 and the ICING model in Chapter 3. It is more of an engineering view of control before an actual clinical control protocol is developed from the results in Chapter 6. The main targets of this chapter are:

- Assess the effectiveness of Glargine as basal insulin replacement for TGC in less critical patients.

- Comparison of glycaemic performance from using Glargine in virtual trials against the clinical results from SPRINT protocol.

Adequate basal insulin is essential for the regulation of glucose in the liver, muscle and adipose tissue. It controls and maintains blood glucose levels, particularly during nocturnal periods by suppression of hepatic glucose output to decrease occurrence of ketogenesis and unchecked gluconeogenesis [Arif and Escaño, 2010; Rossetti et al., 2003]. Basal insulin support using long-acting insulin is the key component for treatment of patients with Type 1 and Type 2 diabetes who require insulin with or without a combination of oral agents [Wong et al., 2008a,b,c].

Glargine is a new long-acting insulin that has been proven to be an effective basal insulin preparation for patients with Type 1 and Type 2 diabetes, including pediatric patients [Schober et al., 2002; Chase et al., 2003; Hathout et al., 2003; Massi Benedetti et al., 2003; Rossetti et al., 2003; Porcellati et al., 2004; Raskin et al., 2000; Rosenstock et al., 2010; Swinnen et al., 2010]. It has been associated with a reduced incidence of hypoglycaemia [Rosenstock et al., 2000, 2010] in comparison to other long-acting insulin namely NPH and Ultralente, lower fasting plasma glucose (FPG), [Rosenstock et al., 2000; Raskin et al., 2000] and lower glycosylated hemoglobin (HbA_{1c}) [Gerich, 2004; Gillies et al., 2000; Swinnen et al., 2010]. Its primary unique dynamic is its very flat pharmacokinetic profile [Lantus, 2001; Campbell et al., 2001]

Hence, analysing the efficacy and safety of using Glargine in a TGC protocol for patients in less acute wards is worthwhile and an interesting step. In particular, if Glargine can be used effectively for stable ICU and less critical patients, nursing workload could significantly be decreased, which has added benefits [Chase et al., 2008a] as discussed in Chapter 1. Thus, a primary goal is to determine whether less acute patients with no intravenous access and lesser insulin requirements can have insulin delivered using subcutaneous Glargine, that works effectively.

5.2 Method

The effectiveness of Glargine for blood glucose control is assessed *in silico*. Patient data were selected retrospectively for the simulation study from a cohort of patients who received insulin therapy under the SPRINT protocol during their stay in the Christchurch Hospital ICU [Chase et al., 2008c]. SPRINT uses insulin boluses and modulates feed rate hourly to maintain blood glucose levels within a desirable range of 4.0–6.1 mmol/L. It takes into account an estimate of the specific patient's insulin sensitivity at any given time to determine the subsequent insulin bolus size and feed rate.

To see how well the selected patient cohort would respond towards glycaemic control using Glargine, clinically validated virtual patient simulation results are compared to actual clinical data. The data is from patients treated using the SPRINT protocol [Chase et al., 2008c]. A brief explanation of the SPRINT protocol follows first.

5.2.1 SPRINT Protocol

Since its first implementation at the Christchurch Hospital Department of Intensive Care in August 2005, SPRINT has been used on over 1000 patients [Chase et al., 2008c]. SPRINT is a model-derived TGC protocol developed from clinically validated computer models used for real-time control in the ICU [Lonergan et al., 2006a,b; Wong et al., 2006b; Chase et al., 2007, 2010c]. It is unique in the way it uses explicit control of both nutrition and insulin inputs to maintain blood glucose levels within a goal range of 4.0–6.1 mmol/L. SPRINT specifies carbohydrate intake, formula and/or goal feed rates [Lonergan et al., 2006a,b]. Carbohydrate intake in other TGC protocols is often left to local standards, and only insulin is solely used to control patient's glycaemic level despite the risk factors associated with various levels of carbohydrate intake in the critically ill [Krishnan et al., 2003; Elia and De Silva, 2008; Der Voort et al., 2006]. Nutrition levels and their variations are a pre-disposing factor for hypoglycaemia. Hence, a lack of knowledge of carbohydrate administration, coming from a range of possible sources in the ICU, can multiply the impact of patient-specific variability on the glycemic outcomes of a TGC protocol.

More specifically, TGC protocols are designed with underlying assumptions of carbohydrate administration that thus guide the insulin dosing recommended at a given blood glucose level. Deviation from this implicit level by a given clinician or unit will result in a different metabolic balance, and thus a wider range of patient-specific glycemic outcomes. These more variable glycemic outcomes will therefore further enhance the overall glycemic variability seen from the protocol, as well as result indifferent insulin dosing.

For successful TGC, carbohydrate administration must be known, if not actually specified, by the algorithm. Without knowledge of carbohydrate administration it will be difficult for the protocol to estimate insulin sensitivity directly, except as a value relative measure, which could thus limit some important aspects of patient-specific, adaptive TGC. The impact of nutrition and implications on TGC protocol is discussed in Chase et al. [2010a].

SPRINT determines the insulin and nutrition intervention based on an estimate of patient-specific insulin sensitivity, S_I, which is also a unique approach. Any patient with a random blood glucose measurement over 8 mmol/L is put on the SPRINT protocol. At entry a patient specific feed level sticker is attached to the feed wheel of Figure A.1(a) in Appendix A. This sticker relates absolute percentage goal feed (e.g. 30-100%) requested by SPRINT to an absolute enteral feed pump rate in mL/hr. These feed rates are patient specific and thus the wheel is patient specific. The values on the feed conversion sticker are computed based on the patients age, body frame size and gender. Weighting factors are assigned to each group of each variable (eg: Male = 1.0, Female = 0.8, Large body size = 1.1, Small body size= 0.8), which are then multiplied together to scale the feed rates on a per-patient basis [Lonergan et al., 2006a]. Normally, when patients are received at the ICU, the weight is unknown. Hence, patient's weight is not directly considered in the model-derived protocol. The range of patient-specific goal nutrition rates is 50 mL/hr to 100 mL/hr.

A further unique feature of SPRINT is the one or two hourly measurement and intervention intervals, which are also determined by patient's own insulin sensitivity, S_I. More importantly, to ensure glycaemic control is not lost in patients who are often metabolically variable, SPRINT does not allow a four-hour measurement like many other protocols [Lonergan et al., 2006a]. All the unique features of SPRINT in comparison to other protocols are thoroughly discussed

in [Chase et al., 2010a,b].

5.2.2 Virtual Trial Patient Cohort

The 15 patient cohort used to create the virtual cohort for simulation covers a more stable portion of the general ICU population. These patient data are a small subset of the full SPRINT cohort [Chase et al., 2008c]. For this study cohort, patients were considered stable based on measurement frequency of 2 hours with no significant change in intervention or glucose levels. These patients are considered to represent a more stable patient group ready for transition to a less acute ward and subcutaneous insulin. Hence, they are the type of patients who might not have intravenous access and for whom a less intensive protocol would prove clinically useful.

The APACHE II score (Median: 19, IQR: 15–21.5), age, sex and mortality for the selected cohort are shown in Table 5.1. The average length of each patient data is 4.3 days (Range: 1.9-11.7 days). It is worth noting that the APACHE II scores have a much higher median and range than the larger cohorts in the glycaemic control research of Van Den Berghe et al. [2001] and Krinsley [2004], but is more similar to Van Den Berghe et al. [2006a] more recent study. This latter point reflects the general medical ICU cohort in SPRINT from which these patients were selected.

5.2.3 Virtual Trial Simulations

Virtual analysis, and clinical, model-based TGC both require a clinically validated patient-specific glucose-insulin model. The patients time-varying insulin sensitivity, S_I, a critical dynamic parameter was fitted hourly to the clinical patient data using Equations (2.38)–(2.44) and an integral fitting method [Hann et al., 2005]. The fitting method uses integrals of differential equations to reduce the nonlinear estimation problem to a set of linear equations that can be easily solved. The method has the advantage as being convex and not starting point dependent. It effectively matches the area under the measured response curve, rather than matching the response trajectory. Hence, this approach converts a

Table 5.1 Long-term virtual trial patient cohort

Patient ID	Medical Group	APACHE II score	Age	Sex	Mortality
5004	Burns	11	43	F	N
5008	Respiratory Failure	23	44	F	N
5020	Pancreatitis	19	68	M	N
5023	Unknown	NA	75	M	N
5028	Respiratory Failure	15	67	M	N
5032	Pneumonia	31	70	M	N
5034	Pancreatitis	20	68	M	N
5050	Trauma	15	20	M	N
5063	Pancreatitis	15	80	M	N
5070	Dissecting Aorta	20	76	F	N
5079	Unknown	NA	50	F	N
5092	Unknown	NA	76	M	N
5102	Sepsis	17	49	M	N
5111	Cardio. Shock	29	58	M	N
5118	Haemorrhage	19	50	F	N
Median		19	57		
IQR		[15–21.5]	[20–80]		

computationally intense non-convex problem into a much simpler convex problem, resulting in speed thus, saving significant computational time. The method has been used in a variety of clinical glycaemic control studies [Hann et al., 2005; Wong et al., 2006b; Chase et al., 2005; Chase and Shaw, 2007; Le Compte et al., 2009].

Constraints are placed on insulin sensitivity, S_I, in the identification process to ensure it is within a physiologically valid range. Insulin sensitivity, S_I is a primary factor in which it determines the resulting glucose level for any given inputs, and thus how much insulin is required to achieve tight control, at least to the dose where insulin effect saturates [Natali et al., 2000; Prigeon et al., 1996; Sowell et al., 2003]. More specifically, in the model used in this study, it accounts for the net effect of any suppression or increase in endogenous insulin and glucose production, and the rate of peripheral glucose uptake. Finally, the cytokines and hormones that drive these affects that result in hyperglycemia are physiologically linked to lowered insulin sensitivity and vary continuously overtime as patient condition evolves. Hence, this overall effective insulin sensitivity is dynamic and time-varying [Lin et al., 2006, 2008; Hann et al., 2005].

The resulting time-varying S_I profiles represent time-varying metabolic status for individual patients. The insulin sensitivity metric, S_I is a well validated

metric and has also shown significant correlation to gold standard research assessments of insulin sensitivity [Lotz et al., 2006; Lotz, 2007; Lotz et al., 2008; Docherty et al., 2009], and in comparison to steady states achieved in these gold standard tests [Chase et al., 2009]. Thus, these profiles of S_I can act as "virtual patients" and patient-specific blood glucose levels for different insulin and nutrition inputs can be determined. More importantly, these virtual patients can be used for testing different glycaemic control protocols for the same patient, a clear advantage in developing new protocols. This "virtual patient" simulation method had been shown to be an accurate way of predicting the effect of different insulin therapies [Chase et al., 2010c, 2007; Lin et al., 2008]. The study by [Chase et al., 2010c] provide the first rigorous validation of a virtual in-silico patient and virtual trials methodology. It fully validates the independence of virtual patients. This shows that the method can accurately simulate clinical results of a TGC protocol. Moreover, it provides added assurance of protocol efficacy and a significant insight into the clinical impact, before a clinical control protocol takes place.

With respect to applying TGC, insulin sensitivity is critical. The variation due to patient condition will drive inter-patient differences and variability. Variation in this value as patient condition evolves will then drive intra-patient variability. As a result, insulin sensitivity, lies behind the main driving factors behind the significant glycemic variability seen in critically ill patients and the success (or lack of it) of TGC protocols.

5.2.4 Control Protocol with Glargine

In this study, the effect of Glargine was first tested where the sum of the clinical daily boluses for a patient is substituted by a single dose of Glargine. This approach assumes the overall stability of Glargine's PK profile can replicate that required with stable patient, as selected here. Virtual trial results are then compared to the clinical SPRINT results to evaluate the performance of Glargine in place of intravenous insulin. This is a first step towards a true Glargine TGC protocol, in that it determines the potential for this insulin type in hospital TGC.

5.3 Virtual Trial Result

Simulation results from Patient 5092 are shown in Figure 5.1. The top panel shows the blood glucose profile throughout the length of stay used. Glargine dose given is the same as SPRINT boluses. With the administration of Glargine alone, it can be seen that Patient 5092's glycaemic level is not well controlled for the first 100 hours, equivalent to approximately 4 days. The median blood glucose level for this first 100 hours is 8.03 [IQR:7.53, 8.81] mmol/L. As blood glucose levels over 7.0-8.0 mmol/L reduce and/or eliminate the effectiveness immune response to infection [Chase et al., 2010a], this patient needs to be better managed in terms of glycaemic level quality.

This result occurs due to the fact that the effective interstitial insulin takes a longer 'build up' time to achieve the same concentration level as when intravenous insulin injections are used in SPRINT protocol [Chase et al., 2008c]. As shown in the second panel of Figure 5.1, depicted by the solid olive line (–), the build up of Glargine's effective interstitial insulin only begins to achieve relatively the same level as the IV insulin in SPRINT around 150th hour (6th day). Hence, an immediate conclusion is that a direct translation to Glargine is not possible due to this build-up period.

The logic behind Glargine's build up is explained through the characteristic of Glargine itself. Since the typical, reported time-action profile of Glargine is 24-26 hours long [Heinemann et al., 2000; Lantus, 2001; Campbell et al., 2001], Glargine is bound to accumulate between each dose interval until it reaches steady state. One study reported a time-action profile of up to 30 hours [Lepore et al., 2000]. Hence, it is unlikely that Glargine would clear up to zero exactly upon each 24 hour interval. This excess leads to an accumulation in the following 24 hour interval of subcutaneous injection. In Luzio et al. [2003], the absorption characteristics of Glargine are compared with NPH in Type 2 patients and it was found that 50% of the residual radioactivity of Glargine was still present at the injection site even after 24 hour, indicating a potential for long term build-up with regular use.

Beginning from the 150th hour until the end of hospital stay, the glycaemic level is well managed with a median BG of 6.29 [IQR:5.61, 6.93] mmol/L. The overall BG performance level throughout the whole stay is 7.02 [IQR:6.14, 7.89]

mmol/L. These results correlate well with Glargine's reported slow absorption rate and the clinical effect seen after the first few days of intensive insulin treatment.

The third panel of Figure 5.1 shows the amount of Glargine used daily throughout the stay, where the amount of Glargine equals to the daily amount administered in the actual clinical data. Since this simulation is more focused on analysing the efficacy of Glargine in place of IV insulin, there is no dose adaptation from day to day. A different amount of Glargine may be seen, when an actual control protocol is developed where previous dose, previous and current glycaemic level as well as nutrition are taken into account. Although not shown in Figure 5.1, the amount of nutrition for all the patients selected in this cohort is kept at the same feed level as in the clinical data. Finally, Patient 5092 in Figure 5.1 is typical of the cohort.

Table 5.2 summarizes the virtual trial results of using Glargine replacing the intravenous insulin administered in the selected patient cohort of SPRINT by showing the glycaemic level performance. The performance measurement is categorized by median and IQR of blood glucose, amount of insulin used per day and percentage in desired band, on a per-patient basis. Overall, the per-patient median BG is 8.34 [IQR:7.57, 8.55] mmol/L. Median percentage spent in desired time band of 4.0–6.1 mmol/L is a very low 2.49% [IQR: 0.0, 11.0]. The lowest median BG, 7.02 [IQR:6.14, 7.89] mmol/L and the best time in band are achieved by Patient 5092 who had the longest stay with 323 hours long, equivalent to 13 days. This patient was shown previously as the simulation example in Figure 5.1.

It can also be seen that Patients 5004, 5008, 5028 and 5092, all of whom had a stay of more than 168 hours (7 day), had better control than other patients. The range of median BG for this group of patients is from 7.02–7.59 mmol/L. This result suggests that control quality for this cohort simulation is associated with patient's length of stay.

This outcome is directly attributed to Glargine's effective interstitial build up mentioned previously, which requires 5 days to reach full effect, during which control is poor.

A similar outcome is that Glargine is less effective when the usage is less

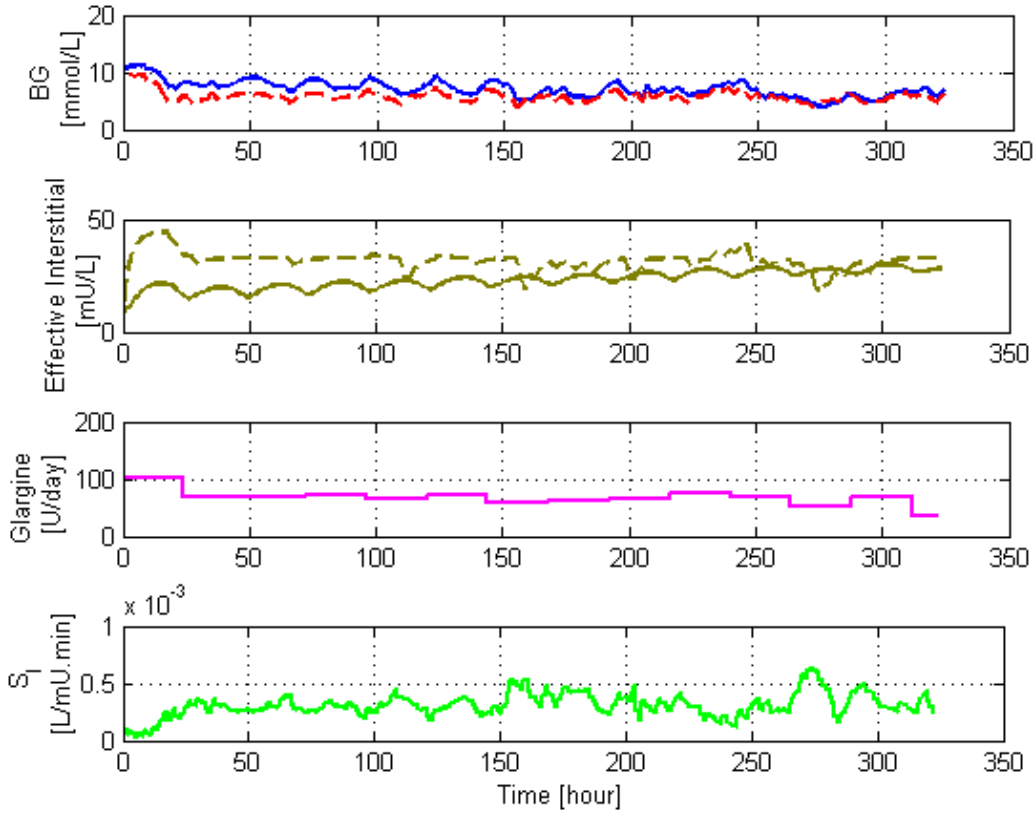


Figure 5.1 Virtual trial simulation result for Patient 5092. The top panel displays the blood glucose profile simulated with the usage of Glargine alone, represented by the solid blue line (–). The dashed red line (- -) represents the patient's blood glucose profile from the actual clinical data while Patient 5092 was under intensive treatment with the SPRINT protocol [Chase et al., 2008c]. The second panel shows the effective interstitial insulin, where solid olive line (–) depicts Glargine and dashed olive line (- -) represents SPRINT clinical data. The third panel displays the total unit of Glargine used daily, replacing the sum of insulin bolus given intravenously in SPRINT protocol. The bottom panel displays the model-fitted insulin sensitivity, S_I.

Table 5.2 Effect of Glargine on the glycaemic level performance by per-patient basis.

Patient ID	Length of stay Hour	Median BG mmol/L	IQR %	Time Band (4.0–6.1mmol/L) %	Time Band (4.0–7.0mmol/L) U/day	Median Glargine U/day	IQR
5004	207	7.55	[7.02,8.09]	3.84	24.03	59	[57.5,68.0]
5008	182	7.59	[6.90,8.75]	7.65	31.14	65.5	[49.0,74.5]
5020	160	7.96	[7.38,8.43]	1.86	11.18	72	[49.5, 75.8]
5023	145	8.48	[7.40,9.44]	1.37	13.69	70	[62.7,71.5]
5028	205	7.04	[6.26,8.09]	21.35	47.57	56	[49.7,56.2]
5032	82	8.55	[7.89,9.00]	0	1.2	64	[44.5,66.5]
5034	15	8.39	[6.82,9.17]	18.75	25	15	[15.0,15.0]
5050	73	7.57	[6.35,8.52]	12. 16	27.0	41	[15.5,63.5]
5063	52	9.41	[8.99,9.74]	0	1.88	59	[23.0,66.5]
5070	163	9.10	[7.80,10.34]	2.44	11.58	82	[75.4,89.7]
5079	19	9.06	[8.30,9.66]	0	0	42	[42.0,42.0]
5092	323	7.02	[6.14,7.89]	23.14	48.45	68	[63.0,71.0]
5102	24	8.56	[8.51,8.83]	0	0	74	[74.0,74.0]
5111	23	8.34	[7.69,8.99]	0	4.17	71	[71.0,71.0]
5118	16	7.96	[7.61,8.62]	5.88	11.76	42	[42.0,42.0]
Median	82	8.34	[7.57,8.55]	2.49	11.76	49.5	[42.0,62.9]
IQR	[23.2,177.2]			[0,11.0]	[2.45,26.52]		

than 24 hours. A group of patients with less than 24 hour stay, have a BG range between 7.96–9.06 mmol/L. Considering the build-up time, these results indicate that Glargine use should only be considered for long stay protocols, over 3–5 days. This is not to be mistaken that Glargine's administration is decided upon length of stay. Rather, the simulation shows that Glargine is more effective with longer stay. Any stay of less than 24 hours in the simulation showed the ineffectiveness of Glargine. In real life, patient is considered stable once they are extubated, not on inotropes and removed of IV lines.

Finally, the worst case was Patient 5070. This patient also used the largest amount of Glargine per day with median 82U and [IQR:75.4, 89.7] U, which indicates the high insulin resistance of the cohort. In patients who are ageing, hyperglycaemia may be even more severe along with patients who suffer from diabetes, obesity, and liver cirrhosis [Desai et al., 1989; Schwartz and Porte Jr, 2005; Garcia-Compean et al., 2009]. From [Rolan and Molnar, 2006], age related differences in pharmacokinetics are primarily due to among others, diminished renal function, altered proportions of body fat and water, and reduced cardiac output. Age could therefore also be one of many other factors that contributed to Patient 5070's loss of glycaemic control who at 76 years of age, is at the cohort's lower end of age upper quartile.

Table 5.2 also shows high BG median values in part due to the Glargine build up time. In the first 3–5 days, some glycaemic control is lost and BG rises using the straight (unit to unit) translation of IV insulin to Glargine. After this point, as seen with Patient 5092, BG levels stabilize but at slightly higher levels than with IV insulin. Hence, the use of Glargine will require a more advanced dosing than a straight, simple 1:1 translation.

5.3.1 Comparison with SPRINT protocol

To see the effect of using Glargine in comparison to the SPRINT protocol, Figure 5.2 compares CDFs of the blood glucose level for the entire cohort used (1,689 hours). The distribution of BG level is significantly different between the two protocols. In SPRINT, the median and IQR for BG achieved is 5.86 [IQR:5.35, 6.51] mmol/L. A much lesser control performance along with a wider BG range are the result from using Glargine, with median BG 7.84 [IQR:6.93, 8.77] mmol/L.

Studies have shown that variability in blood glucose is also potentially harmful [Dossett et al., 2008; Egi et al., 2006; Ali et al., 2008]. As in [Chase et al., 2010a], one of the well reported facts between the interrelationship of glycaemia, TGC, patients and outcome is, mortality increases with blood glucose variability, independent of the mean or median value achieved by any form of glycaemic control [Egi et al., 2006; Bagshaw et al., 2009a].

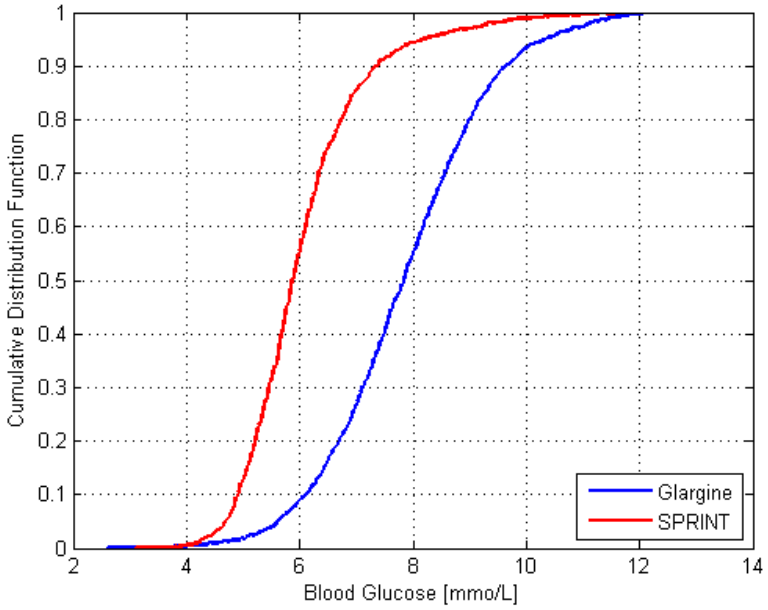


Figure 5.2 Comparison of cumulative distribution functions for BG in SPRINT and by using Glargine. The solid red line (–) represents BG concentration under SPRINT protocol [Chase et al., 2008c] and solid blue line (–) represents BG concentration under Glargine protocol.

To further assess the performance comparison, Figures 5.3 and 5.4 summarise the glycaemic control performance obtained as cumulative distribution functions on per-patient basis for the median, 5th and 95th percentile patients. The CDFs indicate the tightness across patients in the cohort. Results clearly show the differences in the tightness and variability of the glycaemic control performance resulting from the different protocols. Glargine alone shows a significant loss of control for the median and 90% confidence interval patient results due to the lower effective insulin levels it achieves initially.

The median patient with Glargine has less than 15% measurements below 7mmol/L compared to 100% achieved by the SPRINT protocol median patient. Median blood glucose levels should be less than 7.0 mmol/L, and thus allow for reasonable variation in control as patient condition evolves. This goal will also

have lesser impact on immune response to infection, thus reducing the potential for sepsis, multi-organ dysfunction and failure, and thus death [Chase et al., 2010b; Vincent et al., 1998; Moreno et al., 1999] .

At the 5th percentile, around 65% of measurements are below 7mmol/L for Glargine, with none of the 95th percentile having any measurements between 4-7mmol/L. This compared poorly with SPRINT protocol, with 100% of blood glucose values below 7mmol/L at the 5th percentile and 20% of the 95th percentile patient having readings below 7mmol/L.

Hence, the straight 1:1 translation of Glargine, while implied in the literature as a potential solution, results in significant variability across patients.

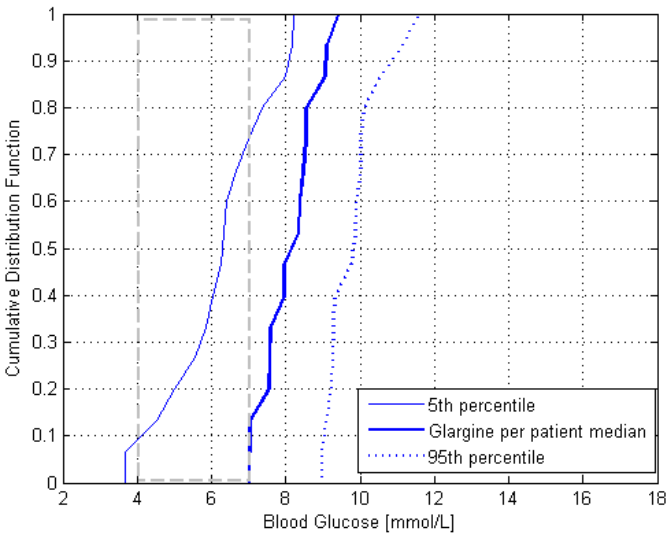


Figure 5.3 Glargine per-patient blood glucose cumulative distribution function (CDF). Dashed box shows 4-7 mmol/L band. The median patient has less than 15% of measurements below 7mmol/L in this case. None of the 95th percentile patient has measurements between 4-7 mmol/L band while around 65% of the 5th percentile has blood glucose values below 7mmol/L.

5.3.2 Interstitial Insulin Build Up

Interstitial insulin in the model portrays the insulin signal at cellular level and the dynamics of glucose uptake are directly correlated with insulin concentration in the interstitial fluid rather than in plasma [Castillo et al., 1994; Yang et al., 1994; Bergman, 1997; Sjöstrand et al., 2002; Bodenlenz et al., 2005]. Studies on glucose

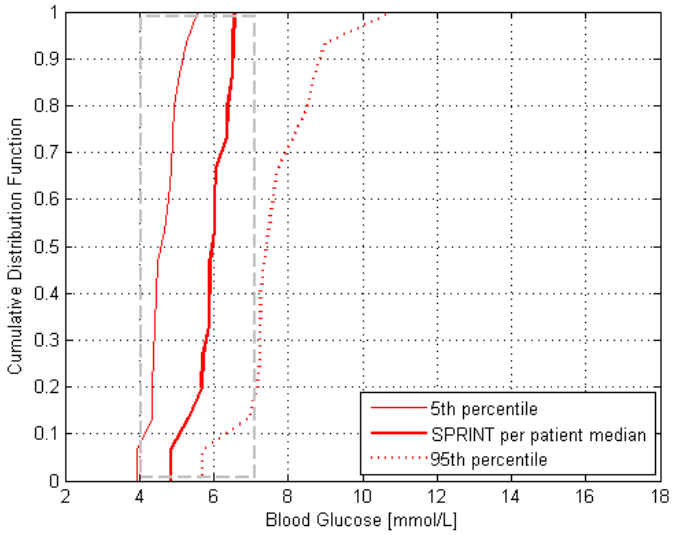


Figure 5.4 Clinical (SPRINT) per-patient blood glucose cumulative distribution function (CDF). Dashed box shows 4-7 mmol/L band. The median patient has 100% of measurements below 7 mmol/L in this case. The 95th percentile patient has only 20% below this value, and the 5th percentile patient has 100% of blood glucose values below 7 mmol/L. Overall, the per-patient CDFs indicate the tightness across patients in the cohort.

correlation with interstitial insulin begin with studies on animals, which provided the essential data [Rasio et al., 1968; Camu and Rasio, 1972; Yang et al., 1992; Bradley et al., 1993; Getty et al., 1998], and have now moved on to human studies including direct measurement on human skeletal muscle tissues [Bodenlenz et al., 2005; Sjöstrand et al., 2002; Sjostrand et al., 2000; Sjöstrand et al., 1999; Jansson et al., 1993]. All of the mentioned studies, came to the same result, despite a range of differences in which included comparing plasma and lymph, which is reflective of the interstitial fluid, or by microdialysis, or by direct measurement in the interstitial fluid. In particular, all these studies concluded that interstitial insulin is significantly lower than plasma insulin. Sjöstrand et al. [1999] reported that it is as significant as 40% lower, while [Bergman, 1997] reported a ratio 3:2 between plasma insulin to interstitial insulin.

In the interstitium, due to the restricted pathway of insulin to the interstitial fluid, the kinetics of insulin are slower than plasma [Yang et al., 1994; Bergman, 1997; Sjöstrand et al., 2002]. Some studies suggested an endothelial barrier that delays the transcapillary transport of insulin, which itself is a time-consuming process resulting in a lag in the interstitial fluid concentration [Jansson et al., 1993; Sjöstrand et al., 1999, 2002]. For patients who are have Type 2 diabetes or

obese, and are thus likely to display significant insulin resistance [Bastard et al., 2002], the delay is even more pronounced [Sjöstrand et al., 2002]. Therefore, in these simulations of Glargine, a slow and long acting insulin that has to go through 4 compartments (precipitate, hexameric, monomeric/dimer and interstitium) before appearing in plasma, the longer build up in the interstitium should be expected. Figure 5.5, shows the stages of a 40U subcutaneous Glargine from precipitate to hexameric, monomeric/dimer, interstitium and lastly appearing as plasma insulin.

This analysis partly explains how TGC is achieved in the SPRINT protocol [Chase et al., 2008c]. In particular, boluses of intravenous insulin, given one or two-hourly, quickly raised the interstitial insulin rapidly. This approach thus promoted a more rapid rate of glucose uptake than would be found using subcutaneous long acting insulin.

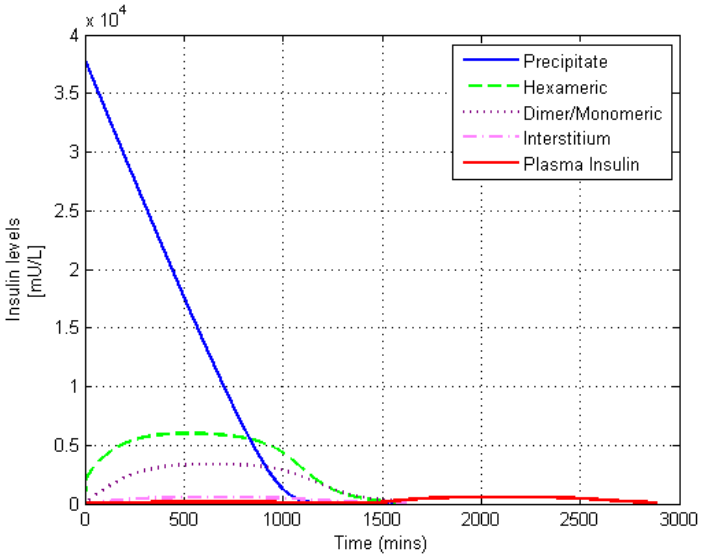


Figure 5.5 A sample of 40U subcutaneous Glargine, as precipitate depicted as solid blue line (–), hexameric (- -), monomeric/dimer (· · ·), interstitium (·-) and appearing as plasma insulin, in solid red line (–). The 4 stages of Glargine from the subcutis before appearing as plasma insulin, contributed to the delay and losses. This explains why IV insulin in SPRINT raised interstitial insulin, Q rapidly compared to subcutaneous Glargine.

Hence, from an engineering perspective, to raise the concentration of the effective interstitial insulin, Q, in the virtual trials, a few supraphysiological simulations of Glargine were run. Effective insulin is actually unutilized insulin that has crossed the plasma through a capillary wall, before appearing in the interstitium. It could also be insulin that had bound and unbound to cell walls, tissues

or insulin receptors [Duckworth and Kitabchi, 1981; Duckworth et al., 1998]. Responses for using Glargine with increasing doses are shown in Figure 5.6. This analysis done for a time frame of 24 hours, clearly shows how the effective interstitial insulin, Q has a different magnitude of build up depending on the amount of Glargine used. Only with doses fourfold greater than the initial amount of Glargine, did the effective interstitial insulin, Q, builds up quickly enough to achieve a relatively similar profile of Q, to that of the identified and simulated SPRINT clinical data on the first day.

Another approach that can be used to raise the effective interstitial is a priming bolus. Using this method, intravenous insulin boluses are maintained throughout the first day with a background of Glargine to raise the concentration of effective interstitial insulin, Q. Figure 5.7 shows the responses of the priming bolus in comparison to SPRINT data and Table 5.3 summarised the cohort results, detailing the BG performance on the first day, the rest of stay and the whole stay. In this specific cohort, only ten patients were simulated, omitting patients with less than 24 hour stay since the comparison between first, rest and whole stay cannot be performed for the patients with a short duration in hospital stay.

In Figure 5.7, the effective interstitial insulin for the first 24 hours is higher compared to SPRINT clinical data resulting in slightly better gycaemic performance with all hourly BG within the 4.0–6.1mmol/L band. However, after the first day, without the IV bolus the effective interstitial insulin quickly drops to the same level as a second day dose of Glargine. The result is thus, a smaller loss of control.

Over the entire cohort, the highest median value of the glucose concentration for all four categories occurred on the first day. The blood glucose levels achieved using Glargine alone is a lot higher compared to the rest, with median BG 10.40 [IQR:8.58, 10.74] mmol/L. However, in terms of blood glucose variability, Glargine alone shows a tighter range with a 90% CI of [7.22, 11.22], as Glargine is known to be less variable in profile [Raskin et al., 2000; Lepore et al., 2000; Scholtz et al., 2005]. The other three categories have a much wider 90% CI interval range, as can be seen in Table 5.3.

Increasing Glargine fourfold, achieved the goal of matching the effective inter-

stitial insulin build up of the IV boluses. However, it carries risk with such large doses and compromised patient safety with 3 episodes of hypoglycaemia. Hypoglycaemia in this trial is defined as blood glucose level lower than <2.2 mmol/L. Finally, the simple priming bolus method resulted in one hypoglycaemic episode. Therefore, in terms of safety and efficacy, only SPRINT protocol performed well during the first day, and attempts to mimic it simply with switching to Glargine carried significant potential patient risk.

For the rest of stay, the three protocols of Glargine only, Glargine fourfold and Priming, all perform relatively the same, with little discrepancy in BG concentration and no occurrences of hypoglycaemia. SPRINT has the best glycaemic control with median BG of 5.69 [IQR:5.28, 6.80] mmol/L. In terms of efficacy in glycaemic control, for the whole duration of stay, the Glargine only protocol is still disadvantaged compared to the other protocols. However, the protocol using a priming bolus, and Glargine fourfold both resulted in hypoglycaemia.

Table 5.3 Cohort comparison for 10 patients with length of hospital stay over 24 hours, between Glargine and SPRINT performance on first day, rest of stay and whole stay.

		Blood Glucose [mmol/L]	90% CI [mmol/L]	Hypoglycaemia [N]
First Day	Glargine	10.40 [IQR:8.58,10.74]	[7.22, 11.22]	0
	SPRINT	8.53 [IQR:6.36,9.23]	[4.73, 10.33]	0
	Glargine 4x	8.93 [IQR:6.50, 10.04]	[4.85, 10.72]	3
	Priming	8.29 [IQR:5.98, 9.02]	[4.44, 10.21]	1
Rest of Stay	Glargine	6.90 [IQR:6.27, 7.54]	[4.95, 8.79]	0
	SPRINT	5.69 [IQR:5.28,6.01]	[4.67, 6.80]	0
	Glargine 4x	6.14 [IQR:5.62, 6.71]	[4.47, 7.77]	0
	Priming	6.75 [IQR:6.16, 7.41]	[4.95, 8.78]	0
Whole Stay	Glargine	7.02 [IQR:6.36, 7.67]	[4.99, 9.23]	0
	SPRINT	5.71 [IQR:5.33, 6.06]	[4.67, 7.36]	0
	Glargine 4x	6.18 [IQR:5.64, 6.83]	[4.48, 8.22]	3
	Priming	6.83 [IQR:6.16, 7.48]	[4.84,8.91]	1

5.4 Discussion

Glargine is an effective basal support on a daily basis for patients with Type 1 and Type 2 diabetes, including pediatric patients [Rosenstock et al., 2000; Rossetti et al., 2003; Porcellati et al., 2004; Raskin et al., 2000]. However, for a hyperglycaemic patient in the ICU or HDU with no prior history of diabetes, the

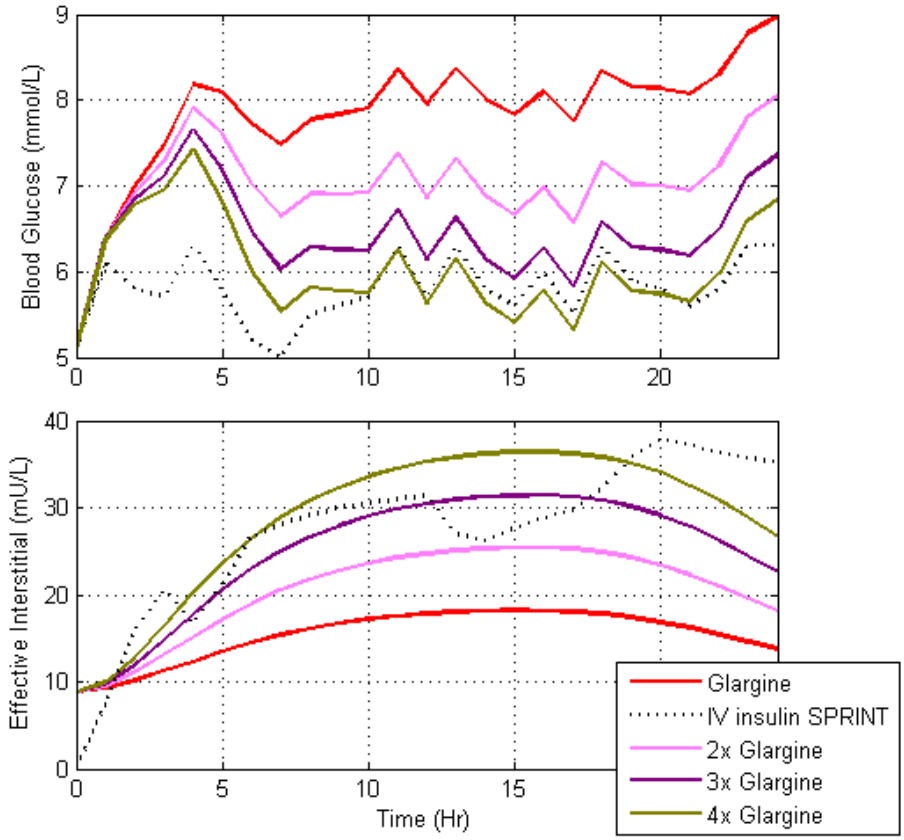


Figure 5.6 Effect of Glargine with increasing doses on the effective interstitial insulin concentration Q(t), which determines the final glucose lowering effect observed. The first panel displays the Blood Glucose level with dotted black line (· · ·) representing the BG effect from IV SPRINT. The solid red line (- -) is the BG lowering effect from Glargine protocol, while solid pink, purple and olive lines (–), are BG levels utilising Glargine with increasing doses. The second panel displays the effective interstitial insulin. The goal is to match the IV insulin only line for equal control.

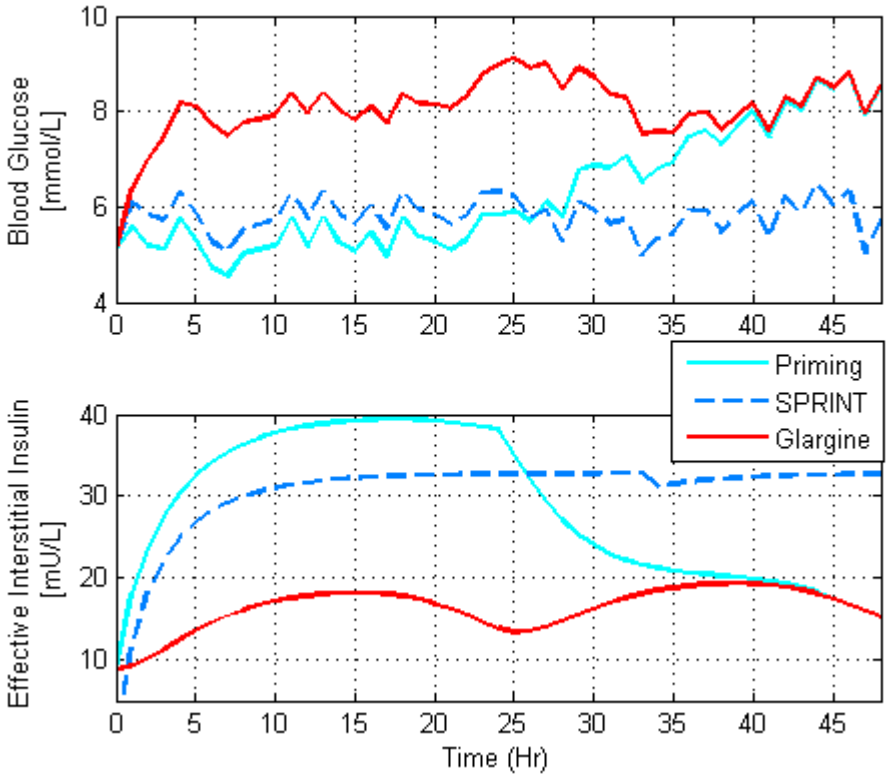


Figure 5.7 Effect of priming bolus with Glargine and intravenous insulin bolus combined, to raise the effective interstitial insulin concentration Q(t), which determines the final glucose lowering effect observed. The first panel displays the Blood Glucose level with solid light blue line (–) representing the BG effect from priming bolus. The dashed blue line (- -) is the BG lowering effect from SPRINT protocol and solid pink line (–) is by the administration of Glargine alone. The second panel displays the effective interstitial insulin. The goal is to match the IV insulin only line for equal control.

benefit of Glargine has not been clinically tested by any group. Virtual trials are thus used in this research to demonstrate the efficacy of using Glargine. Overall, it was found that Glargine alone cannot readily maintain tight control nor can it significantly reduce the elevated glycaemic levels, despite the relatively stable cohort used.

The SPRINT protocol utilizes intravenous insulin injections on an hourly basis to manage glycaemic levels for critically ill patients. Many critically ill patients are metabolically volatile from hour to hour as a result of their critical illness and the medical interventions and drug therapies they receive (Chase et al., 2008). Therefore, intravenous insulin injections suit this situation well because the response is fast and does not linger when patient metabolic status changes. Importantly, if a patient is being weaned from inotropes or other medications that suppress insulin sensitivity, any lingering effect of insulin is undesirable because insulin sensitivity may quickly recover and result in hypoglycaemia. However, the resulting rapid and tight glycaemic control offered by SPRINT comes with an added cost of higher nursing effort.

For the 15 patient cohort in this chapter, their insulin requirement was generally very stable, relatively low and consistent from one hour to the next. These patient's insulin requirements should therefore be able to be directly substituted by Glargine successfully, as they need only a constant and stable supply of effective insulin in the interstitial compartment. The peakless time-action profile of Glargine is thus ideal for such a basal insulin regimen. However, through the virtual patient simulations, it was found that by using Glargine alone, the effective insulin in the interstitial compartment does not build up quickly enough. As a result, patients blood glucose rise significantly and are not well controlled on the beginning of the treatment, particularly on the first day. Subsequent days with similar dosing are thus not able to reduce these levels without adding more insulin which carries risk with long acting subcutaneous insulin.

For any insulin that is given subcutaneously, it takes a while to reach the circulatory systems. Glargine itself is a slow, long acting insulin that goes through 4 compartments before reaching plasma [Campbell et al., 2001; Tarín et al., 2005]. Therefore, its effect in the interstitial compartment builds up very slowly compared to intravenous insulin. Thus, the efficacy of subcutaneously injected Glargine as basal insulin support in the virtual patients will only be demonstrated

in patients with a longer stay.

Glargine is reported to reach a steady state 2-4 days after the first dose [Lantus, 2001; Heise et al., 2002; Lehmann et al., 2009]. Under a single-dose conditions, the time-action profile of Glargine is reported to be 22-26 hours [Lantus, 2001; Heise et al., 2004; Porcellati et al., 2007], even up to 30 hours in some cases [Lepore et al., 2000]. While under steady-state conditions, the duration is around 24-25.6 hours [Klein et al., 2007; Porcellati et al., 2007]. There has always been concern on the cumulative effect of Glargine with the slow absorption and build up process. However, in Heise et al. [2002], it is reported that there is no evidence of accumulation in Glargine during the 12 day trial. The study was performed on 15 Type 1 Diabetic patients and steady state was reached as early as the 2nd day. However, in a review article by the same author, [Heise and Pieber, 2007], it is acknowledged that a slight increase in Glargine's time-action profile under steady-state conditions is due to accumulation of Glargine.

In this chapter, the superposition or accumulation of Glargine is very slow. The slow cumulative effect did not have any negative side effect on the patients in terms of hypoglycaemia. According to Gerich et al. [2006], it has been difficult for patients and physicians to sufficiently titrate basal long-acting insulin therapy for the fear of hypoglycaemia associated with (NPH) or Ultralente due to their near flat pharmacokinetic profiles. Glargine, however, enables attainment of near normoglycaemia with lesser risk. This study successfully demonstrated a safe approach to use Glargine with regard to hypoglycaemia in the less acute wards. The only condition when hypoglycaemia occurred, is through the simulations of the priming bolus approach as well as the instance where supraphysiological Glargine dose is given to quickly raise the effective interstitial insulin, Q. However, in this study, safety traded off with significant losses in control performance.

Hence, any design of a control protocol using Glargine should consider the possible variable absorption kinetics of Glargine, and the day to day variability that often result in patient's glycaemic levels instability. Virtual trials allow this task to be done by providing a validated simulation environment, thus offering additional safety factor to patients before any control protocol could be developed for clinical practice. In particular, a safe means of gradually substituting IV insulin for Glargine will need to be developed, and will likely require a measure of patient-specificity, as enabled by model-based control.

The virtual trials done in this chapter in general, display that the use of Glargine in the long term recovering stable patients, results in blood glucose levels somewhat higher compared to using intravenous insulin injections only. The virtual trial results thus show that this choice is a safe and conservative. It is also less labour intensive. However, the elevation of BG in some cases were significant enough to warrant further analysis into better methods.

The patient cohort for this study was patients that received intensive insulin treatment under the SPRINT protocol in the ICU [Chase et al., 2008c]. Although these patients are considered metabolically stable, and may be reflective of patients in the less acute wards, the results obtained *in-silico*, may not be fully representative of the the actual units. Sufficient data is still needed. However, in these less acute wards, retrospective data is not usually available with the density required for virtual trials. Hence, the need to develop a cohort from the more stable ICU population to begin this study and research area.

Moreover, there are still several issues that need to be addressed. In less acute wards, patients often have meals, rather than the constant naso-gastric feed used in the ICU. It is known for healthy individuals, endogenous insulin is secreted upon consumptions of food (Woods et al. 1998). However it is not known to what degree that less critically ill patients are able to support their own prandial insulin requirements. In addition, the variability in patient endogenous insulin responses will need to be addressed. Endogenous glucose production for these less critically ill patients may be different from ICU patients as well. Hence, any method to quickly raise the effective interstitial insulin, Q could result in a less favourable incident of hypoglycaemia given patients known variability. All these issues should ideally be investigated through clinical data gathering.

All of these aspects will introduce potential further variability. Hence, these results necessitates the use of a more conservative approach prior to clinical testing to ensure both efficacy and patient safety. In the following chapters, Monte Carlo simulations that account for Glargine's and blood glucose variability will be run to better ascertain the impact of these variabilities.

5.5 Conclusion

This chapter presented a validated Glargine compartmental model and an intravenous insulin-glucose pharmacodynamic, ICING model both developed in Chapters 2, 3 and 4. The *in silico* virtual trial results for 15 metabolically stable ICU patients showed that Glargine can provide effective blood glucose management for these long term recovering patients when their stay is longer than 7 days. Differences in Glargine PK made the straightforward 1:1 dosing calculation, from SPRINT boluses to Glargine doses, not the best method. Glargine needs to go through 4 states after subcutaneous injection;precipitate, hexameric, monomeric/dimer and interstitum before reaching plasma insulin, thus explaining the slow absorption kinetics. In IV boluses, the response is much faster as insulin gets to blood stream quickly without having to go through subcutis. A combination of initial intravenous injection and Glargine dosing, or a supraphysiological Glargine amount is required for the first day to quickly lower elevated blood glucose level. Once the patients blood glucose levels are within a desirable range, Glargine alone can provide effective glycaemic management. However, this method is relatively high risk, and resulted in some hypoglycaemia. The overall results show an approach to managing the intravenous to subcutaneous insulin transition that occurs as patients leave intensive care for less acute wards during their hospital stay. Safe, effective approaches to this transition will ensure that clinical burden and workload are not increased, while maintaining the benefits of tight glycemic control.

Chapter 6

Virtual Trials: SPRINT+Glargine Protocol

Virtual trials performed in this chapter, are the first clinical validation step towards developing a comprehensive system for maintaining TGC outside of the ICU. In particular, the focus is on transition from relatively labour intensive intravenous insulin with frequent measurement in the ICU to less intensive, longer acting, subcutaneous insulin in less acute wards with consequently fewer measurements, adjustments and effort. The current standard protocol, SPRINT [Chase et al., 2008c] uses intravenous (IV) insulin injections every 1-2 hours and controls blood glucose levels effectively [Chase et al., 2008c, 2010b]. However, once patients leave the ICU, the standard protocols are to use subcutaneous insulin, often due to lack of intravenous lines or access to deliver insulin. Lower nursing resource means SPRINT would also not be feasible even if intravenous access were available. With no clear switching guidelines, from one scenario (ICU) to the next (less acute wards), the changeover and protocols used are often adhoc and not patient specific. The result is inconsistent levels of care, which can leave ward patients at a disadvantage and result in so-called rebound hyperglycaemia.

Goldberg et al. [2004b] and Barth et al. [2007b] have expressed the need to develop a protocol that could minimize rebound hyperglycaemia once an IV insulin protocol is discontinued. As expressed in Barth et al. [2007b], from their retrospective review of several ICUs, a marked variability in glucose control is seen within 48 hours of protocol discontinuation once patients were transferred to a general medical floor. The patients in that study had a statistically significant increase in mean percent of BG values > 8.3 mmol/L or 150 mg/dL. In Goldberg et al. [2004b], for the first 12 hour after an IV protocol is stopped, mean blood glucose levels climbed to 9.9 ± 3.2 mmol/L (178 ± 57 mg/dL), well above the original target range. By the second 12 hour period, or 13–24 hours, mean blood

glucose levels rose to 11.1 ± 3.9 mmol/L (200 ± 70 mg/dL). Both studies came to the conclusion that there is a significant need for a protocol following patients transferring out of the ICU to less acute wards.

Another study by [Olansky et al., 2009] evaluated the safety and efficacy of a protocol using transition to subcutaneous Glargine from IV insulin in preparation for transfer to a regular nursing floor. In this prospective analysis, from 99 patients included in the study only 1 patient developed hypoglycaemia. From the aspect of efficacy, 70% of the patients had blood glucose level maintained within 3.8–8.3 mmol/L (70–150 mg/dL). This study concludes that efficacy could further be improved if the maximum limit of a 30U Glargine dose was increased, and that this change was not likely to affect protocol safety.

This chapter, as a continuation from the previous chapter, strives to develop a validated, model-based system to maintain good blood glucose control outside of the ICU. The overall goal is to enable a smooth transition of patients from ICU to less acute wards, while keeping nursing effort to a minimum, reflecting the much lower nursing resource available. In Moghissi et al. [2009] the consensus statement of AACE and ADA, the preferred treatment for non-critically ill patients is one that has a scheduled subcutaneous insulin, basal component, nutritional component and correctional component where insulin analogs are the preferred insulin of choice. The said components are thus incorporated in the glycaemic control protocol developed in this chapter.

Because SPRINT [Chase et al., 2008c] operates on the basis of estimating the patient's 'apparent' insulin sensitivity, which is effectively how much glucose can be removed by the amount of insulin bolus given, the protocol is still applicable when there is a background insulin infusion or a dose of Glargine. Hence, in this chapter, to assess the quality or performance of control, virtual trials are performed using SPRINT with daily doses of Glargine. Each performance measure of the protocols will indicate the associated benefit or disadvantage for both patients and nursing effort.

The performance of each protocol will be quantified by comparison of clinically validated virtual trial [Chase et al., 2010c] results to clinical data for the goodness of control. Performance is based on duration of blood glucose levels within a clinically desirable range, amount of insulin and nutrition given, safety

or lack of hypoglycaemic events, and nursing effort intensity. Specifically, nursing effort intensity is measured by the number of interventions required, which includes measuring blood glucose levels, adjusting feed rates, giving SPRINT IV insulin boluses, and giving subcutaneous Glargine doses.

From [Chase et al., 2006; Eslami et al., 2008], time in a glycaemic band is calculated as the time or percentage in a specific band and provides an indication of the tightness of the glycaemic control result computed from all patients. It reflects the proportion of patients being in a target band. In this study, 4.0–6.1 mmol/L band is used as a tighter performance measure and 4.0–7.0 mmol/L band, a less tighter choice but still a good acceptable range. The median and IQR of glycaemic levels measure the tightness of blood glucose control and is unaffected if data is skewed as normally seen from blood glucose data. IQR is the difference between the 75th and 25th percentile, and does not depend on the largest or lowest data. Hence, data evaluation by median and IQR is more robust. A further explanation on performance analysis and data interpretation of blood glucose levels can be found in Rodbard [2007]. Lastly, hypoglycaemic episode is measured as the number of percentage or measurements that are below a defined hypoglycaemic threshold. As defined in Chapter 5 previously, the lowest threshold adopted in this study is 2.2 mmol/L. This performance measure is a critical indicator on the safety of the protocol used.

6.1 Method

The effectiveness of Glargine for blood glucose control is assessed *in silico*. Patient data were selected retrospectively for the simulation study from a cohort of patients who received insulin therapy under the SPRINT protocol [Chase et al., 2008c] during their stay in the Christchurch Hospital ICU. The use of Glargine is intended for patients who are recovering from their critical illness, and hemodynamic stability had been regained.

Because the virtual trials method used is patient-specific, *in silico* trials can be run using only clinically relevant patients. The patients selected for simulation are those who exhibit metabolic stability within 30 hours of ICU admission. Metabolic stability in patients in terms of stable blood glucose-insulin response

is defined by:

- Stable hourly insulin boluses requirement, $\leq$ 3U of insulin per hour, for at least 12 hours.
- Stable feed rate of $\geq$ 60% of the calculated individual patient's goal feed rate. Goal feed is calculated using individual patient's age, gender and frame size.
- No acute renal failure [Vincent et al., 1996].
- Less than 1000ml of fluid given as intravenous boluses in the past 24 hours, indicating hemodynamic or circulating stability and a stable interstitial volume.
- Resolving multiple organ failure (Sequential Organ Failure Assessment (SOFA) Score $\leq$ 6) [Vincent et al., 1996].

In total 30 patients from the entire SPRINT cohort [Chase et al., 2008c] met the inclusion criteria, and are detailed in Table 6.1. They total to 184.2 patient-days, equivalent to 4,420 hours. The cohort represents a general cross-section of the medical ICU population, as well as by diagnosis or medical group, APACHE II score, age, sex and mortality. Males make up 60% of the patients selected for the *in silico* assessments, which also mutates the overall ICU population on SPRINT [Chase et al., 2008c]. Median age of these patients is 56 [IQR: 42, 72] years old, which is slightly younger than SPRINT, as might be expected given the expectation of stability. Median Acute Physiology And Chronic Health Evaluation (APACHE II) score is 18 with IQR=[16,20]. The average length of stay is 5.7 [IQR:4.3, 6.7] days. Since the average stay of patients after ICU in a non-critical setting is less than 6 days, this group of patients represents patients normally seen in those wards. Mortality is 0 for the selected patients, further reflecting these criteria and clinical expectations.

Three different protocols involving the use of Glargine are tested to evaluate their potential for a clinical pilot study. Table 6.2 lists the full descriptions of simulation protocols examined in this study. The simulated protocol with reduced SPRINT boluses of 1U and 2U are considered for safety. The frequency of blood glucose measurements, changes in feed rates and IV insulin boluses are governed

Table 6.1 Long-term virtual trial patient cohort (N=30, 4,420 total hours equivalent to 184.2 day)

Patient ID	LOS (hrs)	Medical Group	APACHE II score	Age (years)	Sex	Mortality
5006	161	Respiratory Failure	23	44	F	N
5013	90	Respiratory	18	56	F	N
5033	100	Trauma	29	66	F	N
5054	158	Respiratory Failure	18	75	M	N
5060	271	Gastrointestinal	15	79	M	N
5061	140	Trauma	16	22	M	N
5071	107	Trauma	12	49	M	N
5076	240	Gastrointestinal	12	32	M	N
5086	127	Respiratory	32	64	M	N
5101	280	Neurological	19	50	F	N
5104	113	Trauma	18	18	M	N
5122	159	Trauma	19	73	M	N
5124	147	Respiratory	16	74	M	N
5149	325	Surgical	21	60	M	N
5158	103	Neurological	22	68	F	N
5173	295	Respiratory	19	67	F	N
5188	129	Trauma	14	73	F	N
5207	155	Respiratory	19	42	F	N
5233	39	Gastrointestinal	16	76	M	N
5276	87	Septic Shock	18	18	M	N
5279	85	Septic Shock	24	45	M	N
5280	141	Trauma	18	45	M	N
5288	77	Meningococcus	23	21	F	N
5299	103	Respiratory	20	56	F	N
5310	34	Neurological	19	60	F	N
5315	196	Respiratory	18	19	M	N
5317	136	Toxicology	19	23	M	N
5322	136	Respiratory	15	72	F	N
5351	166	Respiratory	12	76	M	N
5376	120	Surgical	16	56	F	N
Median	137		18	56		
IQR	[103–161]		[16–20]	[42–72]		

by the SPRINT protocol. SPRINT requires current and previous blood glucose measurements, the amount of previous hour IV insulin bolus and nutrition given in the previous hour, all to determine nutrition and insulin bolus for the next interval. For patient comfort in the clinical environment, blood samples are taken from the arterial cannula hourly until patient becomes metabolically stable. This is defined as having 3 consecutive hourly measurements within 4.0–6.1 mmol/L band. In which case, measurement frequency is changed to 2 hourly until blood glucose levels fail to stay in the 4.0–6.1 mmol/L band.

Table 6.2 Description of protocol simulations

Protocol	Description
Clinical Records	SPRINT Clinical data from [Chase et al., 2008c]
SPRINT+Glargine	Simulation of SPRINT protocol with Glargine as a basal insulin replacement therapy
SPRINT+Glargine-1U	Simulation of SPRINT protocol with Glargine where the boluses calculated using SPRINT are reduced by 1U
SPRINT+Glargine-2U	Simulation of SPRINT protocol with Glargine where the boluses calculated using SPRINT are reduced by 2U

The dosing frequency of Glargine is approximately 24 hours, but can vary form 22-27 hours in several studies [Heinemann et al., 2000; Lepore et al., 2000; Porcellati et al., 2007]. The first dose is given in these protocols and virtual trials at 12 hours after ICU admission. The size of the initial Glargine bolus is the sum of SPRINT insulin boluses administered during the previous 12 hours. The 12 hour period is chosen to ensure patients are in stable condition as would be practiced in real condition (not simulated). The following Glargine boluses are calculated as being half of the total daily insulin (IV boluses + Glargine) from the previous day. This is for safety and Glargine is more effective per unit given than insulin due to insulin like action of other precipitate products from Glargine. Each Glargine dose is given as a bolus of the very long acting insulin and is capped at 40U for safety against hypoglycaemia.

For example, consider an admitted patient who received 2U of insulin hourly for the first 12 hours during the first day of stay. The sum of this IV insulin bolus, equals to the sum of the first subcutaneous Glargine dose of 24U given at 12 hours and is expected to last around 24 hours. If the patient continues to receive 2U per hour from SPRINT on top of the Glargine given for the next 24 hours the subsequent Glargine dose given 24 hours later at hour 36, will be half of

48U+24U or 36U. Importantly, Glargine dose has a ceiling rate of 40U, which is not reached in this example but ensures that excessive Glargine is not given. The goal of this limit it to minimise the risk of hypoglycaemia if insulin requirements drop significantly over one day. Thus, this approach limits the daily change to 50% or 1.75 U/hr (max) before reaching the point where the Glargine dose was too large. The protocol is outlined step by step below:

First Glargine Dose.

1. Add up the amount of insulin given to a patient during last 12 hours. This sum is _____U.
2. Give Glargine dose equals to the amount calculated in step 1. This sum is _____U.
3. This dose is capped at 40U.
4. SPRINT injection is not given the following hour.
5. SPRINT continues.

Each Glargine Interval.

1. Add up the amount of total insulin (SPRINT boluses+ Glargine) given to the patient during the last 24 hours. This sum is _____U.
2. Divide this amount by 2. This sum is _____U.
3. Daily Glargine is prescribed from the amount calculated in step 2.
4. This dose is capped at 40U.
5. SPRINT injection is not given in the following hour.
6. SPRINT continues.

Hypoglycaemia is a major safety concern thus any control protocol should consider immediate recognition and necessary treatment whenever blood glucose drops to an alarming level. For each given Glargine dose, no IV insulin bolus is

given in the following hour, as the rate of uptake to a peak value (rise time), can be variable and the pharmacokinetic's fluctuations could lead to hypoglycaemia [Cryer et al., 2003; Heinemann, 2002].

For clarity, it is important to reiterate the main goals of the protocol studied here. Specifically, these virtual trials and protocols are designed to accomplish the following goals:

1. Learn more about the efficacy of Glargine in ICU cohorts. Studies in normal patients have reported it to have both greater [Murphy et al., 2003; Massi Benedetti et al., 2003; Ratner et al., 2000] and lesser [Fahlen et al., 2005; Hirsch and Brownlee, 2005; Ciaraldi et al., 2001] efficacy than other insulin types. Hence, its total dose is limited here.
2. Learn more about the variability of Glargine pharmacokinetics in ICU patients to understand other sources of variability.
3. Safely test the use of Glargine and it's potential use in weaning patients entirely to Glargine.

Hence, these protocols are safe, first learning steps that are not guaranteed to be finished protocols or products for clinical uptake.

6.2 Virtual Trial Results

A summary of the results for all 30 patients is shown in Table 6.3. The results are given in per-patient median and IQR. As summarized in [Chase et al., 2010a], a TGC cohort may have acceptable median and variability, but the clinical outcome will be highly dependent on how each patient is treated. As some patients are more variable than others, failure to directly identify and account for patient variability means that some patients will receive, all else equal, more variable TGC. Simulated protocol is not compared to SPRINT simulation, for the reason of obtaining a good correlation of the proposed protocol to actual clinical results.

The median blood glucose concentration level from the simulation of SPRINT+ Glargine is relatively the same as the Clinical data. However, this result comes

Table 6.3 Per-patient Protocol Result Summary

Protocol	BG* [mmol/L]	Time 4.0-6.1 mmol/L [%]	Time 4.0–7.0 mmol/L [%]	Hypoglycaemia <2.2 mmol/L [%]	Total Insulin [U/day]	IV Insulin Bolus [U/day]	Glargine [U/day]	Feed [mmol/day]	Intervention Frequency** [N/day]
Clinical	5.31 [4.88, 5.71]	81.45 [71.28, 88.27]	92.30 [89.74, 95.06]	0	52.86 [37.22, 57.31]	52.86 [37.22, 57.31]	0	118 [100,140]	41 [36, 50]
SPRINT+Glargine	5.36 [4.84, 5.91]	73.94 [66.66, 78.17]	87.11 [83.68, 92.30]	0	83.34 [74.90, 92.78]	48.99 [41.45, 57.70]	36.43 [32.98, 37.53]	125 [141,109]	36 [33, 38]
SPRINT-1U+Glargine	5.62 [5.12, 6.28]	66.12 [57.14, 74.21]	86.46 [83.38,90.65]	0	71.20 [62.50,75.07]	35.20 [29.11, 40.97]	35.91 [32.11,36.84]	109 [78.45, 125]	36 [34, 38]
SPRINT-2U+Glargine	6.23 [5.61, 6.90]	43.80 [32.43, 47.66]	77.62 [71.28, 83.24]	0	48.83 [43.78, 52.41]	15.80 [10.0, 19.57]	34.84 [30.84, 36.61]	62.78 [47.08, 94.17]	29 [25, 32]

*BG = Blood Glucose

** Intervention Frequency= BG measurements + feed rate adjustments + number of insulin bolus + number daily subcutaneous insulin.

with a greater amount of total insulin used, which is the combination of IV boluses and Glargine with 83.34 [IQR:74.90, 92.78] U/day. Clinical SPRINT daily amount of insulin is 52.86 [IQR:37.22, 57.31] U/day. Feed rate is also higher compared to the Clinical data with 125 [IQR:141, 109] g/day vs 118 [IQR:100, 140] g/day. In a clinical situation, feed rate is often turned off during various medical procedures. Hence, that is one possible source of the slightly higher rate.

Based on these performance measurements, the protocol seems to be less effective with the larger amount of total insulin used. Equally, they could be also seen as a difference in effect based on the different, much smoother, pharmacokinetic profile that results compared to the bolus driven clinical data from SPRINT [Chase et al., 2008c]. The most noticeable difference as well as a positive effect, that could be seen is the reduction in nursing effort, expressed in intervention frequency. The highest intervention frequency (N/day) in SPRINT is recorded at 41 [IQR:36, 50] interventions per day. With SPRINT-1U+Glargine protocol, the intervention frequency drops to 36 [IQR:34, 38] interventions/day. Importantly, the 75th percentile is 24% lower, from 50 measurements to 38. Hence, at this point there is a good indication that Glargine will be beneficial in terms related to nursing resources.

On top of the usual clinical interventions in ICU, such as using corticosteroids or vasopressers, the 1–2 hourly measurements of blood glucose levels, and the adjustment of IV insulin and dextrose feed, for TGC, require additional work. The additional work for a 24 hour stay is up to 4 hours per patient with SPRINT at the 75th percentile, where the mean time taken for hourly blood glucose monitoring and adjustment of insulin doses alone was 4.72 minutes [Aragon, 2006]. Hence, the reduction from 50–38 is a savings of 1 hour of workload on a more difficult or intensive patient. 1 hour of time saved is a significant amount of time reduced, which would be much appreciated by the nursing staffs. This estimation is done by calculating the highest upper-quartile for SPRINT and SPRINT-1U+Glargine with the mean time of 4.72 mins, which gives to 236 mins (50 x 4.72 mins) and 179 mins (38 x 4.72 mins), respectively.

With the amount of insulin prescribed from SPRINT protocol reduced by 1U, while Glargine doses are given daily, a much lesser amount of IV insulin boluses is administered with 35.91 [IQR:32.11, 36.84] U/day. However, with additional basal insulin from Glargine, the total amount of insulin used is higher

by 18.3 U/day (0.75 U/hr) in comparison to Clinical SPRINT data. The 0.75 U/hr difference in rate may be clinically insignificant given the difference in PK profiles between SPRINT boluses of SPRINT with Glargine. In particular, the long term infusion from Glargine may suffer greater losses to the liver and kidney as it is more consistently present in plasma.

The median BG of SPRINT-1U+Glargine is 5.62 [IQR:5.12, 6.28] mmol/L, where the tightness of blood glucose concentration is slightly reduced with a higher upper quartile. Percentage of BG levels spent within 4.0–6.1 mmol/L band drops almost 20%, although time spent in a less tighter control of 4.0–7.0 mmol/L is relatively maintained with 86.46% [IQR:83.4, 90.7] compared to 92.30 % [IQR:89.7, 95.1] from Clinical. Clinically, this result shows slightly greater, but clinically insignificant difference in variability [Chase et al., 2010b]. Equally, 4.0–7.0 mmol/L is an acceptable range and a much tighter band compared to other clinical standards [Moghissi et al., 2009]. The slight loss of control particularly in having glycaemic level within the desirable band of 4.0–6.1 mmol/L is made up by low intervention frequency with 36 [IQR:34, 38] adjustments/day. In comparison to Clinical data, this 12% reduction of intervention is significant when translated to the time saved in performing the required adjustments either in feed rate, administering SPRINT IV boluses, measuring BG levels or giving subcutaneous Glargine doses.

In the last simulated protocol, SPRINT-2U+Glargine, reducing the prescribed SPRINT IV boluses by 2U compromised the overall TGC performance. This protocol, with daily doses of Glargine is not sufficient to provide effective glycaemic management for these patients eventhough the total amount of insulin used is comparable to Clinical data with 48.83 [IQR: 43.78, 52.41] U/day and 52.86 [IQR:37.22, 57.31] U/day respectively. The percentage of BG spent within 4.0–6.1 mmol/L band is a low 43.80 [IQR:32.43, 47.66] %. Overall, this last protocol, along with the prior two, shows the impact of pharmacokinetics for a different approach and implies that a direct 1:1 translation of insulin dose will not work effectively and completely.

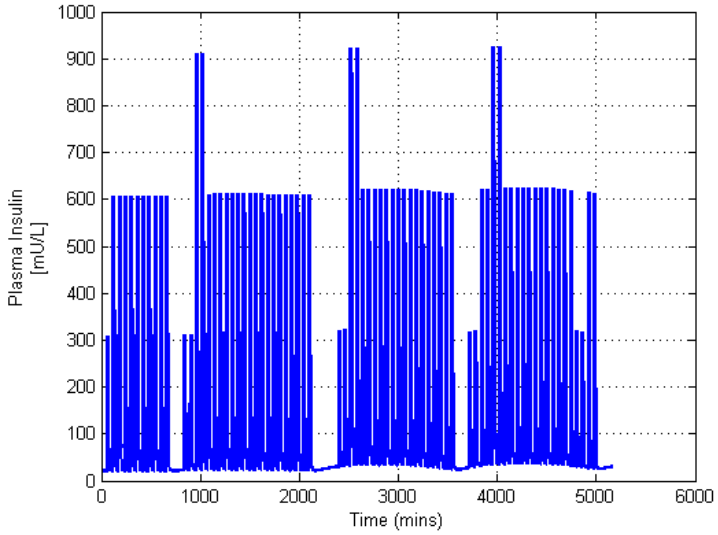
To further understand how the combination protocol used higher insulin compared to SPRINT protocol, the explanation is illustrated in Figures 6.1 and 6.2. Figure 6.1(a) shows the plasma insulin level of a random patient from the cohort under SPRINT-1U+Glargine protocol while Figure 6.1(b) is the same patient re-

ceiving insulin from SPRINT protocol [Chase et al., 2008c]. With the SPRINT-1U+Glargine protocol, the patient (Patient 5276), received 4 Glargine doses in total, beginning with a low 10.5U, to 40U for each of the following 3 cycles. The overall plasma insulin level in SPRINT-1U+Glargine protocol is slightly higher than SPRINT protocol, with the 'minimal boost' of basal Glargine.

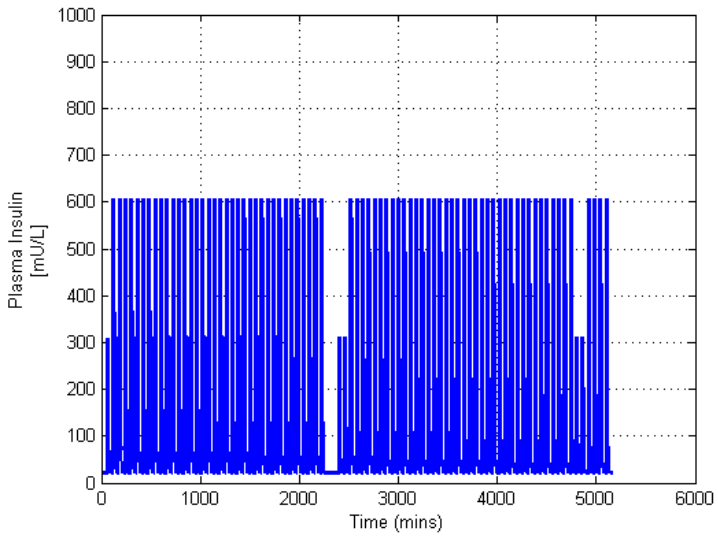
Figure 6.2(a) is the plot of interstitial insulin, Q, where the first cycle of subcutaneous Glargine dose is given at 720 minutes. Comparing Figures 6.2(a) and 6.2(b), it is clearly observed there is a drop in the interstitial insulin an hour after Glargine is given, since no IV bolus is given during this hour. The very conservative dose of Glargine at 10.5U is not able to sustain the level of Q, hence the drop. The level of interstitial insulin, Q only picks up again from the rapid bolus effect of SPRINT, which was continued at minute–840 with 1U of IV insulin. At minutes 960 and 1020, a 3U of IV bolus is administered each and the level of Q, quickly picks up. The amount of IV boluses and Glargine doses are not shown in the plot but are taken from the simulation results. The low level of Q for around 200 minutes, explains why in the SPRINT-1U+Glargine protocol more insulin is eventually used in total. Glucose uptake is strongly promoted by insulin in the interstitial, hence insulin action is less when concentration in the interstitial drops [Castillo et al., 1994].

Figure 6.3 compares the plasma insulin between the two protocols, at a portion after the second dose of Glargine is administered, to get a closer look. The Glargine dose is 40U for this second cycle, which provides a better aspect of comparison rather than the first cycle of Glargine dose with only 10.5U. The insulin clearance rate for IV boluses in SPRINT protocol [Chase et al., 2008c] depicted as red, solid line in Figure 6.3 is slightly faster compared to the clearance rate from SPRINT-1U+Glargine protocol. This could be explained by the fact that high insulin boluses are close to reach saturation level of the modelled insulin clearance. Thus, the effect of Glargine with its own degradation from the subcutaneous site is very minimal. However, clearance rate is slightly faster in SPRINT protocol which means more insulin could bind with the insulin binding receptors, resulting in better glucose-lowering effect as seen with better glycaemic level in clinical data.

Importantly, with respect to protocol safety, none of the simulated protocols had resulted in episodes of hypoglycaemia.

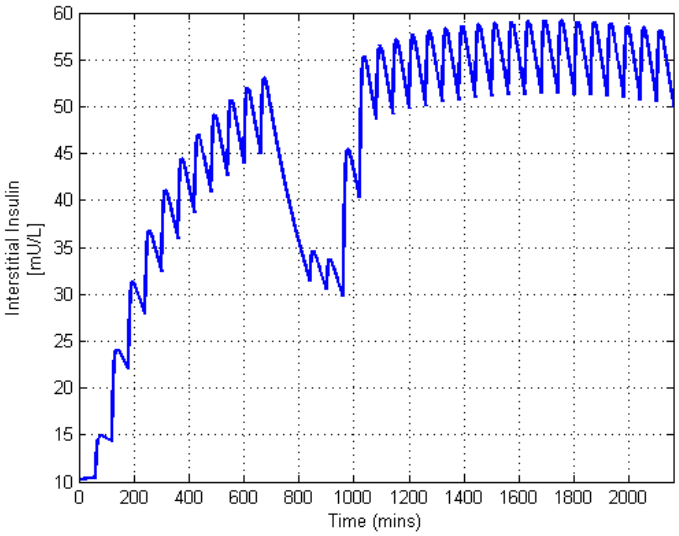


(a) SPRINT-1U+Glargine protocol.

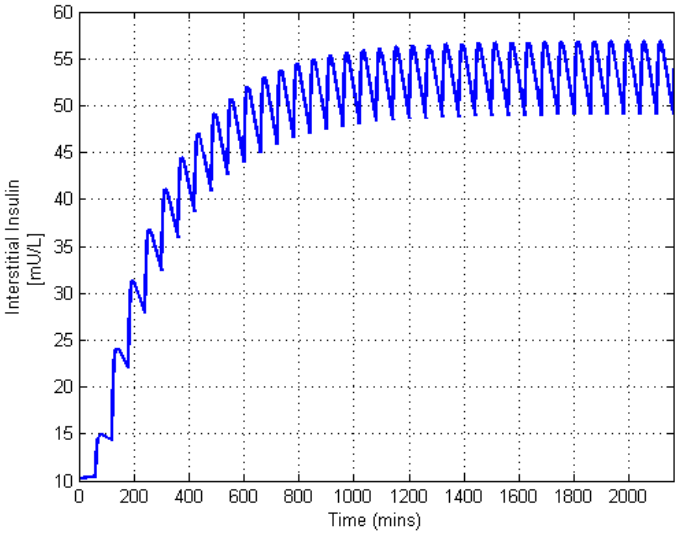


(b) SPRINT protocol.

Figure 6.1 Comparison of plasma insulin levels [mU/L] between two different protocols, SPRINT-1U+Glargine protocol in 6.1(a) and SPRINT protocol [Chase et al., 2008c] in 6.1(b), for a randomly selected Patient 5276 during the whole stay consisting of 5,160 mins.



(a) SPRINT-1U+Glargine protocol



(b) SPRINT protocol.

Figure 6.2 Comparison of interstitial insulin, Q with two different protocols, SPRINT-1U+Glargine protocol in 6.2(a) and SPRINT protocol [Chase et al., 2008c] in 6.2(b). The plot is shown for the interval of 36 hours (2160 mins) when the first Glargine subcutaneous dose is given to the patient. The subcutaneous dose is a very low 10.5U.

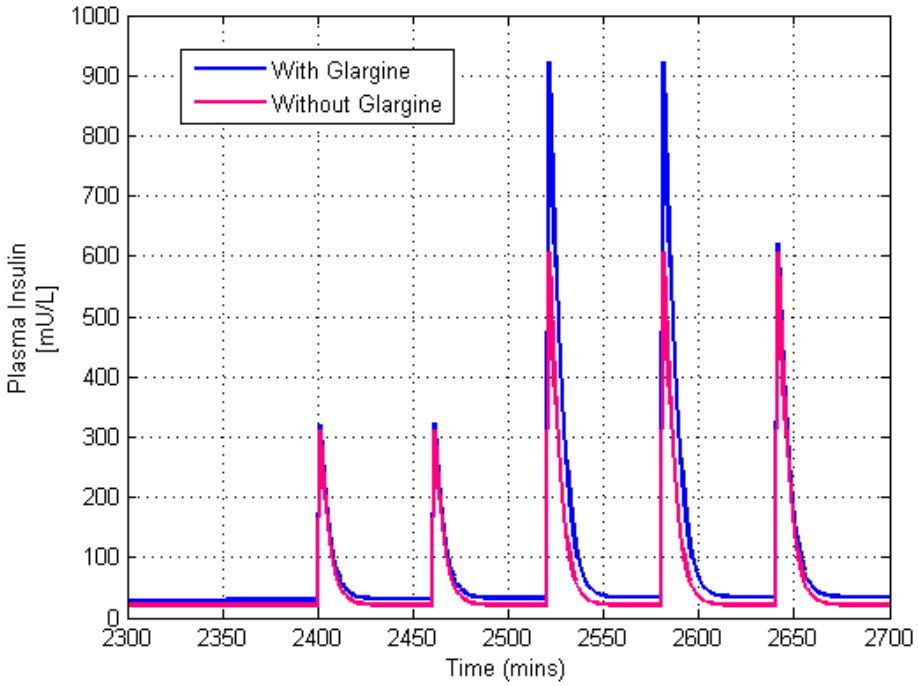


Figure 6.3 Comparison of plasma insulin level between the two protocols, SPRINT and SPRINT-1U+Glargine. The solid red line depicts plasma insulin concentration from SPRINT protocol while the blue solid line is plasma concentrations from SPRINT-1U+Glargine protocol. The plot is during the second interval of Patient 5276's stay, where 2nd Glargine dose of 40U is administered. The plot provides a better insight of plasma insulin differences with a higher level of Glargine dose. The first dose of Glargine is 10.5U, hence given Glargine's slow absorption kinetics and the high bolus effect from IV, a comparison would be difficult to make.

6.2.1 Intervention Frequency

Table 6.4 compares the total number of nursing interventions or actions required by each protocol during the patients stay. The nursing workload strictly relates to the workload associated with implementing TGC. The total number of interventions are the summation of BG measurements made, IV insulin bolus given as prescribed by SPRINT protocol, feed rate adjustments and the daily subcutaneous Glargine doses. All these work relates to TGC protocol and not any other on-going work that may occur in less acute ward. Hence, any reductions in the simulated protocol would exemplify the workload reduced in less critical ward. There would not be an issue that the result would not hold in these less critical wards eventhough data used were from ICU patients.

The actual clinical data from SPRINT protocol has the highest number of measurements with 8331 measurements in total. SPRINT has the highest number of BG measurements and injection from IV insulin boluses, a known aspect of SPRINT protocol that requires higher nursing effort.

With SPRINT operating on top of Glargine, namely protocols of SPRINT + Glargine, SPRINT-1U+Glargine and SPRINT-2U+Glargine, the total number of interventions is greatly reduced. Having Glargine as a basal background, managed to decrease the high nursing effort required, specifically from IV insulin injection and the number of one or two hourly BG measurements. However, noticeable from Table 6.4, this reduction is followed with a higher number of feed adjustments. Modulating nutritional input is necessary to regulate blood glucose concentrations within the desirable range and with these protocols due to the fixed and irrecoverable Glargine dose given that cannot be turned off once given. Hence, with Glargine's fixed dose and different profile, more feed rate adjustments are needed with these first protocol attempts.

A closer look at the estimated time spent in monitoring a TGC protocol for each designated protocol is tabulated in the same Table 6.4. Using the mean time taken in performing hourly adjustments of blood glucose levels and insulin doses of 4.72 mins as stated by Aragon [2006], the total time is calculated by multiplying the total number of adjustments by 4.72 mins. The mean 4.72 mins may be lower than the actual time required in making the total adjustments as additional interventions in this study, which are adjustments of nutritional feed

Table 6.4 Comparison of the total number of intervention frequency representing nursing effort for 30 metabolically stable patients between actual SPRINT clinical data, simulated SPRINT+Glargine, SPRINT-1U+Glargine and SPRINT-2U+Glargine.

Protocol	BG Measurement	IV Bolus	Feed Adjustments	Glargine Doses	Total Interventions	Total Time Spent (mins)	Time Spent per Day (mins)	Time Saved (mins)
SPRINT Clinical Data	2780	4915	636	0	8331	39,322	213	0
SPRINT+Glargine	2572	3268	567	184	6591	31,109	169	44
SPRINT-1U+Glargine	2524	3341	721	184	6770	31,954	173	40
SPRINT-2U+Glargine	2518	1999	718	184	5419	25,578	139	74

and Glargine subcutaneous doses are not accounted for. However, the mean time of 4.72 mins is used for lack of better estimate that could be found in literature.

The highest time spent required from the total nursing interventions in the SPRINT protocol is 39,322 minutes. Averaged to time spent per day, this is equivalent to 213 minutes or 3 hour and 33 minutes for the average patient each day. Clearly, SPRINT protocol requires a high nursing effort and looking at the high effort required in this context sheds light at how a protocol with less nursing effort is significantly needed in less acute wards which do not have the same nursing resources. The total time spent per day, in the SPRINT+Glargine and SPRINT-1U+Glargine protocol is 169 and 173 mins. Around 20% cut in nursing effort, this is a good indicator that protocols with a background Glargine have a potential to work in the area where nursing resources are an issue. The protocol SPRINT-2U+Glargine requires just over 2 hours of daily interventions. However, this protocol has shown to result in loss of control.

A further step is taken to evaluate the actual time saved between the combination protocols of SPRINT and Glargine, in comparison to the actual SPRINT data [Chase et al., 2008c], and the results are shown in Table 6.4. In terms of minutes, in the order of the listed protocols, SPRINT+Glargine, SPRINT-1U+Glargine, and SPRINT-2U+Glargine, the reduced time required in making the total nursing interventions is 44, 40 and, 74 minutes. Therefore, from spending a total of 3 hour and 33 minutes in the SPRINT TGC protocol, the protocols targeted for the usage in less acute wards, are all similar in terms of the total time spent in making the appropriate interventions per day, with just under 3 hour.

Figure 6.4 provides the daily per-patient nursing intervention frequency against the number of hospital stays, beginning from Day 1 to the maximum number of a patient's stay, which is 13 days. The boxes represent the lower quartile, median, and upper quartile values. While, the whiskers are the 5th and 95th percentile values of the daily nursing intervention frequency. The maximum number of per-patient nursing effort intensity is 43 [IQR:41, 45] interventions/day, which occurs on the first day of hospital stay. This reflects well with clinical expectation since patient's glycaemic level on the first day normally requires a higher level of management before their glycaemic level could be stabilized.

After the initial day of starting insulin therapy, the general pattern that can be seen is, nursing effort intensity reduces as the number of hospital stays increases. This trend is observable particularly from Day 1 to Day 7, apart from Days 4 and 5 that have the same median of daily nursing interventions. Day 7 has the lowest intervention with 33.5 [IQR:33, 40] interventions per day. This could be very well explained by the Glargine basal effect that has taken place after 5–6 days, as seen and discussed previously in Chapter 5. After Day 7, the nursing effort increases due to the small number of patients left, with 6 patients in total. Generally, from Day 8 to 13, nursing intervention frequency does not exceed 39 interventions per day. Patients who are still on SPRINT-1U+Glargine protocol after a week, clearly are patients who still require higher level of care which explains the number of nursing effort intensity. On the 13th day, only one patient is left. The highest outlier is 50 interventions per day on Day 1 while the lowest is 24 interventions per day on the third day. In overall, the results not only reduce the clinical burden of nurses but more importantly it leads to a better patient satisfaction and outcome. Less frequent interventions would mean much comfort for the patients, all the while providing the same quality of clinical results from TGC.

6.2.2 BG Measurement Frequency

Measurement frequency and clinical burden are major issues in implementing TGC [Chase et al., 2008a; Aragon, 2006; Mackenzie et al., 2005]. As measurement periods rise so does both glycemic variability and hypoglycemia [Chase et al., 2006; Lonergan et al., 2006b]. The end result is a trade off between the quality of control via measurement frequency and clinical workload or burden, which must be managed to provide good TGC to each patient with minimum variability and hypoglycemia in the glycemic outcome.

In this section, instead of blood glucose levels measured one or two hourly in accordance to SPRINT, the measurement frequency is set apart at 3 and 4 hourly when 3 recent measurements have been within 4.0–6.1 mmol/L. The simulated virtual trial protocol is SPRINT-1U+Glargine. The cumulative distribution function results using these 1-4 hour measurement frequencies are shown in Figure 6.5 where the 1, 2 hourly case is what was previously tested. Interestingly, the 3 hourly measurement frequencies perform almost as well as the Clinical data with

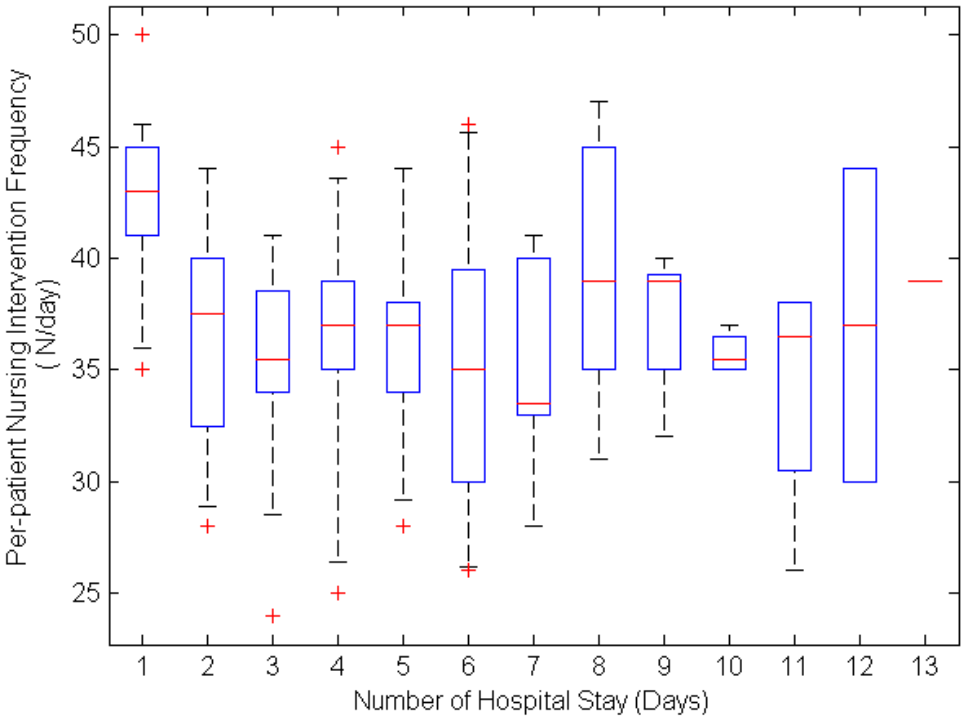


Figure 6.4 Box and whisker plot of daily per-patient nursing intervention frequency for 30 patients under SPRINT-1U+Glargine protocol during their hospital stay. The boxes represent the lower quartile, median, and upper quartile of the daily nursing intensity. The whiskers show the 5th and 95th percentile, while the crosses represent the outliers.

almost identical median BG. Additionally, on a per-patient basis, the median BG achieved is 8–10% lower than the Clinical data, which is significant, but not at all unsafe clinically. Table 6.5 shows a further analysis of 3 hourly measurements, examining the per-patient performance metrics.

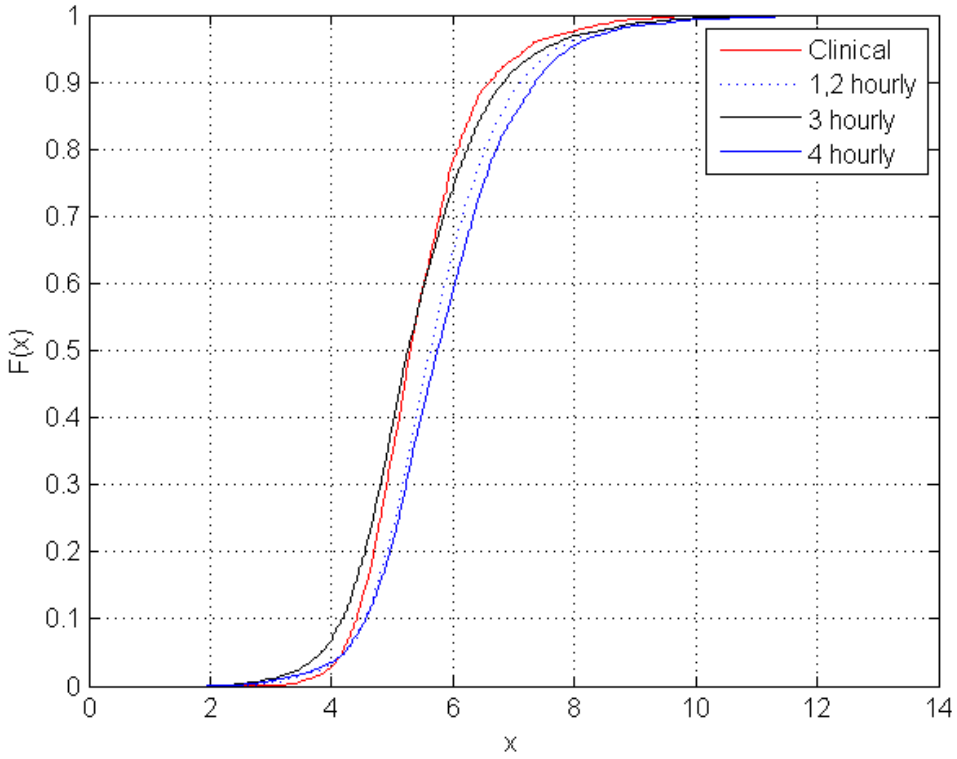


Figure 6.5 Empirical cumulative distribution functions of BG concentrations with different BG measurements for clinical data versus simulated SPRINT-1U+Glargine protocol with 1 and 2 hourly, 3, and 4 hourly measurement frequency. The x-axis refers to BG concentration [mmol/L] while the y-axis is the cumulative distribution function.

Specifically, the 3 hourly measurements approach performs better with lower nursing effort at 34 [IQR:33, 35] interventions per day compared to 36 [IQR:34, 38] interventions per day with 1,2 hourly BG measurements. With 72.86 % [IQR:64.67, 77.35] time spent within 4.0–6.1 mmol/L band, it is 6.74% higher (absolute) than when using a more frequent measurement. The total amount of insulin is slightly higher with 74.82 [IQR:68.20, 79.42] U/day compared to 71.20 [IQR:62.50, 75.07] U/day. As insulin tends to saturate at 5-6 U/hour [Natali et al., 2000; Prigeon et al., 1996], this amount is still relatively low, and differences are likely attributed to the different PKs. Safety is further confirmed with no hypoglycaemic episodes.

Table 6.5 Per-patient comparison of BG intervention frequencies between 1,2 and 3 hourly of the SPRINT-1U+Glargine protocol.

Protocol	unit	1, 2 hourly	3 hourly
BG	mmol/L	5.62 [5.12, 6.28]	5.16 [4.75, 5.90]
Time Band 4.0–6.1	%	66.12 [57.14, 74.21]	72.86 [64.67, 77.35]
Time Band 4.0–7.0	%	86.46 [83.38, 90.65]	86.01 [82.20, 91.13]
Hypoglycaemia	%	0	0
Total Insulin	U/day	71.20 [62.50,75.07]	74.82 [68.20, 79.42]
IV Insulin	U/day	35.20 [29.11, 40.97]	38.29 [34.48, 43.85]
Glargine	U/day	35.91 [32.11,36.84]	35.93 [32.55, 37.26]
Dextrose Feed	g/day	109 [78.45, 125]	97.67 [61.76, 125.57]
Intervention Frequency	N/day	36 [34, 38]	34 [33, 35]

The SPRINT protocol was designed [Lonergan et al., 2006a,b; Chase et al., 2008c, 2010c] for glucose measurements every 1 or 2 hours, to suit the requirements of critically ill patients whose insulin sensitivity, S_I, can change rapidly hour to hour [Lin et al., 2006, 2008]. These virtual results simulating less critical patients showed lowering measurement frequency at 3 hourly, or longer, does not affect the glycaemic control performance. However, in an effort to bring the best simulated protocol to the next step of a proof of concept trial, it is best to work with more frequent BG measurements, if only for safety. This act ensures protocol safety is not compromised in a first clinical trial. In particular, dynamic patients need to be well monitored thus higher measurement frequency is essential.

A further statistical analysis performed on the time the number of BG measurements are within desired band of 4.0–6.1 mmol/L between the 1,2 hourly and 3 hourly measurements showed that two-tailed p-value =0.15.

6.2.3 Sample Patient Analyses

Clinical records and simulation results of SPRINT-1U+Glargine on Patient 5061 are shown in Figure 6.6. The top panel of each subfigure shows the blood glucose levels through time. BG is well controlled with median and IQR of 5.55 [IQR:4.70, 6.10] mmol/L and 5.79 [IQR:5.00, 6.38] mmol/L for clinical and SPRINT-1U+Glargine respectively. The second panel describes the amount of

IV insulin bolus administered as well as Glargine for Patient 5061 on SPRINT-1U+Glargine protocol. The third panel depicts dextrose feed rate received by the patient expressed in g/day while patient's own insulin sensitivity, S_I is shown in the last panel.

The percentage of time spent within the 4.0–6.1 mmol/L band for the whole duration of Patient 5061's stay are quite similar between clinical records and simulated SPRINT-1U+Glargine protocol with 68.8% and 68.3% respectively. Difference can be seen with a wider band of 4.0–7.0 mmol/L where clinical records show a higher percentage with 95.0% and 89.4% from SPRINT-1U+Glargine. There is no occurrence of hypoglycaemia described at BG below <2.2 mmol/L at any period. The median daily feed given in clinical records is 120 g/day against 125 g/day from the SPRINT-1U+Glargine protocol.

In Figure 6.6(a), as seen in the second panel, the frequency and amount of insulin bolus in clinical data are higher than simulated SPRINT-1U+Glargine in Figure 6.6(b). Clinical records showed almost 60% more IV insulin is administered compared to SPRINT-1U+Glargine protocol. However, with Glargine as basal insulin, eventually more insulin is used in SPRINT-1U+Glargine protocol. In terms of nursing effort, clinical records have 239 interventions in total or 41 measurements/day on average, whereas the SPRINT-1U+Glargine protocol has 205 interventions, or 35 measurements/day, saving almost 30 minutes per day. The higher intervention frequency can be mostly attributed to measuring BG.

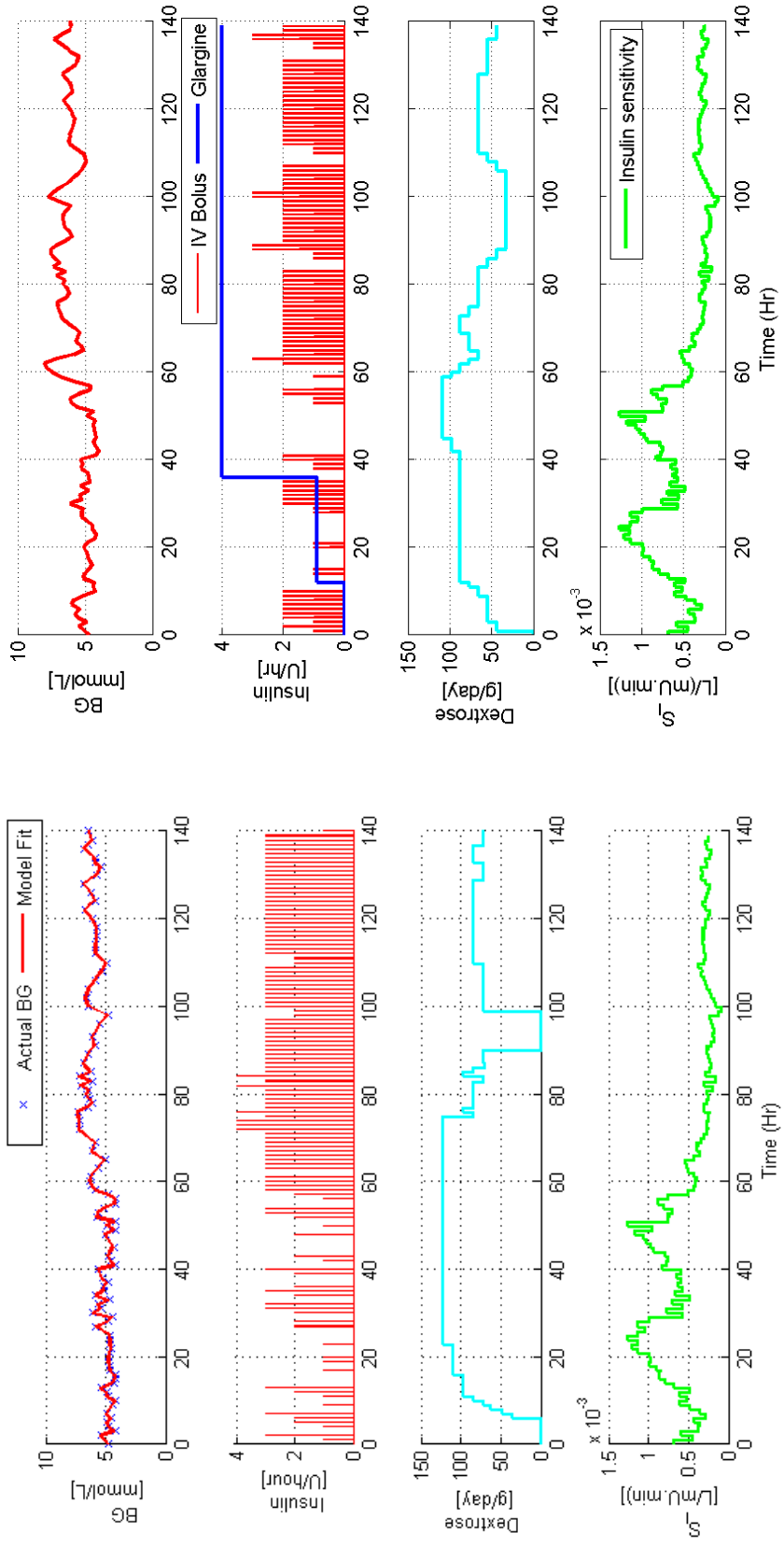
The reduction in the number of IV boluses in SPRINT-1U+Glargine is clearly observable between 40th to 60th hour where there's a period where no injection from IV insulin is required. With high insulin sensitivity, S_I around this period, Glargine alone is effective for Patient 5061's basal coverage. Also in this period, the patient gets the highest amount of dextrose depicted in the 3rd panel of Figure 6.6(b), indicating the patient's recovery is likely going well. This result shows that Glargine is more suitable for patients with higher insulin sensitivity and illustrates how a later protocol might be effective with Glargine alone for some patients. However, after the 60th hour, insulin sensitivity, S_I quickly drops and remains at a low level until the end of stay. This patient, instead of improving over time, appears set for a different course in recovery. Therefore, the expected effect of Glargine build up approaching the 6th day is not translated into reduced insulin and nursing effort. With lower S_I, the requirement for IV insulin boluses

eventually increases and feed rate necessarily decreases to maintain normoglycaemia. This result shows that the combination controller recognizes the periods where patient condition evolves, and need sufficient compensation with insulin and nutrition to maintain normoglycaemia.

Figure 6.7 is an example of Patient 5086 with high insulin sensitivity, S_I throughout the stay with median 0.58 [IQR:0.50, 0.66] x 10^{-3} L/(mU.min). To evaluate if Glargine under the SPRINT-1U+Glargine protocol would perform best in a patient with relatively high insulin sensitivity only, this sample patient is examined. Insulin sensitivity, S_I is shown in the last panel of Figure 6.7. In this reduced protocol, from Figure 6.7(b) it is clear there are more periods where IV boluses are not required, the longest being in the last day from the 113th to 120th hour. With 128 hours in length of hospital stay (5.3 days), the effect of Glargine's interstitial build up is translated into reduced insulin and intervention requirements for at least the last day. This result shows the combination of interstitial insulin build up, Q and patient's level of insulin sensitivity, S_I can have a positive effect in lessening the burden of TGC among nurses and effectively translating patients to Glargine alone, if given enough time.

Comparison of the effective interstitial insulin, Q between the two protocols on Patient 5086 is shown in Figure 6.8. In the SPRINT protocol, the level of effective interstitial insulin is highly dynamic with extreme high and lows due to the bolus insulin delivery. Compared to the protocol with Glargine, the effective interstitial insulin, Q is more stable as Glargine has a flat, infusion-like PK curve. The effect of Glargine, while having SPRINT, is observed with the stability of Q. Figure 6.9 plots the percentage of time spent within 4.0–6.1 mmol/L band vs the median insulin sensitivity, S_I. The plot shows almost all patients that achieved 70% of time spent within 4.0–6.1 mmol/L have median S_I of at least 0.35–0.4 x 10^{-3} L/(mU.min). Hence, this criteria could form a basis of when to use Glargine, rather than specific clinical aspects alone. The sharp drop off of time band below 3.5–4.0 x 10^{-3} L/(mU.min) further supports this criteria. Thus, using a computerized TGC controller, this criteria could be used directly and simply to determine when to switch to Glargine.

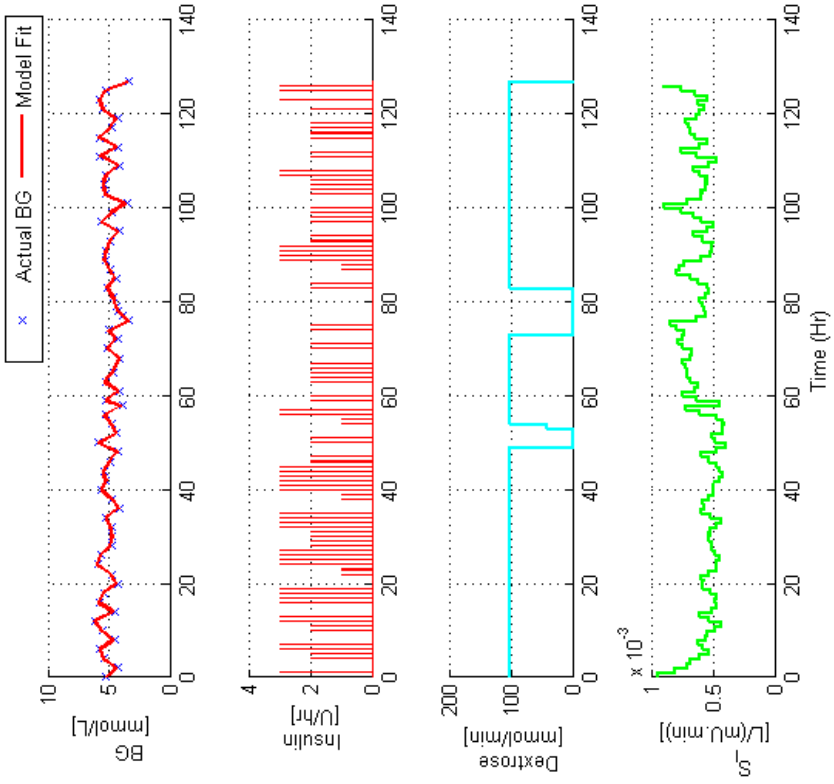
To examine if Patient 5086 exemplifies a patient who is ready to be transferred out of the ICU, the SPRINT-1U+Glargine protocol is maintained until the 108th hour. The final day is instead solely dosed with Glargine. The dose of Glargine



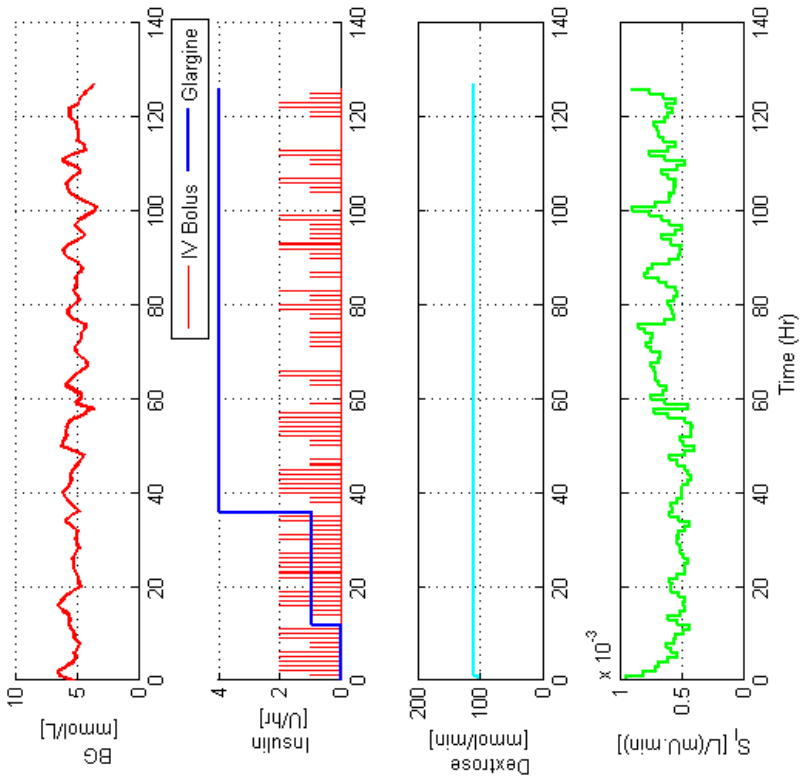
(a) Clinical

(b) SPRINT-1U+Glargine

Figure 6.6 Comparison between clinical and SPRINT-1U+Glargine simulation results on Patient 5122. In the top panel of each subfigure, the solid line (–) illustrates the modeled BG while crosses (×) are the clinically recorded BG. The second panel of each subfigure shows the insulin bolus in solid red line (–) and Glargine in solid blue line (–). Glargine's amount shown in the panel needs to be multiplied by a factor of 10. The third and bottom panel of each subfigure displays the feed and insulin sensitivity, S_I.



(a) Clinical



(b) SPRINT-1U+Glargine

Figure 6.7 Comparison between clinical and SPRINT-1U+Glargine simulation results on Patient 5086. In the top panel of each subfigure, the solid line (–) illustrates the modeled BG while crosses (×) are the clinically recorded BG. The second panel of each subfigure shows the insulin bolus in solid red line (–) while Glargine is depicted by solid blue line (–). Glargine's amount shown in the panel needs to be multiplied by a factor of 10. The third and bottom panel of each subfigure displays the feed and insulin sensitivity, S_I.

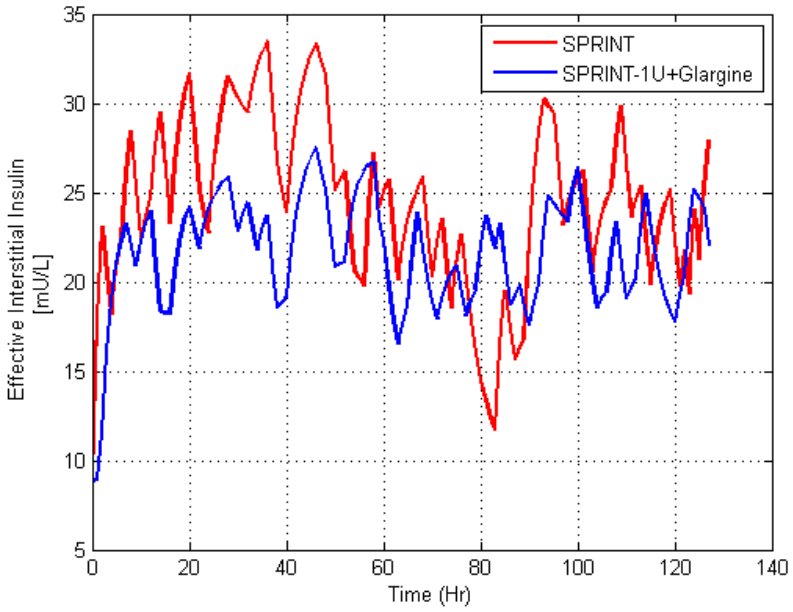


Figure 6.8 Comparison of effective interstitial insulin, Q for Patient 5086 between the SPRINT and SPRINT-1U+Glargine protocol. The solid red line (–) depicts effective insulin, Q obtained from clinical data while solid blue line (–) shows the simulation of reduced SPRINT protocol with background Glargine, SPRINT-1U+Glargine.

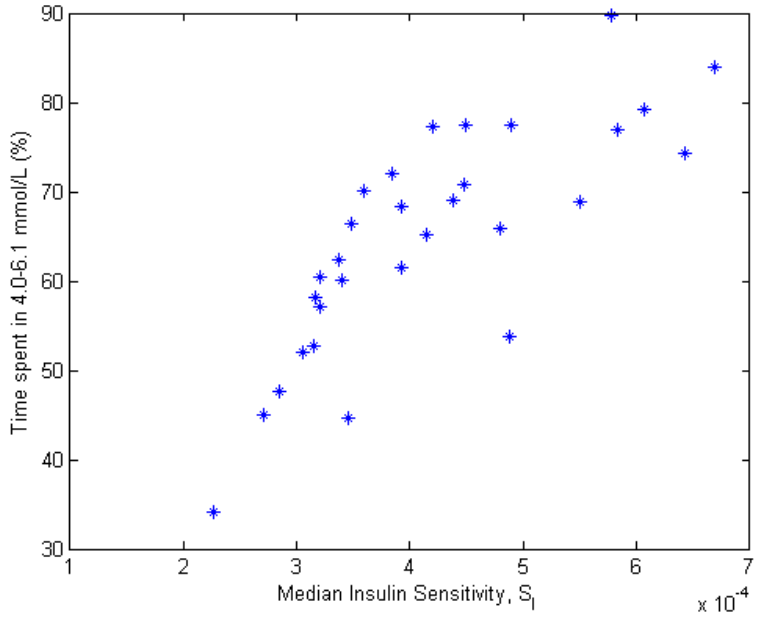


Figure 6.9 Percentage of time spent in 4.0–6.1 mmol/L vs median insulin sensitivity, S_I for all 30 patients under the SPRINT-1U+Glargine protocol.

is simulated at 40U and 60U. Virtual simulation results are shown in Figure 6.10. In the first panel, the performance of BG level with Glargine increased to 60U is almost similar to the Clinical data. In contrast the use of 40U of Glargine results in moderate loss of control. This result demonstrates that a transition protocol can be applied once the patient is stable and that the patient could likely be managed with subcutaneous insulin Glargine alone after the initial build up of effective interstitial insulin over prior days. Thus, this result also shows the need for a transitioning or a weaning buildup period.

This promising result is what is expected from the virtual simulations of SPRINT-1U+Glargine protocol. Patients would gradually have their IV insulin reduced and replaced by Glargine. However, because SPRINT is designed to achieve a steady state of 3U of insulin [Lonergan et al., 2006a,b], the adjustments of prescribed insulin are rather discretized [0,1,2,...6] U/hr. This discretisation explains why IV boluses are continued to be given although with a lesser amount, even while Glargine alone can be effective in controlling the glycaemic level.

6.3 Discussion

A consistent method or protocol is needed for insulin administration for non-critical patients as recommended by AACE [American College of Endocrinology, 2007] and ADA [American Diabetes Association, 2008]. The protocols should be as simple as possible, taking into account nursing resources and patient safety. It should be effective, safe and simple enough to be fully automated by nurses, or keeping expert intervention to a minimum.

The clinically validated virtual patient simulation methods used are an effective and realistic way to assess, evaluate and optimise different TGC protocols safely, *in-silico* before clinical testing. The simulations of SPRINT+Glargine in this study show that Glargine can be used in patients who are insulin resistant but metabolically stable. The results showed significantly reduced nursing effort during the IV to Glargine weaning period, while still delivering tight glycaemic control. The blood glucose levels achieved with SPRINT+Glargine are comparable to the clinical records with SPRINT alone, which was very successful in reducing mortality and negative outcomes. The feed rates are also comparable in

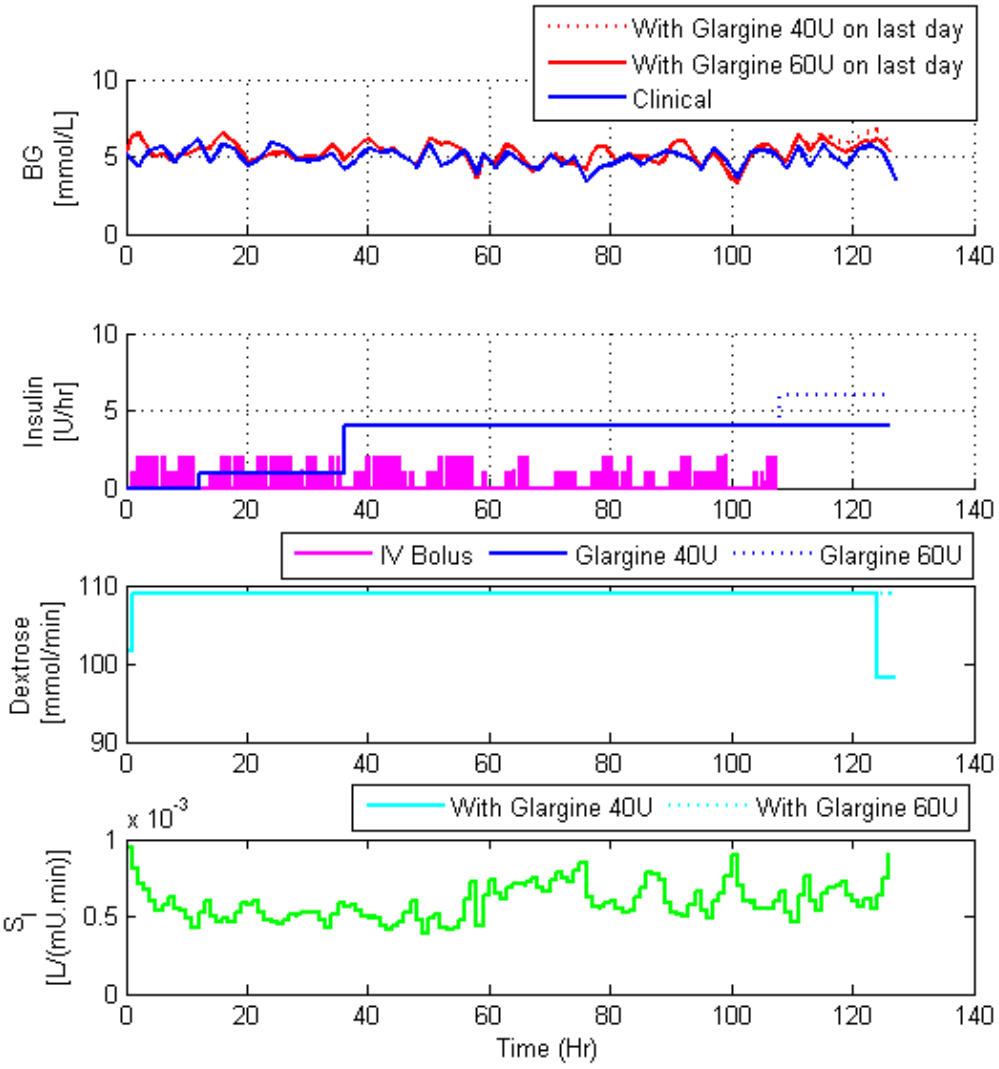


Figure 6.10 Simulation results from SPRINT-1U+Glargine on Patient 5086, where IV insulin bolus is given until the 108th hour. For the last day of stay, patient's BG level would be controlled by Glargine alone. In the top panel, the solid red line (–) illustrates the modeled BG with Glargine on last day administered with 60U. The $(\cdots)$ line is Glargine on last day at 40U while solid blue line (–) illustrates Clinical data. The second panel shows the insulin bolus and Glargine. The amount of Glargine is to be multiplied by a factor of 10. The third and bottom panel displays the feed and insulin sensitivity, S_I.

the two simulated protocols and clinical records. However, the amount of total insulin used in SPRINT+Glargine, that is the sum of IV insulin boluses and subcutaneous Glargine is greater than clinical records. This outcome is likely due to the slow build up of Glargine, which could take 3 days or longer [Lehmann et al., 2009] as has been discussed previously in Chapter 5, and equally, to the different PK's of Glargine versus IV boluses and the impact of clearance rates on these different PK profiles.

By reducing the amount of bolus in SPRINT by 1U while still maintaining Glargine (SPRINT-1U+Glargine), the control in blood glucose levels is not compromised and comparable to clinical records. Although percentage of time spent within 4.0–6.1 mmol/L band drops in this protocol, the overall results make this protocol the best option. This decision is made upon median BG, time within 4.0–6.1 mmol/L and 4.0–7.0 mmol/L band, and intervention frequency among others, as listed in Table 6.3. Further analysis is performed, specifically in the frequency of measuring blood glucose levels. Instead of 1 or 2 hourly measurement frequency, as how SPRINT works, the frequency is set apart at 3 or 4 hourly. The virtual simulations showed that less measurement does not affect the performance, instead it works potentially better. Nursing effort is thus also further reduced, while the percentage of time spent in 4.0–6.1 mmol/L increased. The overall result of this protocol achieved almost identical performance as in the Clinical SPRINT data.

The simulations of SPRINT-2U+Glargine on the other hand, are not sufficient to provide effective glycaemic management for these patients even though the total insulin used is comparable to clinical data. This could be explained by the slow build up of Glargine as mentioned above. The average ICU stay of 5.7 days may also not be adequately long for full adaptation to Glargine. Even though the patients selected for this study are reasonably stable, critically ill patients in general appear to require more rigorous insulin therapy than using long term insulin supplement such as Glargine. Thus, this protocol also indicates a need for a graduated or longer weaning process, if it can be managed without excessive complexity.

The goal of this study is to develop a protocol that can aid patient recovery, and seamlessly transition IV insulin in the intensive care unit to subcutaenous insulin that will be the sole form of TGC input used in less acute wards, all the

while reducing the nursing workload imposed by TGC. The primary hypothesis is Glargine can effectively act as a basal insulin support for stable ICU patients and patients in less acute wards who only require a minimal basal boost. However, the protocol SPRINT in the virtual simulations did not seem to be fully sensitive to Glargine supplementing a patient's insulin requirement. This result is likely due to the Glargine buildup period noted in Chapter 5 and the differing PK profiles, but remain to be proven. When IV boluses are stopped before the last day, leaving BG control under 60U of Glargine, the simulations showed BG control is just as effective as Clinical. This result may be due to the design of SPRINT aiming to achieve a steady state of 3U insulin and 60% of feed in patients with limited, discrete interventions preventing flexibility. Finally, the use of Glargine is very conservative in this study, being less than or equal to half of the daily insulin requirement from the previous day. This choice was made to address the course of recovery for patients where they are expected to slowly regain normal insulin sensitivity or basal insulin production, as well as to create a safe, easy protocol for first clinical trials.

The virtual trials also indicate that a protocol using Glargine on top of SPRINT is perhaps more suitable for patients who are consistently stable and are reflective of those seen in less acute wards or ready to be transferred to them. The analysis of this cohort results show that patients with relatively higher S_I were more likely to respond to Glargine and these protocols with good TGC performance. However, an early, smooth transition from IV insulin to a combination may also further help by reducing undesirable variations in blood glucose levels [Egi et al., 2006]. It is clear the use of Glargine is shown to supplement patient's basal insulin requirement and has the potential to reduce nursing effort.

Finally, this study only included 30 patients. Therefore, its results are only a positive 'proof-of-concept', and not conclusive. As mentioned in Chapter 5, the volume of patients in less acute wards with useful clinical data were not enough for virtual trials. Hence, the choice of cohort development from metabolically stable ICU patients was made. Although the simulated patients met the inclusion criteria for defined metabolic stability, virtual results may not necessarily be fully representative of the behaviour of patients in actual less acute units. However, patients who are ready for transition to less acute wards do have higher insulin sensitivity, and Glargine is shown to be effective in the virtual simulations for the period where patient's S_I improved. However, as these simulated patients were

ICU patients, albeit stable, their insulin sensitivity, S_I did not always continue to improve over time in these records, while they were on SPRINT. Hence the insulin requirements did not always decrease throughout the stay, to a point where Glargine alone was suitable. Thus, it is clear that there may be a missing gap of relevant data that was not available for this study but not to the point that it could invalidate the model. Rather, retrospective data with sample of continuous improvement in S_I would show the efficacy of administering Glargine alone.

The fact that results of this study , given in per-patient median and IQR of the glycaemic performance measure does have an importance. In [Chase et al., 2010a], the foremost goal of effective TGC must be to obtain tight glycaemic control for each patient in a cohort. It is the per-patient results that matter the most and achieving successful outcomes, such as reduced mortality, is likely going to be strictly a function of being able to manage patient variability across a cohort to provide consistent TGC.

Based on the promising results from virtual trial simulations in Section 6.2, a protocol tailored for the ' Proof of Concept Study of Insulin Glargine as Basal Insulin in the ICU and HDU' is developed. This protocol, SPRINT-1U+Glargine, has the potential to be effectively employed in a clinical pilot study. A clinical pilot study will provide valuable information on the practicality and clinical benefit of Glargine in stable ICU patients and the likelihood of its efficacy in less acute wards. This trial will be the first step towards designing transition glycaemic control protocols for patients from the ICU going to less acute wards. Because SPRINT has been proven to provide safe TGC and gained considerable trust in the Christchurch Hospital ICU, where it is first implemented, a clinical pilot study incorporating SPRINT will be significantly easier to deploy compared to a protocol without it. In the next chapter, the protocol's robustness will be further investigated and assessed in an effort to employ a successful transition protocol.

6.4 Conclusion

This study investigated the use of Glargine as basal insulin support in stable, recovering ICU patients. A clinically validated insulin Glargine compartmen-

tal kinetics model and an insulin-glucose pharmacodynamic model are used to perform virtual patient simulations of protocols using Glargine. A cohort of 30 metabolically stable patients who received insulin therapy under SPRINT protocol during their stay in Christchurch Hospital ICU were selected for *in silico* assessments. Protocols using daily injections of Glargine reduced nursing effort provided blood glucose levels are largely maintained within a desirable range. The total amount of insulin used is greater compared to the clinical data and SPRINT is likely due to the buildup period of Glargine, a conservative protocol, and different insulin PKs in plasma. Patients with relatively higher insulin sensitivity were found to perform best, and a model-based S_I limit of 3.5–4.0 x 10^{-3} L/mU.min was found to provide a suitable threshold. Finally, use of Glargine is shown to safely supplement a patient's basal insulin requirement without the risk of hypoglycaemia, particularly after the first 3–5 days of stay. Although patients data are limited, the virtual trials do provide an insight into the implementation potential of this combination protocol for less critically ill patients. These results, if robust, are enough to justify a clinical pilot trial.

Chapter 7

Monte Carlo Analysis

This chapter presents an *in silico* Monte Carlo analysis to quantify the performance and robustness of the SPRINT-1U+Glargine protocol of Chapter 6. In particular, it analyzed robustness to physiological variability and sensor errors. For clinical implementation, it is crucially important to ensure the protocol is robust towards a wide range of expected variability seen in a clinical setting.

Measurement error is characterized in terms of glucose sensor reliability. The issue of using a reliable glucose meters device has been addressed before and possible failure of TGC in some studies has been suggested to be linked with a wrong choice in blood glucose measurements device [Ting and Nanji, 1988; Critchell et al., 2007; Wahl, 2009]. In a study analysis by Wiener et al. [2008], it found that many TGC studies with no mortality improvement used POC (point of care) glucose meters or capillary blood samples. The NICE-SUGAR study Finfer and Heritier [2009], used a variety of glucose meters, which most of the glucose meters are unsuitable for used among the critically-ill patients [Scott et al., 2009]. Scott et al. [2009] also reported Van der Berghe's study was successful partly due to the use of arterial blood glucose instrument that gives precise blood glucose measurements. In contrast, SPRINT [Chase et al., 2008c] was successful, but used standard glucose meters, namely Glucocard Test Strip. Hence, it could be argued that the impact of sensor error is protocol dependent and must be tested.

Equally, in critical care settings, frequent and accurate measurements in blood glucose levels are important. The FDA stated that critically ill patients should not be tested with blood glucose meters due to inaccuracies in results. However, as noted SPRINT used POC glucose meters and reported the tightest control and least hypoglycaemia. Equally, it had one of the more frequent measurement

rates averaging 161 measurements per day.

However, faster return on blood glucose measurements is essential, particularly in TGC. Hence, bedside glucose measurement devices are typically used instead of being clinically lab tested or using a blood gas analyzer. Moreover, SPRINT requires one or two hourly BG measurements, which is not possible for BG concentrations to be lab tested while providing rapid results. Due to these drawbacks, the model-based glycaemic controller's performance during adverse events, such as sensor errors, should be thoroughly assessed to ensure the maximum benefit of a model-based control protocol. There is no consensus on how to optimally assess accuracy of glucose sensors. According to ISO 15197, blood glucose meters must provide results that are within 20% of a laboratory standard 95% of the time. Clarke Error Grid, is thus used here as elsewhere, to quantify clinical accuracy of blood glucose estimates compared to a reference value. Hence, it can equally be used to show sensor performance or in Monte Carlo simulation.

As a second source of significant variation, repeated doses of subcutaneous insulin do not produce the same metabolic effect. This result is valid within (intra-) and between (inter-) patients [Heinemann, 2002; Heise et al., 2004]. Insulin action and absorption vary considerably and this variability consistently deters reproducible insulin therapy, as discussed previously in Chapter 4.

Unexpected highs or lows in patient glycaemic level are a major course of concern. If factors influencing the pharmacokinetics and pharmacodynamics of insulin are not well understood, the result will be a greater variability. Age, physical activity, smoking or non-smoking, injection site, injection depth are among many other known factors that influence insulin absorption and action of a subcutaneous insulin [Berger et al., 1982; Heinemann, 2008].

Failure to account for inter- and intra- patient variability would result in poor TGC, particularly for the more dynamic patients (intra- patient variability) or those for whom dosing is inappropriate due to inter- patient variability. Managing variability means that any protocol must be able to adapt and provide patient-specific interventions that evolve with patient condition. Thus, any control protocol should account for these significant, yet very common fundamental errors or variability. Monte Carlo simulations allow these errors of variability to be generated and safely tested in a clinically validated *in silico* environment

[Chase et al., 2010c]. Hence, it can be used to test the accuracy and robustness of any developed model-based glycaemic control protocol.

7.1 Method

Virtual patients are created from data of 30 patients data who met the inclusion criteria. They were all selected from the SPRINT cohort based on periods of long term stability and low insulin requirements, indicating patients who would benefit from a transition to subcutaneous insulin administration. These are the same patients simulated in Chapter 6.

The SPRINT-1U+Glargine protocol seeks to use Glargine, gradually replace intravenous insulin. As noted, it is a first step and protocol towards developing a complete, more final solution. To capture the impact of sensor error, normally distributed error is added to each patient's simulated glucose profile in virtual trials of the protocol. Glucose measurement errors are assumed normally distributed with precision as reported in Kimberly et al. [2006]. Clarke Error Grid analysis [Clarke et al., 1988] is used to evaluate the normally distributed sensor noise to an accepted standard reported error of of 20% [Mann et al., 2007].

7.1.1 Monte Carlo Error

For each patient, 100 simulations were performed to generate statistics on performance. Each virtual trial had an added sensor noise in the simulated blood glucose measurement. In addition, variability in subcutaneous Glargine absorption was added to account for these variations. Sensor error is simulated to be normally distributed with a standard deviation of 5%, and max error of $\pm$ 4 standard deviations, with a saturated max of $\pm$ 20%. The latest generation of glucose meters are more advanced with greater accuracy [Chan et al., 2009; Cohen et al., 2006]. Hence, the error simulated is typical of today's devices or slightly larger.

The parameters $k_{prep,gla}$, $k_{1,gla}$, and α_{gla} are the three Glargine pharmacokinetics parameters that were varied. Details on the variability of the Glargine pharmacokinetics parameters is in Chapter 4. The impact of varying the three

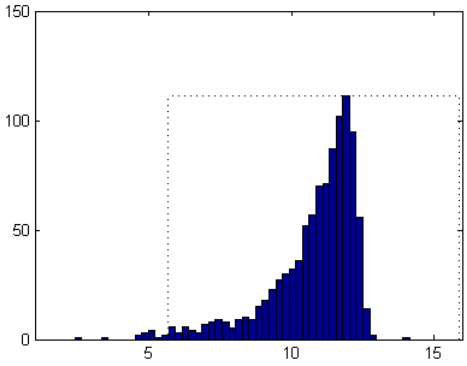
Glargine pharmacokinetics parameters generated a range of possible values of maximal plasma insulin concentration, C_{max} and time to maximal plasma insulin, T_{max}. These values are physiologically valid, as reported in literature and as seen in Figure 7.1. Using a lognormal distribution in the Glargine model parameters eliminates the possibility of obtaining non-physiological values, as the Glargine PK parameters can thus never exhibit a negative value.

Thus, variability is accounted for in Glargine PK parameters and glucose sensor error. There are 3000 simulations in total (30 patients X 100 simulations), each being unique due to different random errors generated. Simulated error reflects the clinical variability, which gives a realistic feature to assess the model-based control protocol. The main assessments taken into account are accuracy and repeatability. Safety and performance are the two primary criteria of the controller, evaluated by avoidance of hypoglycaemia (<2.2mmol/L), median and IQR of blood glucose measurements, percentage in desired band (4.0-6.1mmol/L, 4.0-7.0mmol/L), amount of insulin prescribed (IV boluses+Glargine), amount of nutrition given, and nursing effort intensity based on the number of interventions required.

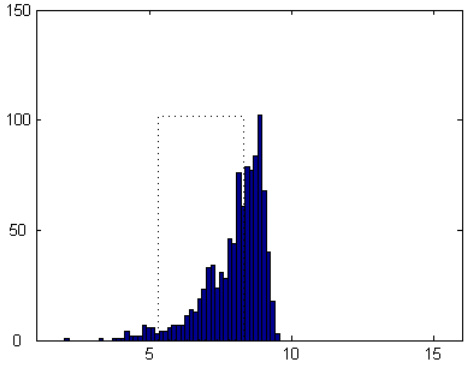
7.2 Results

The Clarke Error Grid analysis of a patient with the maximum measurement error of 20% is shown in Figure 7.2. The analysis showed that, with five different regions, 100% of a 200 reference data set is within the clinically acceptable regions, with 92% in Zone A and the rest in Zone B. This outcome is in agreement with the clinical accuracy defined in the grid analysis. High clinical accuracy should result in a better patient outcome for a given protocol. The figure also shows that the SPRINT-1U+Glargine control protocol leads to good clinical management in the ICU or less acute wards because the BG range is relatively tight. Studies have shown that most meters cannot achieve the high target of total error being <5%, as set by ADA. Each zone as in Clarke et al. [1988] is defined:

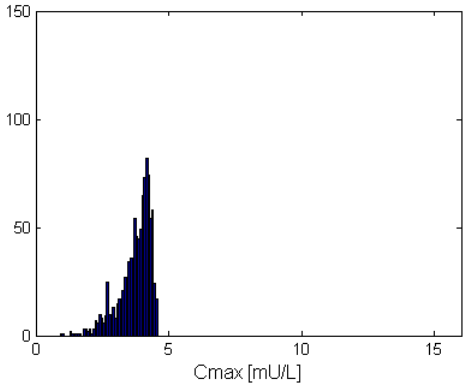
Zone A: measured as measurements that deviate from the reference by no more than 20% and all values determined to be in low range <70 mg/dL or 3.88 mmol/L. Blood glucose values in zones A result in appropriate treatment



(a) 32U Injection of Glargine



(b) 24U Injection of Glargine



(c) 12U Injection of Glargine

Figure 7.1 Distribution of maximal plasma insulin concentration, C_{max}, computed 1000 Monte Carlo runs with variability in $k_{prep,gla}$, $k_{1,gla}$, and α_{gla}. 7.1(a) a 32U dose, boxed area refers to range quoted in [Scholtz et al., 2005]. 7.1(b) a 24U dose, boxed area refer to range quoted in [Lepore et al., 2000] and 7.1(c) a 12U dose. No quoted range [Owens et al., 2000]. This figure is repeated from Chapter 4, of Figure 4.9.

and are therefore clinically accurate.

Zone B: include patient-determined values which deviate from the reference by more than 20% but which result in benign treatment decisions.

Zone C: include patient-determined values which are outside the target range when the reference is within the target range and therefore mandate treatment which results in glucose levels outside the target range.

Zone D: patient-determined glucose values are within the target range when the reference values would demand attention.

Zone E: patient-determined values are outside of the target range, but at the opposite level of the reference values. Hence, measurements here would lead to erroneous treatment decisions.

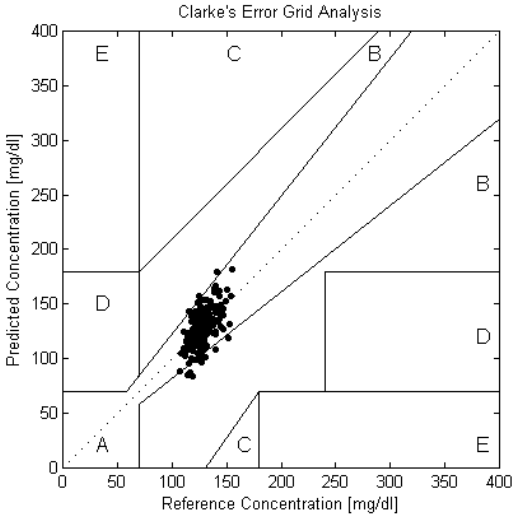


Figure 7.2 Clarke Error Grid analysis of the error distribution produced in a sample patient. Error is shown for a normally distributed sample blood glucose reference data set of size 200. To convert mg/dL values to mmol/L, multiply by 0.0555.

7.2.1 Monte Carlo Analysis

Table 7.1 shows the results of Monte Carlo simulations for the 30 patient cohort. The result of each MC performance measurement is almost similar to the non-error simulations. There is zero hypoglycaemia in any analysis. In the SPRINT-1U+Glargine virtual trials, the per-patient median BG is 5.62 [IQR: 5.12, 6.28]

mmol/L with 66.12% [IQR:57.14, 74.21], 86.46% [IQR:83.38, 90.65] time in the 4.0–6.1 and 4.0–7.0 mmol/L bands. Median insulin per-patient was 71.2 [IQR: 62.5, 75.07] U/day, with carbohydrate administration of 109 [IQR: 78.46, 125] gram/day. Median nursing effort was 36 [IQR:34, 38] interventions/day . Monte Carlo simulations show; 5.65 [IQR:5.27, 6.16] mmol/L, 65% [IQR:55.12, 72.72] and 87.19% [IQR:81.39, 89.84] for blood glucose performance. Monte Carlo insulin and nutrition were 70.8 [IQR:61.67, 74.47] U/day, 109 [IQR: 88.29, 145.19] gram/day, requiring an identical 36 [IQR:34.6, 38] interventions/day.

The primary overall result is that the variations and errors considered do not appear to have any great impact on the protocol design or its ability to manage patients variability. It is important to note that median (IQR) results in Table 7.1 show the middle, much more likely the, 50% of the results. Hence, this result should hold as a general trend across a wide range of possibilities. This Monte Carlo virtual analysis result is parallel with Monte Carlo analysis of SPRINT and other protocols using clinically validated virtual patients, which revealed little difference with added measurement error [Lonergan et al., 2006b]. Overall, it can be concluded that the robustness of the SPRINT-1U+Glargine protocol in a noisy clinical environment is validated with this Monte Carlo analysis.

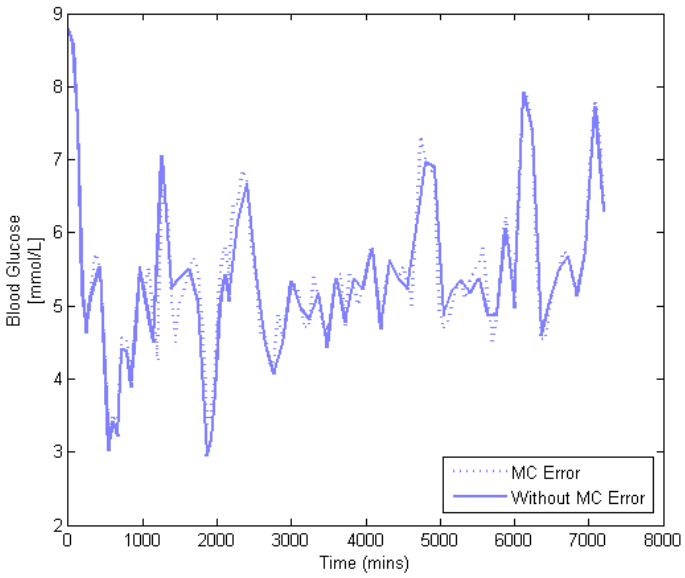
Table 7.1 Per-patient performance measurement with and without Monte Carlo

Performance	MC Error	Without MC Error
BG [mmol/L]	5.65 [IQR: 5.27,6.16]	5.62 [IQR:5.12, 6.28]
Time Band 4–6.1mmol/L [%]	65.00 [IQR: 55.12, 72.72]	66.12 [57.14, 74.21]
Time Band 4–7.0mmol/L [%]	87.19 [IQR:81.39, 89.84]	86.46 [IQR:83.38, 90.65]
Nursing Effort	36 [IQR:34, 38]	36 [IQR:34, 38]
Total Insulin [U/day]	70.84 [IQR:61.67,74.47]	71.2 [IQR: 62.5, 75.07]
IV Daily [U/day]	37.23 [IQR:28.41, 40.11]	35.20 [IQR:29.11, 40.97]
Glargine Daily [U/day]	35.84 [IQR:32.03, 36.81]	35.91 [IQR:32.11, 36.84]
Feed [gram/day]	109.87 [IQR:88.29,145.19]	109.00 [IQR:78.45,125.00]
Hypo	0	0

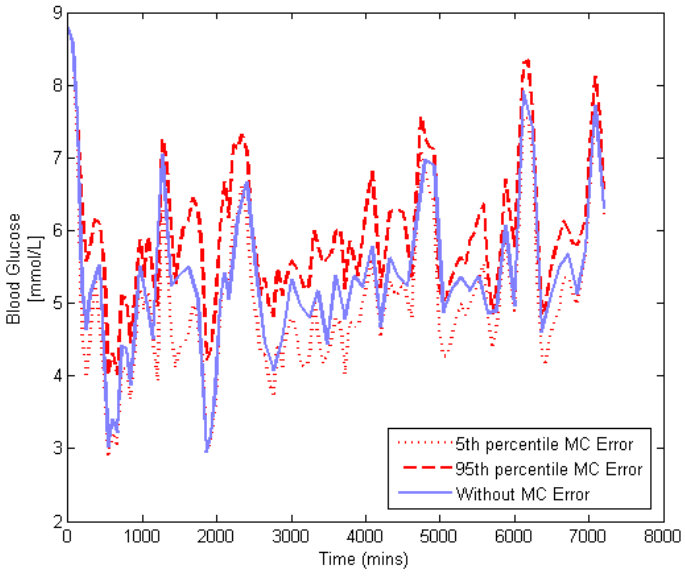
Figure 7.3(a) is the BG profile comparison for a sample patient with median of 100 MC simulations against the simulations without introduced error. This sample patient is representative of the cohort. Both resulting BG profiles are almost similar as expected, since the median would be expected to be as similar as possible to the actual profile overall possible random variations and errors. The largest differences would be seen at the 5th and 95th percentile. Hence, an upper and lower envelopes representing the 5th and 95th percentile of all possible blood glucose concentration are shown in Figure 7.3(b). The 5th and 95th percentile range are quite tight particularly towards the end of Patient 5376's stay from 6000 to 7500 mins. The results also show that BG values are more varied between the values of 3–6 mmol/L, where the biggest difference between the 95th percentile range and median MC simulations could be seen around 1500–5500 mins. These results provide valuable information on the range of all possible BG values in the presence of patient extreme variability in Glargine absorption and sensor error.

Interestingly, at higher BG concentrations, particularly over 7 mmol/L, the possibilities of obtaining even higher BG concentrations are greatly reduced. This outcome is depicted at three main peaks of minutes 1500, 6200 and 7200. It occurs because larger errors in sensor values mean there is always a possibility of incorrect dosing with the returned erroneous BG concentrations. Hypo- or hyperglycaemia and their consequences would thus be a result of too large or too small doses being given. Therefore, this result provides a clear indication of the overall protocol's safety and lack of aggressiveness, since even with a range of possible BG concentrations, hyperglycaemia and hypoglycaemia are both avoided at the highest and lowest BG values seen. Note that hyperglycaemia here is defined typically as blood glucose values more than 10 mmol/L (180 mg/dL). These results are typical across all 30 patients and can be seen in Appendix 7.5. Thus, the control protocol, SPRINT-1U+Glargine maintains the stability of the patient despite dynamic variations in the physiological process.

In Figure 7.4, the rest of the profile for Patient 5376 is shown, comparing the simulated trial with the median MC error and non-error. As can be seen, the results are almost identical. Figure 7.5 shows the histogram plot of the Glargine pharmacokinetics, $k_{prep,gla}$, $k_{1,gla}$, and α_{gla} actual distributions from the 100 Monte Carlo simulations of Patient 5376. The overall results confirms the validity of the SPRINT-1U+Glargine protocol and the approach taken in this study.

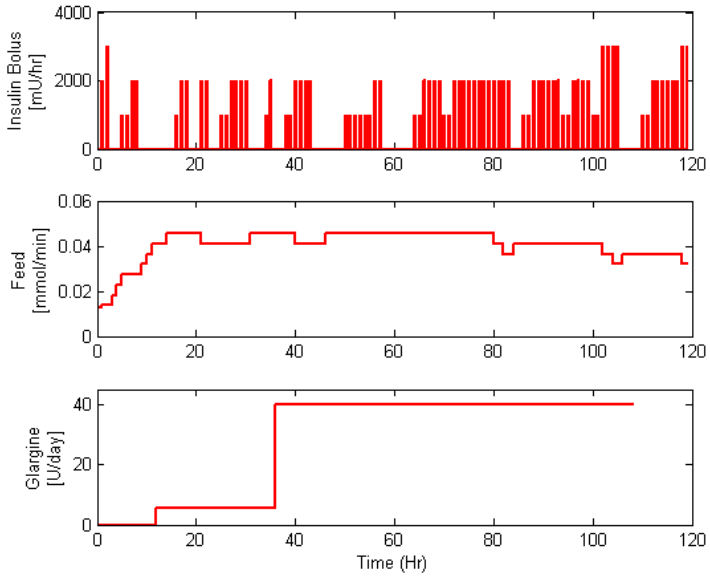


(a) Median MC Error

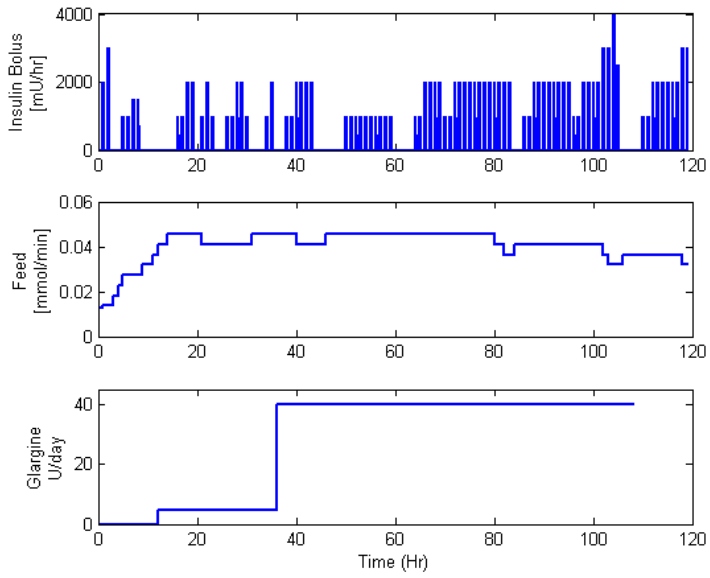


(b) 5th and 95th Percentile MC Error

Figure 7.3 Comparison of BG profile for Patient 5376 simulated 100 runs with and without error. Errors introduced are normally distributed with standard deviation of 5% and max error of ± 4 SDs, with a saturated max of ± 20% BG measurement sensor error and a lognormal distribution variation in Glargine PK model parameters. Figure 7.3(a) compares the actual BG profile in solid blue line, (-) against median of 100 MC error runs shown as blue dotted line, (· · ·). Figure 7.3(b) compares the actual BG profile depicted in solid blue line (-) against the 5th and 95th percentile of 100 MC error. The 5th percentile error is shown in red dotted line, (· · ·) while 95th percentile error is in red dashed line (- -).

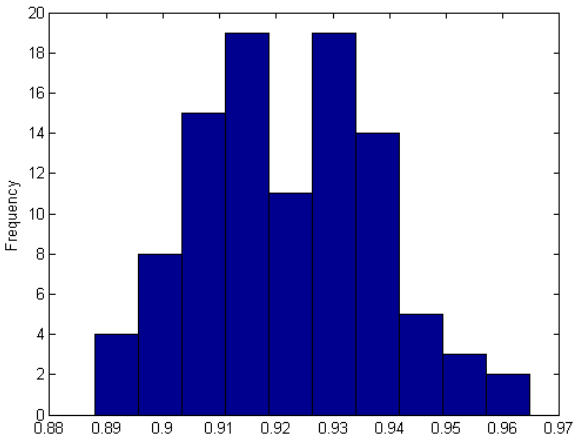


(a) Actual Profile

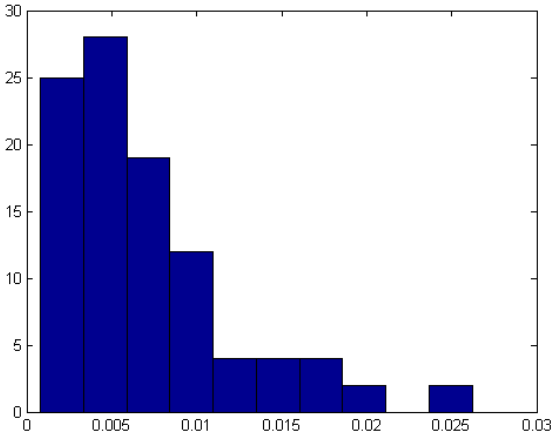


(b) Profile Simulated with MC Error

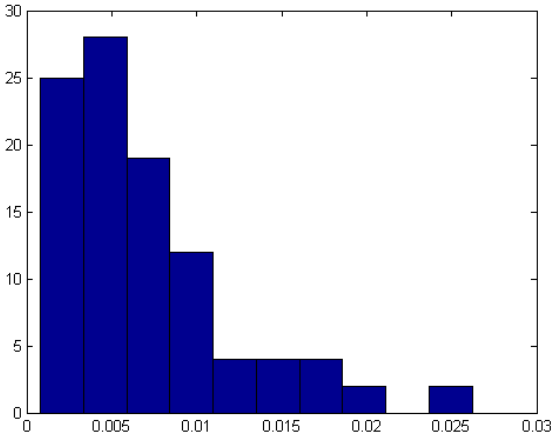
Figure 7.4 Comparison of Patient 5376's profile for simulated 100 runs with and without MC error. Errors introduced are normally distributed with standard deviation of 5% and max error of ± 4 SDs, with a saturated max of ± 20% BG measurement sensor error and a lognormal distribution variation in Glargine PK model parameters. Figure 7.4(a) shows the actual profile without MC error with insulin bolus shown in first panel as solid red line, (-). The middle and last panel are nutrition and Glargine. Figure 7.4(b) is the profile of Patient 5376 with MC error runs. The first, middle and last panel are IV insulin bolus, nutrition and subcutaneous Glargine.



(a) α_{gla}



(b) $k_{1,gla}$



(c) $k_{prep,gla}$

Figure 7.5 Histogram plot of the actual variability of Glargine pharmacokinetics parameters, $k_{prep,gla}$, $k_{1,gla}$, and α_{gla}, and the frequency they occurred in the 100 Monte Carlo simulations for Patient 5376. Figure 7.5(a) shows the distributions of α_{gla}, Figure 7.5(b) is the distribution of $k_{1,gla}$ and Figure 7.5(c) is the distribution plot of $k_{prep,gla}$.

7.3 Discussion

With TGC protocol that highly depends on patient's hourly glycaemic levels, fast easy to use devices are often employed to read blood glucose level, along with the accepted loss of sensor performance error compared to the gold-standard lab tests. Some studies have cited measurement error as one factor in the difficulty found in achieving adequate control of blood glucose levels [Wilinska et al., 2008; Shulman et al., 2007] leading to a push for better or more frequent bedside sensors. However, the experience of SPRINT [Chase et al., 2008c] and several others has been that measurement error was not a factor or was not cited, despite using bedside glucose meters with standard errors of 7-15% depending on blood glucose level, or blood gas analysers with much lower errors of 1-3%.

With respect to designing and implementing TGC the analysis and results do reinforce the need to account for variability in a patient-specific fashion, and to do so in the protocol directly and by design. Inter-patient variability can be very high across cohorts, especially in medical ICUs. Intra-patient variability can also be significant as patients evolve dynamically. More specifically, while the 5–95% range of results shown for one patient and typical of the others, was acceptable, the range seen is still quite wide clinically. The rest of the simulated virtual patients are shown in the Appendix section, comparing the BG profile with and without MC error at the 5th, median and 95th percentile.

Hence, another outcome of this analysis is that successful TGC mandates a protocol that is adaptive across a wide range of insulin resistance to provide equal glycemic control to each patient. This variability requires any TGC algorithm to be able to identify and manage these variations in their interventions to provide TGC. More specifically, to obtain clinical and mortality benefits from TGC, a protocol must provide tight control with minimal risk of hypo-or hyper-glycemia. This goal must also be achieved for all patients from the 5th to the 95th percentile.

Monte Carlo simulations allow sensor errors to be generated in the data, as well as adding valid physiological variances. Both are instrumental in portraying the real and potentially quite different physiological conditions of patients, which mix with sensor errors to yield the glycaemic variability observed clinically. In particular, in any clinical environment, there is variability between and within individuals, as well as measurement error in sensor devices. Importantly, only

a validated *in silico* virtual patient environment offers the ability to include the effect of parameter uncertainty and sensor error in the virtual simulations.

The specific Monte Carlo results presented confirm the robustness of SPRINT-1U+Glargine protocol to realistic, physiological variations and sensor errors. The results clearly define, quantitatively the impact of variability across the cohort and for individual patients. Finally, the results provide a qualitative measure robustness and confidence in the developed protocol.

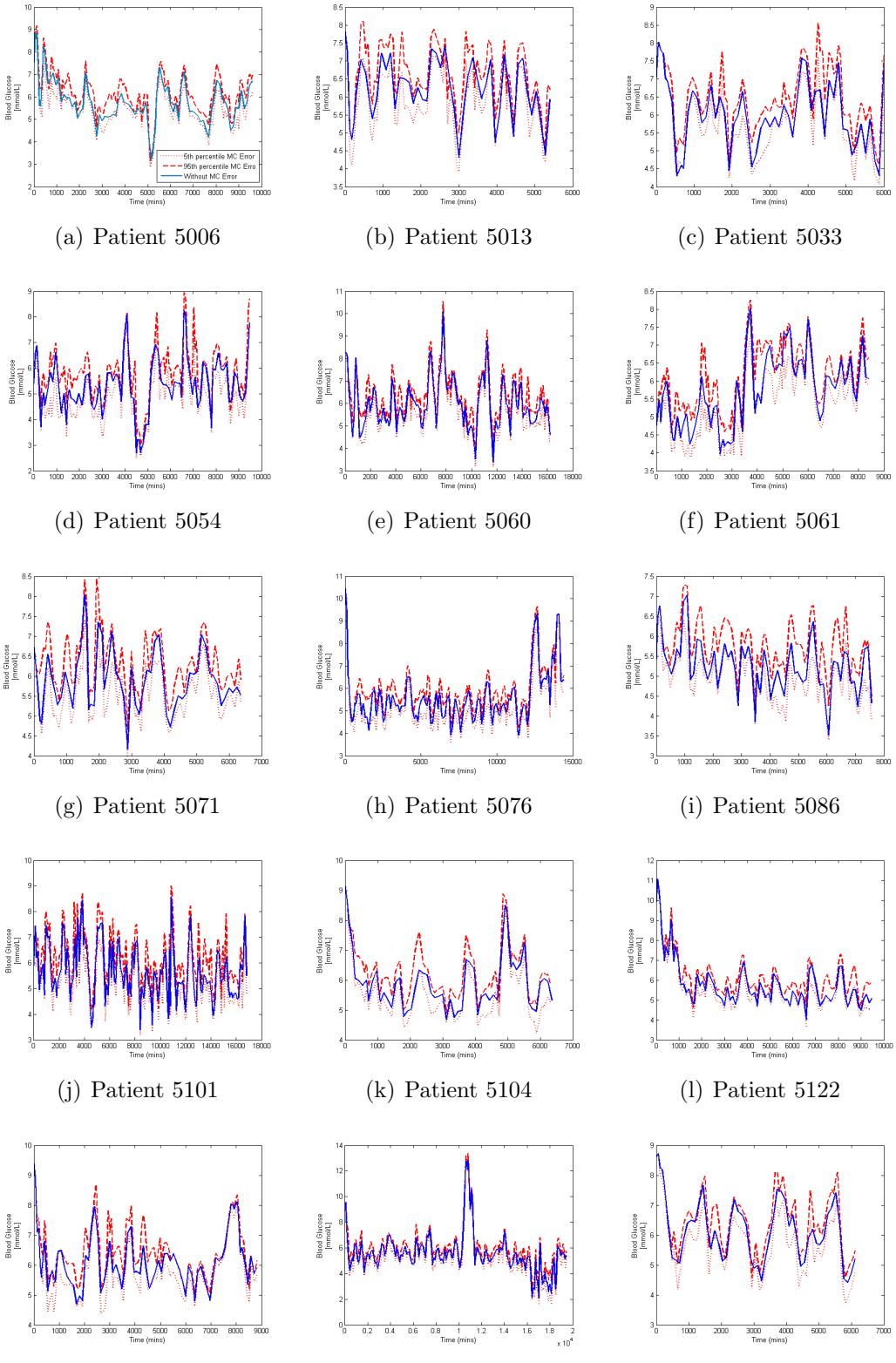
However, in reality, it is reasonable to assume that more uncertainties could be present. More parameters apart from the varied parameters in the simulation may differ, varying from patient to patient. For example, patients who are transferred to less acute wards, might start eating as their condition improves, which is a clinical variation that is not in the scope of this protocol or analysis. Hence, there would be definite uncertainties in the glucose absorption model as the exact amount of nutrition would have to be an estimate. Even nutrition given enterally or parenteral nutrition have different physiological response. Thus, for future work MC analysis on nutrition would best to be considered. Equally, and more relevantly, clinical changes in condition, such as the loss of intravenous access or large intervention timing errors may play a risk. However, prior analysis have shown that these are either unavoidable or secondary effects [LeCompte, 2009]. Overall, the varied model parameters and sensor error in this analysis, are the most distinct to adequately represent a true physiological clinical environment

7.4 Conclusion

An effective, robust and safe subcutaneous transition protocol is presented. *In silico* analysis allowed accurate quantification of nursing effort and other performance measurements of the protocol. Monte Carlo analysis provide a further valuable approach to test the robustness of the control protocol and robustness is achieved with the ability of the control protocol accounting for possible BG concentrations and variations of Glargine absorption. In particular, the middle 50% of likely outcomes indicates that there is no change of clinical significance in control quality and nursing effort. The 5–95% range shows that safety and acceptable control quality are guaranteed. Overall, the results meet the primary

goal of the analysis to justify a clinical pilot study to fully validate these *in silico* results.

7.5 Appendix



(a) Patient 5006 (b) Patient 5013 (c) Patient 5033

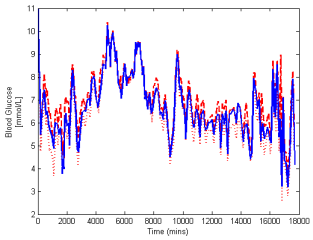
(d) Patient 5054 (e) Patient 5060 (f) Patient 5061

(g) Patient 5071 (h) Patient 5076 (i) Patient 5086

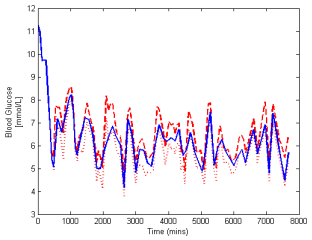
(j) Patient 5101 (k) Patient 5104 (l) Patient 5122

(m) Patient 5124 (n) Patient 5149 (o) Patient 5158

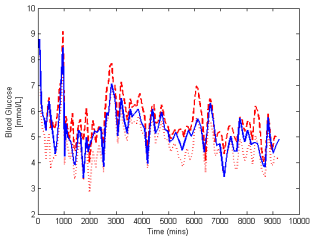
Figure 7.6 Comparison of the actual BG profile for depicted in solid blue line (-) against the 5th and 95th percentile of 100 MC error. The 5th percentile error is shown in red dotted line, $(\cdots)$ while 95th percentile error is in red dashed line (- -).



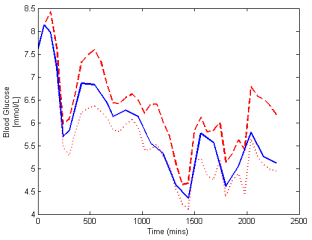
(a) Patient 5173



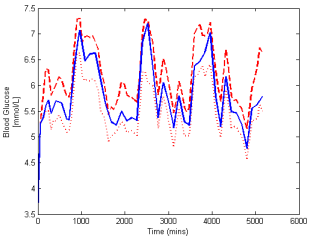
(b) Patient 5188



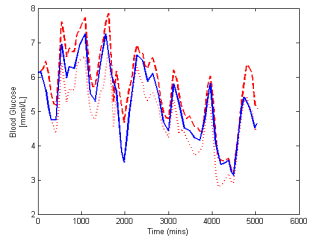
(c) Patient 5207



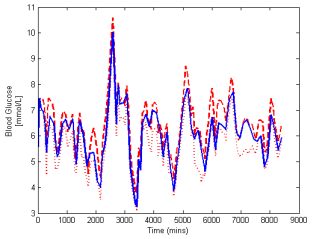
(d) Patient 5233



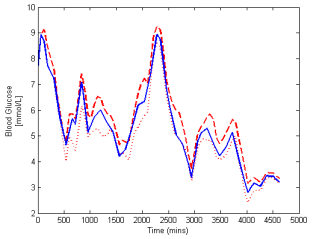
(e) Patient 5276



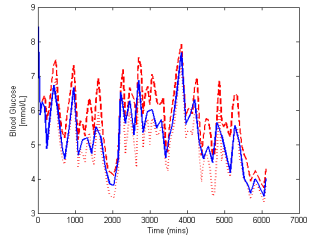
(f) Patient 5279



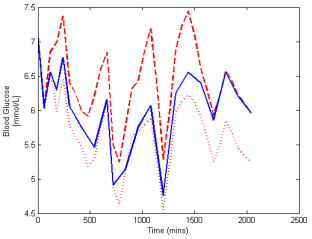
(g) Patient 5280



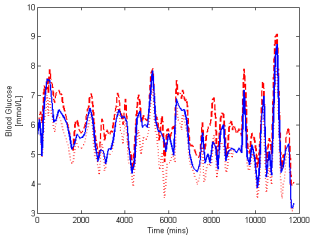
(h) Patient 5288



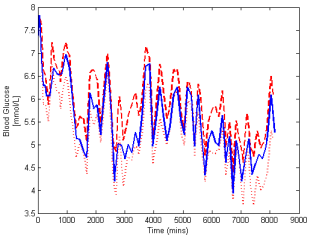
(i) Patient 5299



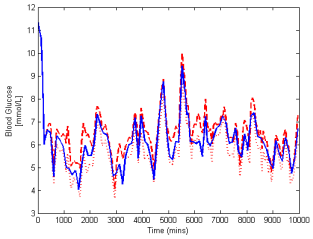
(j) Patient 5310



(k) Patient 5315



(l) Patient 5317



(m) Patient 5351

Figure 7.7 Comparison of the actual BG profile depicted in solid blue line (-) against the 5th and 95th percentile of 100 MC error. The 5th percentile error is shown in red dotted line, (· · ·) while 95th percentile error is in red dashed line (- -)

Chapter 8

Conclusions

The use of intensive insulin therapy in less acute wards, or a transition protocol following patients discharged from ICU to less acute wards, is not a common practice in hospitals. Although it is generally agreed that better control of blood glucose levels does improve patient outcome, most hospitals still take a relaxed approach towards hyperglycaemia particularly in the less acute wards where nursing resources are at a premium. Elevated blood glucose levels in this area are not considered a major issue. Nursing resources, non-standard glycaemic target and hypoglycaemia are among the limiting factors.

However, there is significant room for improvement. Monitoring the transition of less critically ill patients requires systematic care to achieve normoglycaemia without over burdening the nurses. Hospitals need to have a protocol to address the management of hyperglycaemia and there are good clinical reasons that less critically-ill patients should be given the same level of glycaemic management as ICU patients received.

For TGC to provide equal control to all patients, the glycaemic control protocol must be patient-specific and able to directly account for patient-variation, measurement frequency and nutritional intake. In essence, it is the interaction between insulin sensitivity, S_I, the insulin and nutrition administered, and the patients variability over time that determines glycemic outcome in TGC in any situation or ward. Not knowing or understanding any of these variables means patient-specific control cannot be delivered.

This research developed a comprehensive, more physiologically relevant glucose-insulin dynamic system, named the ICING (Intensive Control Insulin-Nutrition

Glycaemic) model for this problem. It modified and added existing subcutaneous insulin models to account for this low burden delivery avenue. The overall model is the integration of two clinically-validated models created and/or extended in this research.

The ICING model, compared to its predecessor is more distinctly expressed, in particular with respect to glucose utilisation, endogenous production, and a more robust glucose absorption model for digestion. To account for the body's ability to eliminate insulin, this model also includes explicit pathways of insulin clearance and utilisation, namely liver, kidney and saturable cell degradation. Specifying a specific clearance, instead of defining clearance as the sum of individual clearances (hepatic, renal, cell, etc), is necessary in making accurate physiological predictions, particularly if using slow release or infused insulins that the prior ICU focused models did not manage as well. With the knowledge gained of specific clearance values, a better informed decision can be made for insulin dosage adjustments that maintain average plasma concentration.

Identification of critical constant population parameters is carried out parametrically, optimising one hour forward prediction error, thus avoiding model identifiability issues. The identified population values are $p_G = 0.006$ 1/min, $EGP_b = 1.16$ mmol/min and $n_I = 0.003$ 1/min, all of which are within reported physiological ranges. The relatively low value of n_I may indicate a significantly impaired transcapillary transport for patients who are critically ill, which is a unique result. It is expected that the value of n_I would increase once patients are recovering. However, this would not affect the developed ICING model, since the effect would simply be translated towards an increased S_I. Hence, the model's fitting and prediction ability would not be compromised since ultimately the prediction accuracy is critical. Even so, the range of n_I must be within a physiological range to ensure a good fitting and predictive ability. All these brings us back to how studies on plasma insulin and C-peptide are needed.

Model validation was evaluated by fitting and prediction error. The model achieves median fitting error <1% in data from 173 patients (N = 42,941 hours in total) who received insulin while in the ICU and stayed for more than 72 hours. More importantly, the median per-patient one-hour ahead prediction error is a very low 2.80% [IQR: 1.18, 6.41%]. A sensitivity study, as part of an internal model validation to assess the reliability of the model, confirms the validity

of limiting time-varying parameters to S_I only. It is significant that the 75th percentile prediction error is now within the lower bound of typical glucometer measurement errors of 7–12%, which is better than any other reported model. The result confirms that the new ICING model is suitable for developing model-based insulin therapies, and capable of delivering tight blood glucose control, in a real-time model based control framework with a tight prediction error range.

A TGC protocol should not burden nurses in any ward with round the clock monitoring. Glargine, an insulin analogue known for its long acting time-action profile, is incorporated in designing this glycaemic control protocol. The unique peakless property of Glargine, with its once-daily administration makes it suitable for achieving normoglycaemia in less acute wards, where nursing resources are often limited. Patients in the less acute wards might only require a minimal boost for their impaired glucose-insulin regulatory system, thus Glargine is the ideal basal choice for the basal insulin support of these less acute patients. Other option, such as CSII is not favourable since it is not cost effective, expensive, requires patient's involvement and physicians need to place an order each time dose needs to be adjusted. Moreover, Glargine is known for inducing less hypoglycaemia. Thus, a detailed pharmacokinetics/pharmacodynamics model of the subcutaneous absorption of Glargine was developed.

The model is more physiologically valid compared to a prior model used as fundamental structure with the introduction of Michalis-Menten saturation. An advanced method of model validation is used with an external evaluation, using 4 data sets, apart from the 6 sets of data used to identify the three critical Glargine PK parameters, $k_{prep,gla}$, $k_{1,gla}$, and α_{gla}. The external evaluation method further confirms the validity of the model with independent data sets ranging from data in children to adults. Finally, to account for patient variability in Glargine absorption, a Monte Carlo simulation analysis produced a range of maximal plasma insulin concentration, C_{max} and time to maximal plasma concentration, T_{max} typically seen among patients. Including this variability ensured the model is accurate and robust in protocol design. Hence, the glycaemic control protocol designed with this model could be used to cater for a far broader and wider range of patients.

With these two clinically-validated, physiologically linked models, a complete system of glucose regulation and the interaction between glucose and plasma in-

sulin is available. The source of insulin, either from IV injection or/and subcutaneous Glargine, create a complete system targeted for model-based tight glycaemic control in the less acute wards. The model is able to accurately capture patient's dynamics, and is clinically-validated.

The performance of the ICING and Glargine compartmental model in controlling less critically-ill patient's glycaemic levels are tested *in silico*. *In silico* simulation is an important and integral aspect in the developments of any glycaemic control protocols. It provides the mean for safe and effective development, evaluation and validation prior to a clinical testing. Hence, virtual trials serve as the best platform and instrumental in testing a proposed control protocol for any effects from a known intervention.

Virtual patients results using Glargine on 15 metabolically stable patients totalling to 1,689 hours conclude that Glargine can provide effective blood glucose management provided a patient's stay is longer than 7 days. Glycaemic level on first day alone, is poorly controlled as the concentration of effective interstitial insulin, Q, takes a longer time to build up with Glargine. It is found that the level of Q using Glargine, only reached to the same level as Q in IV boluses, after several days. Methods to raise Q using supraphysiological values of Glargine and priming boluses, resulted in a single case of hypoglycaemia. Although median cohort BG levels improved, these methods are considered to pose a high risk given patients variability and are a fundamental limit in transitioning to this type of subcutaneous insulin.

The ability to achieve tight glycemic control and potentially reduce the risk of death for a given patient will be a function of the ability of the TGC method to manage that patient specifically. More specifically, the benefits of TGC work at an individual level. Only patients who are tightly controlled will receive benefit based on the physiological factors. 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. Thus, based on this work it is critical to manage Glargine and its effect in a patient-specific fashion.

In Chapter 6, performance assessment is concentrated upon per-patient analysis for a subcutaneous transition to Glargine from SPRINT. SPRINT has a superior ability to adapt to inter- patient variability across the patient cohort.

In a move to incorporate a proven clinical protocol, the IV insulin bolus prescribed by SPRINT is combined with daily subcutaneous Glargine in a transition protocol. This combination protocol is designed with the target that eventually Glargine will be the sole insulin used, seamlessly replacing IV insulin bolus from SPRINT as soon as the effective interstitial insulin concentration, Q reached a steady-state. This approach is a first design to transitioning to Glargine in a fashion that alleviates issues with its 3-7 days buildup of concentration in the body.

From the virtual analysis, the SPRINT-1U+Glargine protocol, which is the optimum protocol from all the tested protocols, showed that nursing effort in comparison to the SPRINT clinical data, is significantly reduced while still delivering effective and safe TGC. The nursing effort intensity reduces as patient's stay increases. An hour of reduced work in the per-patient analysis, offers a better opportunity for the nurses to provide better care for the patients. Primarily, patient comfort and satisfaction are improved with less frequent interventions that might disrupt patients sleep pattern, day rest or even patients who are generally uncomfortable having their blood drawn. Without background Glargine, the time needed to provide TGC for the average patient is up to 4 hours. This result provides a good insight into reducing nursing effort associated with labour intensive TGC. The primary implication of this is simply that, Glargine works well in recovering patients, who in real-life are characterized by improving insulin sensitivity until issued discharge.

However, with the limited clinical data in this study, which is sourced from metabolically stable ICU patients, virtual trials were performed on patients who do not always continue to have improved S_I overtime, representing also a realistic scenario. Despite meeting the definition of metabolic stability, these patient's overall S_I is still quite dynamic. In the period where S_I is high and improving, Glargine alone without SPRINT IV bolus can well manage patient's glycaemic level. However, once these periods deteriorate, the expected continuation to Glargine alone did not materialize in the simulations. The continued requirement from SPRINT IV insulin, is thus highly likely to be patient-specific and a function of the TGC protocol, as well. However, in terms of safety, there is no incidence of hypoglycaemia allowing safe management for all patients.

Undoubtly, there is a need to firmly establish the importance of TGC not

only in the ICU, but extending TGC to less acute wards as well. Glycaemic control should be a standard of care in hospitals and not an option based on the physiological evidence to date of the negative effects of hyperglycaemia. Instead of abandoning any work to improve glycaemic control in the less acute wards either for fear of hypoglycaemia, or rather for viewing glycaemic control as not a major cause of concern, there should be a growing effort to develop a clear strategy. We need to bridge the gap between ICU and less critical wards. The intensity of glycaemic management between critically ill and recovering critically ill patients in from one setting to another should be maintained. A randomized controlled study is pivotal to support the need of TGC in the less acute wards. A protocol designed and pilot tested in a single unit, might not be solid enough to cover the expected variability seen among patients. For example, different units (hospitals) have different regimes and practice, which vary considerably. Nevertheless, any move initiated towards reducing the risk and harm of hypo/hypergylcaamia while at the same time reducing the clinical burden in less acute wards is pivotal.

This research thus, provides a first analysis and design of these type of protocols and clearly highlights both the potential for success, as well as the main difficulties. Beginning from the model development of glucose-insulin regulatory system, to the subcutaneous absorption model of Glargine, the overall results of this thesis provide a promising approach to achieve and maintain normoglycaemia from the ICU to the less acute wards.

To ensure the overall research will reached broader treatment, saving lives and in future create potential commercial opportunity, the next important step is to have the research clinically verified. Thus, in the following and final chapter under 'Future Avenues', a 'Proof-of-concept study of Glargine as basal insulin support in the intensive care and the high dependency units and validation of an Insulin Glargine pharmacokinetics model' is presented.

Chapter 9

Future Avenues: Proof of Concept Clinical Protocol

Ethics from Upper South B Regional Ethics Committee has been granted for a pilot clinical trial based on this study, 'Proof-of-concept study of Glargine as basal insulin support in the intensive care and the high dependency units and validation of an Insulin Glargine pharmacokinetics model'. The pilot trial will be conducted in the near future at the Christchurch ICU Hospital, New Zealand. This proof-of-concept study will be the first study to validate Glargine pharmacokinetics in a clinical setting and thus the models developed in this research. In addition, it will be the first study to test the effectiveness of Glargine as basal insulin support for recovering critically ill patients. This research will be very valuable for future development of TGC protocols in ICU and less acute wards.

Glargine pharmacokinetics in this study have been identified from 4 studies consisting of 6 plasma insulin data sets. However, the model fitted and model generated plasma insulin from Glargine have been made using a standard weight of an 80kg patient. Hence, improvements can be made by fixing the Glargine dose to each patient's body weight, as it may be affected by patient's physical condition, either obese or lean. Insulin kinetics are delayed in obese patients. Issues concerning the actual duration of Glargine's basal effect and action can also be resolved. The patient's natural insulin released following a meal will also be studied. This data alone will be valuable for future development of glycaemic control protocols in the less acute wards.

Equally, it will treat patients who are eating meals as opposed to getting constant nasogastric nutrition support in the ICU. Meal models in this study accommodate nasogastric feed. Thus, models that could accommodate patients

who started eating normally are clearly needed. Such models would be quite a challenge since it would be difficult to estimate exactly how much food has been consumed by the patient, thus presenting a significant variability issue.

The proposed proof-of-concept study will also be a first clinical step towards developing a comprehensive sytem for maintaning tight glycaemic control outside of the ICU. The focus, as discussed in previous chapters, would be on the transition from using relatively labour intensive intravenous insulin in the ICU to less intensive, longer acting, subcutaneous insulin in the less acute wards. Consequently, the benefit of tight glycaemic control can be extended from the ICU to the less acute wards, improving overall inpatient health care. There have been only 2-3 such studies and none have proven particularly successful. Thus, the study outcomes will be an important contribution to knowledge in their own right.

The potential significance of this proof-of-concept study, which basically addresses the limitations of the models developed in this study thus:

- Determination of the exact insulin pharmacokinetics of Glargine in the critically ill.
- Knowledge on addressing the difficult transition between intravenous and subcutaneous insulin.
- Better insight into the endogenous insulin production of critically ill patients, particularly upon meal consumption, of which almost nothing is known.

To validate the Glargine pharmacokinetics model developed in this study, plasma insulin and C-peptide levels in study participants following a subcutaneous Glargine injection will be studied. Blood samples will be collected by nursing staffs while medical staff will assist in collecting non-routine laboratory tests, such as C-peptide and insulin levels. Patient's blood sample will be taken for assays of plasma insulin and C-peptide levels on the first two days of them being given Glargine. Blood samples will be taken for a further 2 days once patients start to receive meals (as oppose to nasogastric feed). Apart from patients benefitting from intensive blood glucose monitoring, study of the endogenous insulin

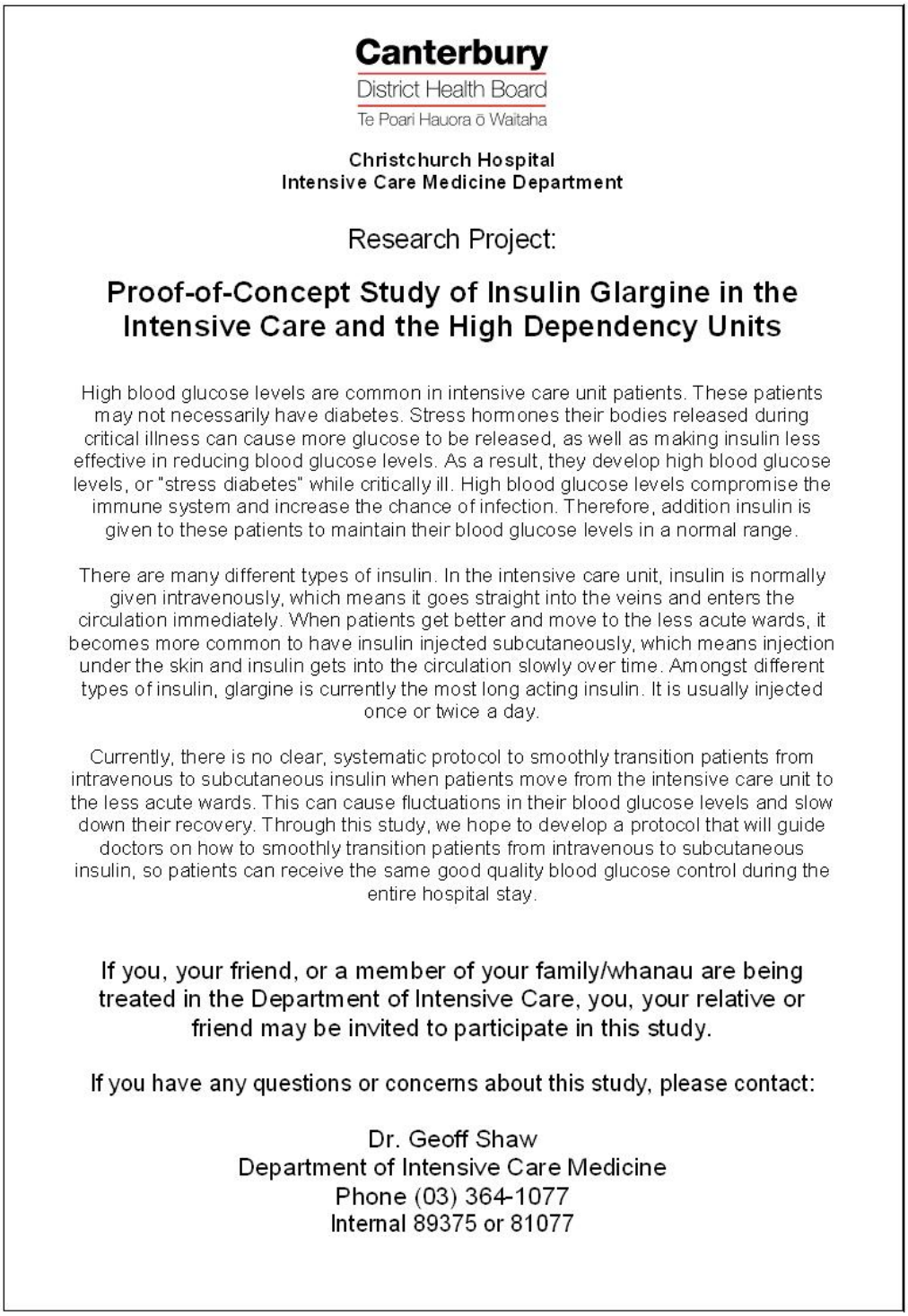
response may be of benefit for diagnostic of potential diabetes. Information such as blood glucose, insulin and nutrition will be taken from patient charts. Photos of meals will be taken before and after mealtime to estimate the actual nutritional intake, particularly the amount of carbohydrate and non-carbohydrate calories consumed. Although the method is not high-tech, it is the best that could be done at this stage before an actual, reliable meal model can be developed. Equally, it will help us understand the variability of (likely) consumption and thus the glycaemic variability one might need to robust to. The quality of glycaemic control for patients transferring to less acute wards from ICU with and without Glargine will be assessed based on the duration of blood glucose levels within a clinically desirable range, safety or from hypoglycaemic events, amount of total insulin given, and nutrition requirements.

The data collected will lead to a comprehensive glycaemic control system that allows a smooth transition between intravenous and subcutaneous insulin throughout a patient's hospital stay. In addition, the study will examine the current state of glycaemic control outside of ICU thus providing a platform from which to improve.

Patients will be screened and consented for the study in the intensive care unit. Patients will then be divided into the Glargine group and the Control group using permuted block randomisation with 10 patients per block. All patients will have blood glucose levels tested, naso-gastric feeding rate adjusted, and intravenous insulin injection given every 1–2 hours as per the standard ICU practice using SPRINT. Figure 9.3 shows the recruitment invitation for interested patients to participate in this proof-of-concept study.

The inclusion criteria include:

- Critically ill patients who are on SPRINT glycaemic control protocol.
- Presence of an arterial line.
- Stable hourly insulin requirement, equal or less than 3U of insulin per hour, for at least 12 hours.
- Stable feed rate, equal or greater than 60% of the calculated goal feed. (Goal feed is calculated using individual patient's age, gender and frame size.)



Canterbury
District Health Board
Te Poari Hauora ō Waitaha

Christchurch Hospital
Intensive Care Medicine Department

Research Project:

Proof-of-Concept Study of Insulin Glargine in the Intensive Care and the High Dependency Units

High blood glucose levels are common in intensive care unit patients. These patients may not necessarily have diabetes. Stress hormones their bodies released during critical illness can cause more glucose to be released, as well as making insulin less effective in reducing blood glucose levels. As a result, they develop high blood glucose levels, or "stress diabetes" while critically ill. High blood glucose levels compromise the immune system and increase the chance of infection. Therefore, addition insulin is given to these patients to maintain their blood glucose levels in a normal range.

There are many different types of insulin. In the intensive care unit, insulin is normally given intravenously, which means it goes straight into the veins and enters the circulation immediately. When patients get better and move to the less acute wards, it becomes more common to have insulin injected subcutaneously, which means injection under the skin and insulin gets into the circulation slowly over time. Amongst different types of insulin, glargine is currently the most long acting insulin. It is usually injected once or twice a day.

Currently, there is no clear, systematic protocol to smoothly transition patients from intravenous to subcutaneous insulin when patients move from the intensive care unit to the less acute wards. This can cause fluctuations in their blood glucose levels and slow down their recovery. Through this study, we hope to develop a protocol that will guide doctors on how to smoothly transition patients from intravenous to subcutaneous insulin, so patients can receive the same good quality blood glucose control during the entire hospital stay.

If you, your friend, or a member of your family/whanau are being treated in the Department of Intensive Care, you, your relative or friend may be invited to participate in this study.

If you have any questions or concerns about this study, please contact:

Dr. Geoff Shaw
Department of Intensive Care Medicine
Phone (03) 364-1077
Internal 89375 or 81077

Figure 9.1 Recruitment invitation to patients who are interested to participate in the 'Proof-of-concept study of Glargine as basal insulin support in the intensive care and the high dependency units and validation of an Insulin Glargine pharmacokinetics model'.

- No acute renal failure (creatinine <250 μmol/L)
- Equal to or less than 5000ml positive fluid balance given as intravenous bolus in the past 24 hours, estimated from their original weight, indicating stable interstitial volume.
- Resolving multiple organ failure (Sequential Organ Failure Score SOFA $\leq$ 6) [Vincent et al., 1996].

Patients who are not expected to survive more than 48 hours will be excluded from the study.

The Control group is for comparing blood glucose levels only and no non-standard ICU blood samples will be taken. The overall protocol in flowchart form is shown in Figure 9.2. Consistency is important in the administration of Glargine. Hence, the first dose is always given in the morning, and the timing has to be maintained until patient is discharged. After patients are discharged from the ICU, data from less acute wards relating to blood glucose control will be retrospectively gathered.

The study aims to obtain complete results from at least 10 ICU patients in the Glargine group. Results will be considered complete if the patient has completed Glargine+Meal study for 2 days. More than 20 patients (up to 60) are expected to be enrolled in the study as patients might not complete the entire study procedure. Patients can request withdrawal from the study at any time and individual study may be terminated if there are unexpected clinical deterioration. This is a proof-of-concept study. Hence, powered statistical significance is not a concern and not applicable to this study.

All potential patients will be identified daily by the clinician according to the entry criteria. When study patients are transferred to wards, a personnel will be arranged to continue the study in the wards. The intensive clinicians will approach the patient or if patient cannot consent him/herself a family/representative will be approached. Study information sheet that explains the study detail will be given to patient/family. Written consents are preferable from the patients or any family members. If written consents are impractical, clinical staff is to obtain oral consent and sign on behalf with a second signature from a witness. Figure 9.3 is the Glargine consent form that will be given to patients,

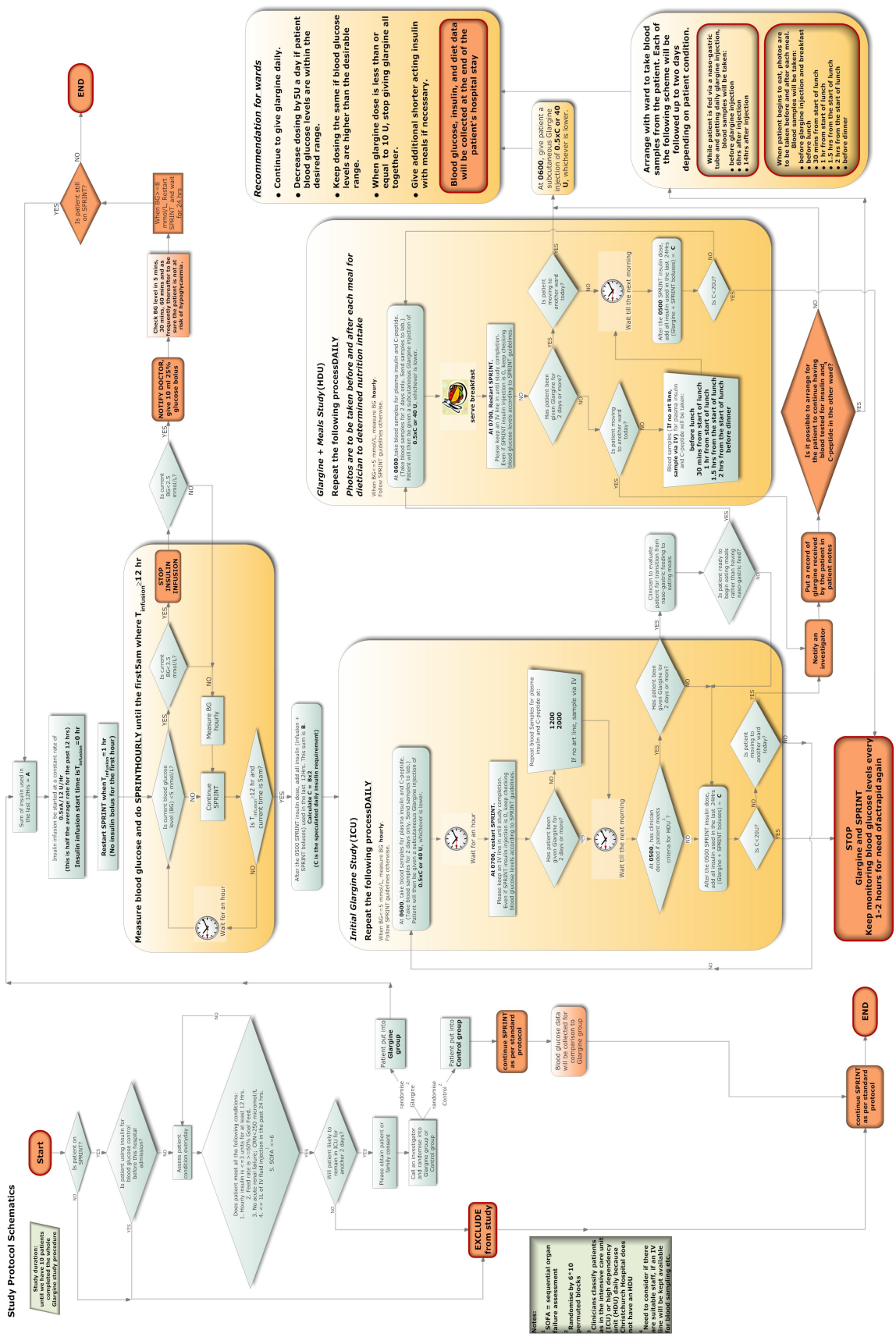


Figure 9.2 Study Protocol Schematic of 'Proof-of-concept study of Glargine as basal insulin support in the intensive care and the high dependency units and validation of an Insulin Glargine pharmacokinetics model'.

while Figure 9.4 is the consent form for relative/family or friend acting on behalf of patients.

A variety of disciplines are brought together in this study, each bringing their own expertise in the area to create a novel transition protocol that would benefit ICU and less acute patients. These includes:

- Intensive Care Specialist, Surgeon.
- Engineering Professor and students of all levels.
- Physicians.
- Dietician.
- Nurses.

Results from this pilot study would enable an expansion of patient population with a larger clinical trial. All the guidelines should be followed accordingly, with caution. There is a risk of hypoglycaemia, as when any form of insulin is being used. However, the current protocol, SPRINT is shown to be very safe regarding low blood glucose levels. Glargine in this study is used conservatively, and it is not expected to cause serious low blood glucose levels. If hypoglycaemia occurs at any time, insulin will be stopped and an injection of glucose may be given to quickly restore blood glucose level to a normal level.

The aim to investigate the use of Glargine in recovering intensive care patients will lead to the development of a sytematic protocol guiding the transition between intravenous insulin in the ICU, to subcutaneous insulin in the less acute wards, that will directly benefit to this particular group. The study will be conducted using the paper-based SPRINT protocol, for ease of nurses. In the near future, a computerized hand-held device protocol might replace the paper-based protocol as pilot study incorporating the computerized SPRINT protocol is in progress at the moment. The study, known as STAR trial uses a computer tablet instead of a hand-held device.

Incorporating a computerized decision support would reduce the chances of human error and protocol violations. Moreover, equipping the computerized protocols with alarms alerting dangerous blood glucose levels and such, would be

Canterbury
District Health Board
Te Poari Hauora ō Waitaha

Statement by Patient

Proof-of-Concept Study of Insulin Glargine as Basal Insulin Support in the Intensive Care and the High Dependency Units

Name of Participant			
Ethnicity of Participant			
English	I wish to have an interpreter	Yes	No
Maori	E hiahia ana ahau ki tetahi kaiwhakamaori/kaiwhaka pakeha korero	Ae	Kao
Samoan Tongan Cook Island	Oute mana'o e iai se fa'amatala upu 'Oku fiema'u ha fakatonulea Ka inangaro au I tetai tangata uri reo	Ioe Io Ae	Leai Ikai Kare
Niuean	Fia manako au ke fakaaoga e tagata fakahokohoko vagahau	E	Nakai

I have read and I understand the information sheet dated _____ for people taking part in the study designed to help develop a insulin transition protocol for patients transferring from the Intensive Care Unit to less acute wards. I have had the opportunity to discuss this study. I am satisfied with the answers I have been given.

I understand that taking part in this study is voluntary and that I may withdraw from the study at any time if I wish. This will not affect my continuing health care.

I understand that my participation in this study is confidential and that no material which could identify me will be used in any reports on this study.

I understand that the treatment will be stopped if it should appear to be harmful.

I understand the compensation provisions for this study.

I know whom to contact if I have any side effects to the study or if anything occurs which I consider a reason to withdraw from the study.

I know whom to contact if I have any questions about the medication of the study.

This study has been given ethical approval by the Upper South B Regional Ethics Committee. This means that the Committee may check at any time that the study is following appropriate ethical procedures.

I would like a copy of the results of the study. (circle) **YES / NO**

I agree to my GP being informed of my participation in this study. (circle) **YES / NO**

Signed: _____ Date: _____/_____/ 20_____
dd mm yy

Printed Name :_____
Address for results:_____

Figure 9.3 Glargine consent form for patients to participate in the 'Proof-of-concept study of Glargine as basal insulin support in the intensive care and the high dependency units and validation of an Insulin Glargine pharmacokinetics model'.

Statement by Relative, Friend, Family/Whanau

Proof-of-Concept Study of Insulin Glargine as Basal Insulin Support in the Intensive Care and the High Dependency Units

Name of Participant			
Ethnicity of Participant			
English Maori	I wish to have an interpreter E hiahia ana ahau ki tetahi kaiwhakamaori/kaiwhaka pakeha korero	Yes Ae	No Kao
Samoan	Oute mana'o e iai se fa'amatala upu	Ioe	Leai
Tongan	'Oku fiema'u ha fakatonulea	Io	Ikai
Cook Island	Ka inangaro au I tetai tangata uri reo	Ae	Kare
Niuean	Fia manako au ke fakaaoga e tagata fakahokohoko vagahau	E	Nakai

I have read and I understand the information sheet dated 14 July 2010 for people taking part in the study designed to help develop a insulin transition protocol for patients transferring from the Intensive Care Unit to less acute wards. I have had the opportunity to discuss this study. I am satisfied with the answers I have been given.

I believe my relative/friend would have chosen and consented to participate in this study if he/she had been able to understand the information that I have received and understood.

I understand that taking part in this study is voluntary and that my relative/friend may withdraw from the study at any time if he/she wishes. This will not affect his/her continuing health care.

I understand that his/her participation in this study is confidential and that no material which could identify him/her will be used in any reports on this study.

I understand that the treatment will be stopped if it should appear to be harmful.

I understand the compensation provisions for this study.

I know whom to contact if my relative/friend has any side effects to the study or if anything occurs which I think he/she would consider a reason to withdraw from the study.

I know whom to contact if I have any questions about the medication of the study.

This study has been given ethical approval by the Upper South B Regional Ethics Committee. This means that the Committee may check at any time that the study is following appropriate ethical procedures.

I/my relative/friend would like a copy of the results of the study. (circle) **YES / NO**

I believe my relative/friend would agree to his/her GP being informed of his/her participation in this study. (circle) **YES / NO**

Signed: _____ Date: _____/_____/ 20_____
dd mm yy

Printed Name: _____ Relationship to Participant: _____

Address for results: _____

Figure 9.4 Glargine consent form for relative/friend/family of patients to participate in the 'Proof-of-concept study of Glargine as basal insulin support in the intensive care and the high dependency units and validation of an Insulin Glargine pharmacokinetics model'.

Statement by Investigator

I _____(name of investigator) declare that this study is in the potential health interest of the group of patients of which _____(name of participant) is a member and that participation in this study is not adverse to _____'s (name of participant) interests.

I confirm that if the participant becomes competent to make an informed choice and give an informed consent, full information will be given to him/her as soon as possible, and his/her participation will be explained. If the participant makes an informed choice to continue in the study, written consent will be requested and if the participant does not wish to continue in the study, he/she will be withdrawn.

Signed: _____ Investigator

Date: _____/_____/20_____ dd mm yy

Statement by Participant (If applicable at a later stage)

I, _____ *(name of participant)* having been fully informed about this study agree to continue taking part in it.

Signed, Participant:	**Date:**

Figure 9.5 Glargine statement form for investigators approving patients to participate in the 'Proof-of-concept study of Glargine as basal insulin support in the intensive care and the high dependency units and validation of an Insulin Glargine pharmacokinetics model'.

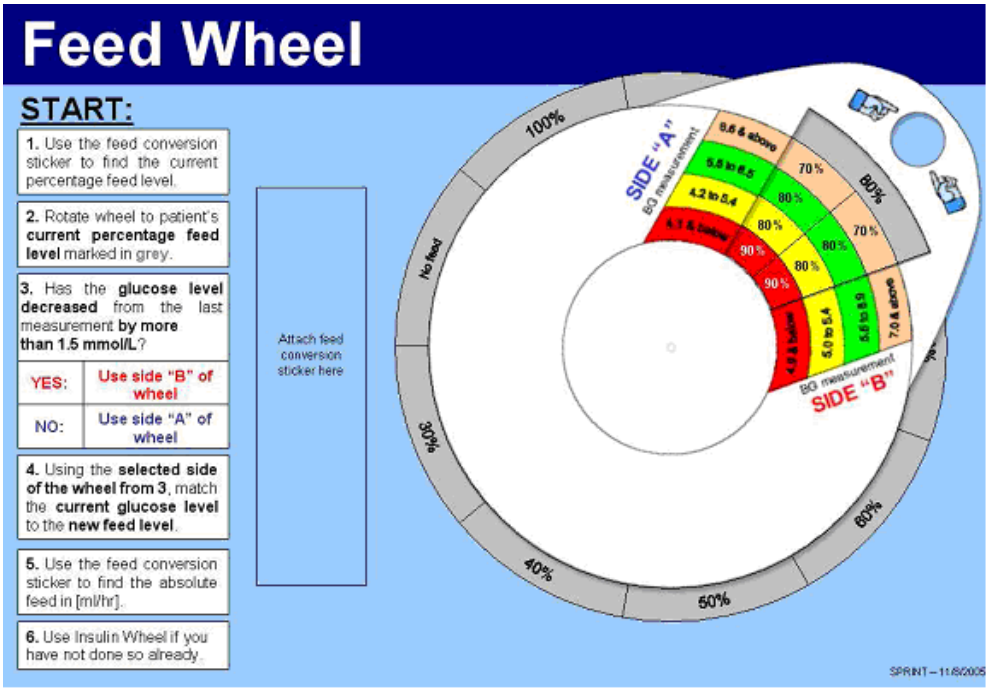
safer. Early recognition of hypo/hyperglycaemia would prevent adverse events. Records of blood glucose measurements, amount of insulin administered and nutrition could be better managed by linking straight to hospital database for each patient electronic records, another step to minimize human error. Handwritten records might be misread if written or rather scribbled due to time constraint as the measurements needed to be taken frequently. Significantly, a direct uploading to patient database would do wonders to future studies. Time spent in extracting data from large number of patients involved in study would be greatly reduced as there are substantial amount of data. Finally, a more important factor on the success of TGC implementation is educating staff, particularly nurses. Each hospitals need to develop a program on equipping staff with the importance of TGC and necessary responsibilities held by each nurses, so that they would be better informed and would familiarize themselves around standards of care with TGC. Particularly, with control protocols involving transition of care, there needs to be a dynamic between the ICU nurses and less critical ward's nurses. A clinical practice change is not an easy task, people often resist being taken out of their own comfort zone. A good example is the sliding-scale insulin, which has continued to survive despite the well known fact, that more often than not, sliding-scale doesn't work. The reason is simply because of the hospital culture that had developed for so many years. The doctors in charged learned from the previous doctors, and the cycle continues.

However, there are other issues surrounding the study as well. Patients who are discharged from the ICU show a sign in progress. Besides starting to eat normally, these patients would also have more movement than before, either assisted or own their own. Mild exercise, such as leg or arm movement, might be performed to reduce muscle weakness. Patients would also begin to walk. These physical rehabilitation activities would have an effect on patient's own glucose regulation as increased insulin sensitivity has been associated with exercise. To what extent this effect of exercise will be seen, is still unknown. However, studies have shown physical activities are linked with better management in blood glucose among patients. Hence, in the future a model that could predict the changes or improvement in glycaemic control associated with exercise, would benefit from studies of the data from patients in this group. In fact, among the critically ill, there have been physical rehabilitation performed on patients, thus avoiding muscle wasting which is common as patients are confined to bed for a considerable length of time.

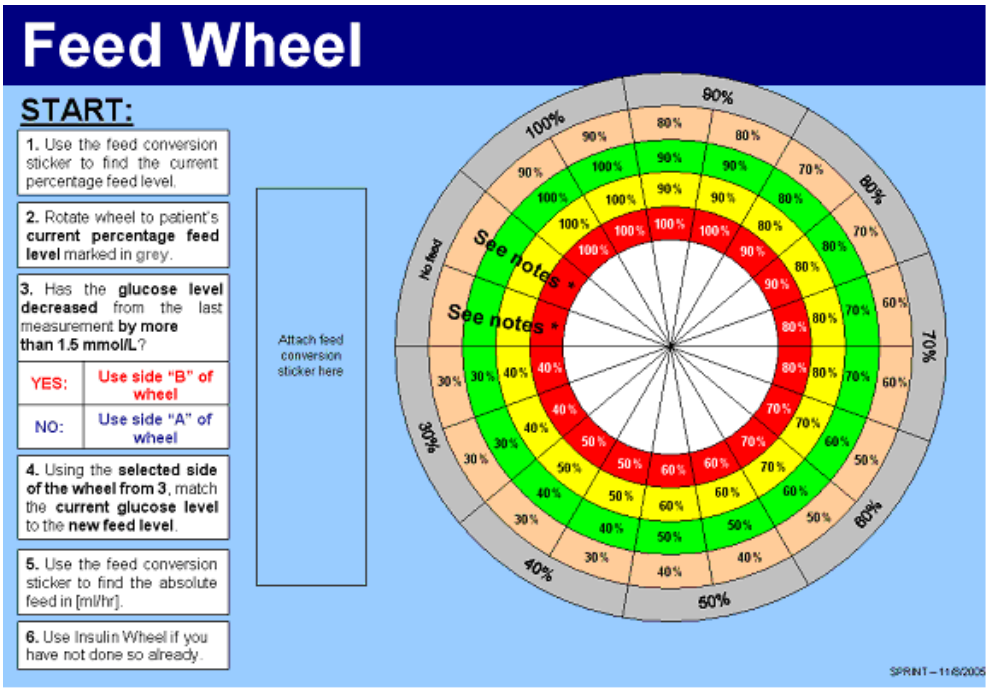
Overall, this study is the next major step forward from the research in this thesis. The size and complexity of the design of this study and in its implementation precluded its inclusion in this thesis. Thus, it represents the main step necessary in this overall research are for both modeling and clinical research aspects. This thesis provide potential directions and goals for designing and implementing the next generation of TGC protocols in the less acute wards. Proper treatment and consideration of the issues surrounding TGC in the less acute wards, particularly in protocol design and implementation should result in increased success of TGC protocols in practice.

Appendix A

Appendix

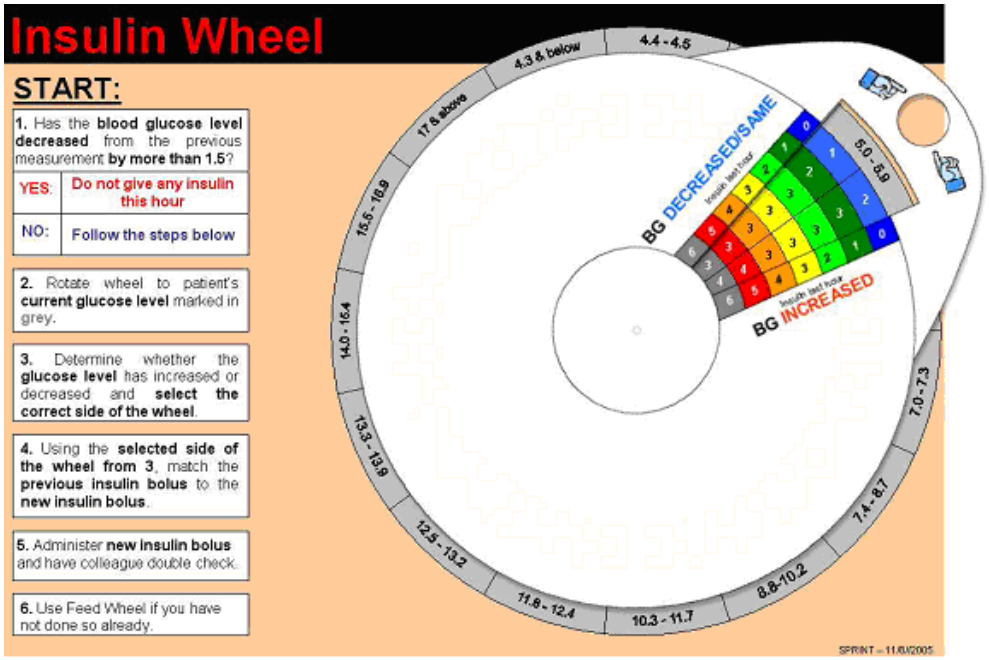


(a)

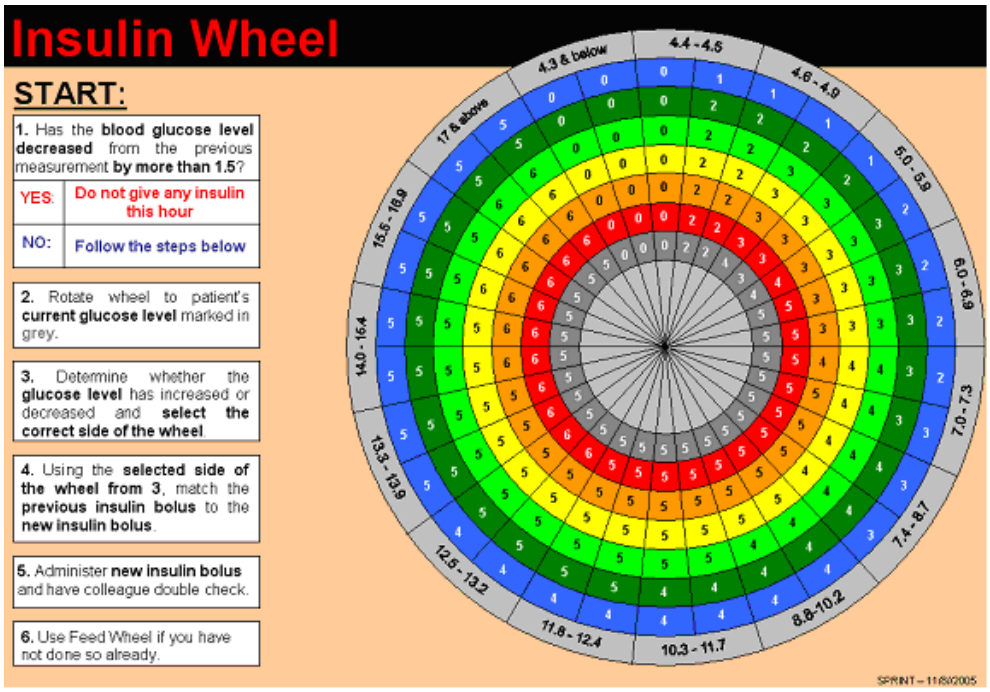


(b)

Figure A.1 The paper based SPRINT protocol used in this research in the transition protocol with long-acting subcutaneous Glargine, developed from computerized insulin-nutrition glycaemic control implemented through 2 look-up tables. SPRINT feed wheel from [Lonergan et al., 2006b] with (A.1(a)) and without dial (A.1(b)) .



(a)



(b)

Figure A.2 The paper based SPRINT protocol used in this research in the transition protocol with long-acting subcutaneous Glargine, developed from computerized insulin-nutrition glycaemic control implemented through 2 look-up tables. SPRINT insulin wheel [Lonergan et al., 2006b] with (A.2(a)) and without dial (A.2(b)).

References

Ackerman, E., Rosevear, J., and McGuckin, W. (1964). A mathematical model of the glucose-tolerance test. *Physics in Medicine and Biology*, 9:203.

Ader, M. and Bergman, R. N. (1990). Peripheral effects of insulin dominate suppression of fasting hepatic glucose production. *Am J Physiol Endocrinol Metab*, 258(6):E1020–1032.

Ahrens, C., Barletta, J., Kanji, S., Tyburski, J., Wilson, R., Janisse, J., and Devlin, J. (2005). Effect of low-calorie parenteral nutrition on the incidence and severity of hyperglycemia in surgical patients: a randomized, controlled trial. *Critical care medicine*, 33(11):2507–2512.

Aiken, L., Clarke, S., Sloane, D., Lake, E., and Cheney, T. (2008). Effects of hospital care environment on patient mortality and nurse outcomes. *The Journal of nursing administration*, 38(5):223.

Ali, N., O'Brien Jr, J., Dungan, K., Phillips, G., Marsh, C., Lemeshow, S., Connors Jr, A., and Preiser, J. (2008). Glucose variability and mortality in patients with sepsis*. *Critical care medicine*, 36(8):2316.

American College of Endocrinology (2007). American Association of Clinical Endocrinologists medical guidelines for clinical practice for the management of diabetes mellitus. *Endocrine Pract*, 13(suppl 1):59–63.

American Diabetes Association (2008). Standards of Medical Care in Diabetes. *Diabetes Care*, 31(suppl 1):S12–S54.

Andersen, K. and Højbjerre, M. (2005). A population-based bayesian approach to the minimal model of glucose and insulin homeostasis. *Statistics in medicine*, 24(15):2381–2400.

Andersen, S. K., Gjedsted, J., Christiansen, C., and Tønnesen, E. (2004). The roles of insulin and hyperglycemia in sepsis pathogenesis. *Journal of Leukocyte Biology*, 75(3):413–21.

Aragon, D. (2006). Evaluation of nursing work effort and perceptions about blood glucose testing in tight glycemic control. *American Journal of Critical Care*, 15(4):370–377.

Araujo-Vilar, D., Rega-Liste, C. A., Garcia-Estevez, D. A., Sarmiento-Escalona, F., Mosquera-Tallon, V., and Cabezas-Cerrato, J. (1998). Minimal model of glucose metabolism: modified equations and its application in the study of insulin sensitivity in obese subjects. *Diabetes Research and Clinical Practice*, 39(2):129–41.

Arif, S. and Escaño, A. (2010). Barriers to Implementing an Insulin Order Form In a Non-ICU Medical Unit. *Pharmacy and Therapeutics*, 35(1):30.

Arkray (2001). Glucocard^{TM} test strip 2 data sheet.

Arnold, L. and Keller, D. (2009). Hyperglycemia Management in Non-critically Ill Hospitalized Patients. *Journal of Pharmacy Practice*, 22(5):467.

Avogaro, A., Vicini, P., Valerio, A., Caumo, A., and Cobelli, C. (1996). The hot but not the cold minimal model allows precise assessment of insulin sensitivity in NIDDM subjects. *Am J Physiol*, 270(3 Pt 1):E532–40.

Bagshaw, S., Bellomo, R., Jacka, M., Egi, M., Hart, G., George, C., et al. (2009a). The impact of early hypoglycemia and blood glucose variability on outcome in critical illness. *Critical Care*, 13(3):R91.

Bagshaw, S., Webb, S., Delaney, A., George, C., Pilcher, D., Hart, G., and Bellomo, R. (2009b). Very old patients admitted to intensive care in Australia and New Zealand: a multi-centre cohort analysis. *Critical Care*, 13(2):R45.

Baker, E., Janaway, C., Philips, B., Brennan, A., Baines, D., Wood, D., and Jones, P. (2006). Hyperglycaemia is associated with poor outcomes in patients admitted to hospital with acute exacerbations of chronic obstructive pulmonary disease. *Thorax*, 61(4):284.

Bardell, T., Legare, J., Buth, K., Hirsch, G., and Ali, I. (2003). ICU readmission after cardiac surgery. *European Journal of Cardio-Thoracic Surgery*, 23(3):354–359.

Baron, A. D., Brechtel, G., Wallace, P., and Edelman, S. V. (1988). Rates and tissue sites of non-insulin- and insulin-mediated glucose uptake in humans. *Am J Physiol*, 255(6 Pt 1):E769–74.

Barth, E., Albuszies, G., Baumgart, K., Matejovic, M., Wachter, U., Vogt, J., Radermacher, P., and Calzia, E. (2007a). Glucose metabolism and catecholamines. *Critical care medicine*, 35(9):S508.

Barth, M., Oyen, L., Warfield, K., Elmer, J., Evenson, L., Tescher, A., Kuper, P., Bannon, M., Gajic, O., and Farmer, J. (2007b). Comparison of a nurse initiated insulin infusion protocol for intensive insulin therapy between adult surgical trauma, medical and coronary care intensive care patients. *BMC Emergency Medicine*, 7(1):14.

Bastard, J., Maachi, M., Van Nhieu, J., Jardel, C., Bruckert, E., Grimaldi, A., Robert, J., Capeau, J., and Hainque, B. (2002). Adipose tissue IL-6 content correlates with resistance to insulin activation of glucose uptake both in vivo and in vitro. *Journal of Clinical Endocrinology & Metabolism*, 87(5):2084.

Beardsall, K., Vanhaesebrouck, S., Ogilvy-Stuart, A., Ahluwalia, J., Vanhole, C., Palmer, C., Midgley, P., Thompson, M., Cornette, L., Weissenbruch, M., et al. (2007). A randomised controlled trial of early insulin therapy in very low birth weight infants," NIRTURE"(neonatal insulin replacement therapy in Europe). *BMC pediatrics*, 7(1):29.

Becker, R., Frick, A., Teichert, L., Nosek, L., Heinemann, L., Heise, T., and Rave, K. (2008). Fluctuation and reproducibility of exposure and effect of insulin glargine in healthy subjects*. *Diabetes, Obesity and Metabolism*, 10(11):1105–1113.

Berger, M., Cüppers, H., Hegner, H., Jörgens, V., and Berchtold, P. (1982). Absorption kinetics and biologic effects of subcutaneously injected insulin preparations. *Diabetes Care*, 5(2):77.

Bergman, R. (1997). New concepts in extracellular signaling for insulin action: the single gateway hypothesis. *Recent progress in hormone research*, 52:359.

Bergman, R. (2002). Pathogenesis and prediction of diabetes mellitus: lessons from integrative physiology. *The Mount Sinai journal of medicine*, 69(5):280–290.

Bergman, R., Phillips, L., and Cobelli, C. (1981). Physiologic evaluation of factors controlling glucose tolerance in man: measurement of insulin sensitivity and beta-cell glucose sensitivity from the response to intravenous glucose. *J Clin Invest*, 68(6):1456–1467.

Bergman, R., Prager, R., Volund, A., and Olefsky, J. (1987). Equivalence of the insulin sensitivity index in man derived by the minimal model method and the euglycemic glucose clamp. *J Clin Invest*, 79(3):790–800.

Binder, C. (1969). Absorption of injected insulin. *Acta Pharmacologica et toxicologica*, 27(S2):1–83.

Binder, C., Lauritzen, T., Faber, O., and Pramming, S. (1984). Insulin pharmacokinetics. *Diabetes Care*, 7(2):188.

Bingham, E. M., Hopkins, D., Smith, D., Pernet, A., Hallett, W., Reed, L., Marsden, P. K., and Amiel, S. A. (2002). The role of insulin in human brain glucose metabolism: an 18fluoro-deoxyglucose positron emission tomography study. *Diabetes*, 51(12):3384–90.

Bistrian, B. (2001). Hyperglycemia and infection: Which is the chicken and which is the egg? *J Parenter Enteral Nutr*, 25(4):180–181.

Blakemore, A., Wang, S.-H., Le Compte, A. J., Shaw, G. M., Wong, X.-W., Lin, J., Lotz, T., Hann, C. E., and Chase, J. G. (2008). Model-based insulin sensitivity as a sepsis diagnostic in critical care. *Journal of Diabetes Science and Technology*, 2(3):468–177.

Bodenlenz, M., Schaupp, L., Druml, T., Sommer, R., Wutte, A., Schaller, H., Sinner, F., Wach, P., and Pieber, T. (2005). Measurement of interstitial insulin in human adipose and muscle tissue under moderate hyperinsulinemia by means of direct interstitial access. *American Journal of Physiology- Endocrinology And Metabolism*, 289(2):E296.

Bolie, V. (1961). Coefficients of normal blood glucose regulation. *Journal of Applied Physiology*, 16(5):783.

Bradley, C. (2002). Intensive insulin therapy in critically ill patients. *Intensive & critical care nursing: the official journal of the British Association of Critical Care Nurses*, 18(2):128.

Bradley, D., Poulin, R., and Bergman, R. (1993). Dynamics of hepatic and peripheral insulin effects suggest common rate-limiting step in vivo. *Diabetes*, 42(2):296.

Brownlee, M. (2001). Biochemistry and molecular cell biology of diabetic complications. *Nature*, 414(6865):813–20.

Brunkhorst, F. M., Engel, C., Bloos, F., Meier-Hellmann, A., Ragaller, M., Weiler, N., Moerer, O., Gruendling, M., Oppert, M., Grond, S., Olthoff, D., Jaschinski, U., John, S., Rossaint, R., Welte, T., Schaefer, M., Kern, P., Kuhnt, E., Kiehntopf, M., Hartog, C., Natanson, C., Loeffler, M., Reinhart, K., and for the German Competence Network Sepsis (SepNet) (2008). Intensive insulin therapy and pentastarch resuscitation in severe sepsis. *The New England Journal of Medicine*, 358(2):125–39.

Bruttomesso, D., Costa, S., and Baritussio, A. (2009). Continuous subcutaneous insulin infusion (csii) 30 years later: Still the best option for insulin therapy. *Diabetes/metabolism research and reviews*, 25(2):99–111.

Bryant, N. J., Govers, R., and James, D. E. (2002). Regulated transport of the glucose transporter GLUT4. *Nat Rev Mol Cell Biol*, 3(4):267–77.

Campbell, R., White, J., Levien, T., and Baker, D. (2001). Insulin glargine. *Clinical therapeutics*, 23(12):1938–1957.

Camu, F. and Rasio, E. (1972). Peripheral glucose uptake in relation to physiological levels of plasma and lymph insulin. *European Journal of Clinical Investigation*, 2(3):188–194.

Capes, S., Hunt, D., Malmberg, K., and Gerstein, H. (2000). Stress hyperglycaemia and increased risk of death after myocardial infarction in patients with and without diabetes: a systematic overview. *The Lancet*, 355(9206):773–778.

Care, D. (2003). Report of the expert committee on the diagnosis and classification of diabetes mellitus. *Diabetes Care*, 26(1).

Carson, E. and Cobelli, C. (2001). *Modelling methodology for physiology and medicine*. Academic Pr.

Castillo, C., Bogardus, C., Bergman, R., Thuillez, P., and Lillioja, S. (1994). Interstitial insulin concentrations determine glucose uptake rates but not insulin resistance in lean and obese men. *Journal of Clinical Investigation*, 93(1):10.

Caumo, A. and Cobelli, C. (1993a). Hepatic glucose production during the labeled ivgtt: estimation by deconvolution with a new minimal model. *American Journal of Physiology-Endocrinology And Metabolism*, 264(5):E829–E841.

Caumo, A. and Cobelli, C. (1993b). Hepatic glucose production during the labeled IVGTT: estimation by deconvolution with a new minimal model. *Am J Physiol*, 264(5 Pt 1):E829–41.

Caumo, A., Vicini, P., Zachwieja, J., Avogaro, A., Yarasheski, K., Bier, D., and Cobelli, C. (1999). Undermodeling affects minimal model indexes: insights from a two-compartment model. *American Journal of Physiology- Endocrinology And Metabolism*, 276(6):E1171.

Chambrier, C., Laville, M., K, R. B., Odeon, M., Boulétreau, P., and Beylot, M. (2000). Insulin sensitivity of glucose and fat metabolism in severe sepsis. *Clin Sci*, 99(4):321–8.

Chan, P., Rozmanc, M., Seiden, I., and Kwan, J. (2009). Evaluation of a point-of-care glucose meter for general use in complex tertiary care facilities. *Clinical biochemistry*, 42(10-11):1104–1112.

Chase, H., Dixon, B., Pearson, J., Fiallo-Scharer, R., Walravens, P., Klingensmith, G., Rewers, M., and Garg, S. (2003). Reduced hypoglycemic episodes and improved glycemic control in children with type 1 diabetes using insulin glargine and neutral protamine Hagedorn insulin. *The Journal of pediatrics*, 143(6):737–740.

Chase, J., Andreassen, S., Pielmeier, U., Hann, C. E., McAuley, K., and Mann, J. (2009). A glucose-insulin pharmacodynamic surface modeling validation and comparison of metabolic system models. *Biomedical Signal Processing and Control*, 4(4):355–363.

Chase, J., Le Compte, A., Suhaimi, F., Shaw, G., Lynn, A., Lin, J., Pretty, C., Razak, N., Parente, J., Hann, C., et al. (2010a). Tight glycemic control in critical care-The leading role of insulin sensitivity and patient variability: A review and model-based analysis. *Computer Methods & Programs in Biomedicine*.

Chase, J., Pretty, C., Pfeifer, L., Shaw, G., Preiser, J., Le Compte, A., Lin, J., Hewett, D., Moorhead, K., and Desaive, T. (2010b). Organ failure and tight glycemic control in the SPRINT study. *Critical Care*, 14(4):R154.

Chase, J., Shaw, G., Lotz, T., LeCompte, A., Wong, J., Lin, J., Lonergan, T., Willacy, M., and Hann, C. (2007). Model-based insulin and nutrition administration for tight glycaemic control in critical care. *Current drug delivery*, 4(4):283–296.

Chase, J., Suhaimi, F., Penning, S., Preiser, J., Le Compte, A., Lin, J., Pretty, C., Shaw, G., Moorhead, K., and Desaive, T. (2010c). Validation of a model-based virtual trials method for tight glycemic control in intensive care. *BioMedical Engineering OnLine*, 9(1):84.

Chase, J. G., Andreassen, S., Jensen, K., and Shaw, G. M. (2008a). Impact of human factors on clinical protocol performance: a proposed assessment framework and case examples. *Journal of Diabetes Science and Technology*, 2(3):409–16.

Chase, J. G., Le Compte, A. J., Shaw, G. M., Blakemore, A., Wong, J., Lin, J., and Hann, C. E. (2008b). A benchmark data set for model-based glycemic control in critical care. *Journal of Diabetes Science and Technology*, 2:584–594.

Chase, J. G., Shaw, G., Le Compte, A. J., Lonergan, T., Willacy, M., Wong, X., Lin, J., Lotz, T., Lee, D., and Hann, C. E. (2008c). Implementation and evaluation of the SPRINT protocol for tight glycaemic control in critically ill patients: a clinical practice change. *Crit Care*, 12(2):R49.

Chase, J. G., Shaw, G., Lin, J., Doran, C., Hann, C. E., Robertson, M., Browne, P., Lotz, T., Wake, G., and Broughton, B. (2005). Adaptive bolus-based targeted glucose regulation of hyperglycaemia in critical care. *Med Eng Phys*, 27(1):1–11.

Chase, J. G., Shaw, G., Wong, X., Lotz, T., Lin, J., and Hann, C. E. (2006). Model-based glycaemic control in critical care - a review of the state of the possible. *Biomedical Signal Processing & Control*, 1(1):3–21.

Chase, J. G. and Shaw, G. M. (2007). Is there more to glycaemic control than meets the eye? *Critical Care*, 11(4):160.

Chase, J. G., Shaw, G. M., Lin, J., Doran, C. V., Bloomfield, M., Wake, G. C., Broughton, B., Hann, C., and Lotz, T. (2004). Impact of insulin-stimulated glucose removal saturation on dynamic modelling and control of hyperglycaemia. *International Journal of Intelligent Systems Technologies and Applications (IJISTA)*, 1(1/2):79–94.

Chee, F., Fernando, T., Savkin, A., and Van Heeden, V. (2004). Expert PID control system for blood glucose control in critically ill patients. *Information Technology in Biomedicine, IEEE Transactions on*, 7(4):419–425.

Chee, F., Fernando, T., and van Heerden, P. (2003). Closed-loop glucose control in critically ill patients using continuous glucose monitoring system (CGMS) in real time. *Information Technology in Biomedicine, IEEE Transactions on*, 7(1):43–53.

Cherrington, A. (1999). Banting lecture 1997. control of glucose uptake and release by the liver in vivo. *Diabetes*, 48(5):1198–214.

Cherrington, A. D., Edgerton, D., and Sindelar, D. K. (1998). The direct and indirect effects of insulin on hepatic glucose production in vivo. *Diabetologia*, 41(9):987–96.

Chiasson, J., Atkinson, R., Cherrington, A., Keller, U., Sinclair-Smith, B., Lacy, W., and Liljenquist, J. (1980). Effects of insulin at two dose levels on gluconeogenesis from alanine in fasting man* 1. *Metabolism*, 29(9):810–818.

Ciaraldi, T., Carter, L., Seipke, G., Mudaliar, S., and Henry, R. (2001). Effects of the long-acting insulin analog insulin glargine on cultured human skeletal muscle cells: comparisons to insulin and IGF-I. *Journal of Clinical Endocrinology & Metabolism*, 86(12):5838.

Clarke, W., Becker, D., Cox, D., Santiago, J., and White, N. (1988). Evaluation of a new system for self blood glucose monitoring*,**. *Diabetes Research and Clinical Practice*, 4(3):209–213.

Cobelli, C., Caumo, A., and Omenetto, M. (1999). Minimal model SG overestimation and SI underestimation: improved accuracy by a Bayesian two-compartment model. *Am J Physiol*, 277(3 Pt 1):E481–488.

Cobelli, C., Toffolo, G., and Foster, D. (1992). Tracer-to-tracee ratio for analysis of stable isotope tracer data: link with radioactive kinetic formalism. *American Journal of Physiology- Endocrinology And Metabolism*, 262(6):E968.

Cohen, M., Boyle, E., Delaney, C., and Shaw, J. (2006). A comparison of blood glucose meters in Australia. *Diabetes research and clinical practice*, 71(2):113–118.

Cohen, P. J., Alexander, S. C., Smith, T. C., Reivich, M., and Wollman, H. (1967). Effects of hypoxia and normocarbia on cerebral blood flow and metabolism in conscious man. *Journal of Applied Physiology*, 23(2):183–9.

Coyle, M. (2001). Transfer anxiety: preparing to leave intensive care. *Intensive and Critical Care Nursing*, 17(3):138–143.

Critchell, C., Savarese, V., Callahan, A., Aboud, C., Jabbour, S., and Marik, P. (2007). Accuracy of bedside capillary blood glucose measurements in critically ill patients. *Intensive care medicine*, 33(12):2079–2084.

Cryer, P., Davis, S., and Shamoon, H. (2003). Hypoglycemia in diabetes. *Diabetes Care*, 26(6):1902.

Dalla Man, C., Caumo, A., Basu, R., Rizza, R., Toffolo, G., and Cobelli, C. (2004). Minimal model estimation of glucose absorption and insulin sensitivity from oral test: validation with a tracer method. *American Journal of Physiology-Endocrinology and Metabolism*, 287(4):E637–E643.

Danne, T., Lüpke, K., Walte, K., von Schuetz, W., and Gall, M. (2003). Insulin detemir is characterized by a consistent pharmacokinetic profile across age-groups in children, adolescents, and adults with type 1 diabetes. *Diabetes Care*, 26(11):3087.

Dartois, C., Lemenuel-Diot, A., Laveille, C., Tranchand, B., Tod, M., and Girard, P. (2007). Evaluation of uncertainty parameters estimated by different population PK software and methods. *Journal of Pharmacokinetics and Pharmacodynamics*, 34(3):289–311.

Davidson, P., Steed, R., and Bode, B. (2005). Glucommander A computer-directed intravenous insulin system shown to be safe, simple, and effective in 120,618 h of operation. *Diabetes Care*, 28(10):2418–2423.

De La Rosa, G., Donado, J., Restrepo, A., Quintero, A., González, L., Saldarriaga, N., Bedoya, M., Toro, J., Velásquez, J., Valencia, J., Arango, C., Aleman, P., Vasquez, E., Chavarriaga, J., Yepes, A., Pulido, W., Cadavid, C., and Grupo de Investigacion en Cuidado intensivo: GICI-HPTU (2008). Strict glycaemic control in patients hospitalised in a mixed medical and surgical intensive care unit: a randomised clinical trial. *Critical Care*, 12(5):R120.

Deepak, P., Sunitha, K., Nagaraj, J., Sanjukta, A., and Bhattacharyya, A. (2003). Inpatient management of diabetes: survey in a tertiary care centre. *Postgraduate medical journal*, 79(936):585.

DeFronzo, R. and Ferrannini, E. (1991). Insulin resistance. a multifaceted syndrome responsible for NIDDM, obesity, hypertension, dyslipidemia, and atherosclerotic cardiovascular disease. *Diabetes Care*, 14(3):173–94.

Der Voort, P., Feenstra, R., Bakker, A., Heide, L., Boerma, E., and Der Horst, I. (2006). Intravenous glucose intake independently related to intensive care unit and hospital mortality: an argument for glucose toxicity in critically ill patients. *Clinical endocrinology*, 64(2):141–145.

Derouich, M. and Boutayeb, A. (2002). The effect of physical exercise on the dynamics of glucose and insulin. *Journal of Biomechanics*, 35(7):911–917.

Desai, D., March, R., and Watters, J. (1989). Hyperglycemia after trauma increases with age. *The Journal of Trauma*, 29(6):719.

Docherty, P. D., Chase, J. G., Lotz, T., Hann, C. E., Shaw, G. M., Berkeley, J., Mann, J. I., and McAuley, K. A. (2009). DISTq: An iterative analysis of glucose data for low-cost, real-time and accurate estimation of insulin sensitivity. *The Open Medical Informatics Journal*, 3:65–76.

Doran, C., Chase, J., Shaw, G., Moorhead, K., and Hudson, N. (2004a). Automated insulin infusion trials in the intensive care unit. *Diabetes Technology & Therapeutics*, 6(2):155–165.

Doran, C., Hudson, N., Moorhead, K., Chase, J. G., Shaw, G., and Hann, C. E. (2004b). Derivative weighted active insulin control modelling and clinical trials for ICU patients. *Med Eng Phys*, 26(10):855–66.

Dortch, M., Mowery, N., Ozdas, A., Dossett, L., Cao, H., Collier, B., Holder, G., Miller, R., and May, A. (2008). A computerized insulin infusion titration protocol improves glucose control with less hypoglycemia compared to a manual titration protocol in a trauma intensive care unit. *Journal of Parenteral and Enteral Nutrition*, 32(1):18.

Dossett, L., Cao, H., Mowery, N., Dortch, M., Morris, J., and May, A. (2008). Blood glucose variability is associated with mortality in the surgical intensive care unit. *The American Surgeon*, 74(8):679–685.

Duckworth, W. and Kitabchi, A. (1981). Insulin metabolism and degradation. *Endocrine Reviews*, 2(2):210.

Duckworth, W. C., Bennett, R. G., and Hamel, F. G. (1998). Insulin degradation: progress and potential. *Endocr Rev*, 19(5):608–24.

Dungan, K., Braithwaite, S., and Preiser, J. (2009). Stress hyperglycaemia. *The Lancet*, 373(9677):1798–1807.

Dunn, C., Plosker, G., Keating, G., McKeage, K., and Scott, L. (2003). Insulin glargine: an updated review of its use in the management of diabetes mellitus. *Drugs*, 63(16):1743–1778.

Egi, M., Bellomo, R., Stachowski, E., French, C., and Hart, G. (2006). Variability of blood glucose concentration and short-term mortality in critically ill patients. *Anesthesiology*, 105(2):244–52.

Egi, M., Bellomo, R., Stachowski, E., French, C., Hart, G., Taori, G., Hegarty, C., and Bailey, M. (2010). Hypoglycemia and outcome in critically ill patients. In *Mayo Clinic Proceedings*, volume 85, page 217. Mayo Clinic.

Elahi, D., Meneilly, G., Minaker, K., Andersen, D., and Rowe, J. (1989). Escape of hepatic glucose production during hyperglycemic clamp. *Am J Physiol*, 257(5 Pt 1):E704–11.

Elia, M., Ceriello, A., Laube, H., Sinclair, A., Engfer, M., and Stratton, R. (2005). Enteral nutritional support and use of diabetes-specific formulas for patients with diabetes. *Diabetes Care*, 28(9):2267–2279.

Elia, M. and De Silva, A. (2008). Tight glucose control in intensive care units: an update with an emphasis on nutritional issues. *Current Opinion in Clinical Nutrition & Metabolic Care*, 11(4):465.

Ellemann, K., Thorsteinsson, B., Fugleberg, S., Feldt-Rasmussen, B., Andersen, O., Gronbaek, P., and Binder, C. (1987). Kinetics of insulin disappearance from plasma in cortisone-treated normal subjects. *Clin Endocrinol (Oxf)*, 26(5):623–628.

Elliott, M. (2006). Readmission to intensive care: a review of the literature. *Australian Critical Care*, 19(3):96–104.

Eslami, S., de Keizer, N., De Jonge, E., Schultz, M., and Abu-Hanna, A. (2008). A systematic review on quality indicators for tight glycaemic control in critically ill patients: need for an unambiguous indicator reference subset. *Critical Care*, 12(6):R139.

Esposito, K., Marfella, R., and Giugliano, D. (2003). Stress hyperglycemia, inflammation, and cardiovascular events. *Diabetes care*, 26(5):1650–1651.

Fahlen, M., Eliasson, B., and Oden, A. (2005). Optimization of basal insulin delivery in Type 1 diabetes: a retrospective study on the use of continuous subcutaneous insulin infusion and insulin glargine. *Diabetic Medicine*, 22(4):382–386.

Ferrannini, E. and Cobelli, C. (1987a). The kinetics of insulin in man. I. general aspects. *Diabetes Metab Rev*, 3(2):335–63.

Ferrannini, E. and Cobelli, C. (1987b). The kinetics of insulin in man. II. role of the liver. *Diabetes Metab Rev*, 3(2):365–97.

Finfer, S. and Heritier, S. (2009). The nice-sugar (normoglycaemia in intensive care evaluation and survival using glucose algorithm regulation) study: statistical analysis plan. *Crit Care Resusc*, 11(1):46–55.

Finney, S., Zekveld, C., Elia, A., and Evans, T. (2003). Glucose control and mortality in critically ill patients. *Jama*, 290(15):2041–2047.

Foster, L. J. and Klip, A. (2000). Mechanism and regulation of GLUT-4 vesicle fusion in muscle and fat cells. *Am J Physiol, Cell Physiol*, 279(4):C877–90.

Freeman, D. et al. (2001). Drug-induced hyperglycaemia. *Annals of Clinical Biochemistry*, 286:1945–8.

Frost, D., Srivastava, M., Jones, R., Nabarro, J., and Sonksen, P. (1973). The kinetics of insulin metabolism in diabetes mellitus. *Postgraduate medical journal*, 49.

Furnary, A., Wu, Y., and Bookin, S. (2004). Effect of hyperglycemia and continuous intravenous insulin infusions on outcomes of cardiac surgical procedures: the Portland Diabetic Project. *Endocrine Practice*, 10:21–33.

Garber, A. J., Moghissi, E. S., and Bransome, E. D. (2004). American college of endocrinology position statement on inpatient diabetes and metabolic control. *Endocr Pract*, 10(Suppl 2):4–9.

Garcia-Compean, D., Jaquez-Quintana, J., Gonzalez-Gonzalez, J., and Maldonado-Garza, H. (2009). Liver cirrhosis and diabetes: risk factors, pathophysiology, clinical implications and management. *World Journal of Gastroenterology: WJG*, 15(3):280.

Garfield, M., Jeffrey, R., and Ridley, S. (2000). An assessment of the staffing level required for a high-dependency unit. *Anaesthesia*, 55(2):137–143.

Gerich, J. (2004). Insulin glargine: long-acting basal insulin analog for improved metabolic control. *Current Medical Research and Opinion®*, 20(1):31–37.

Gerich, J., Becker, R., Zhu, R., and Bolli, G. (2006). Fluctuation of serum basal insulin levels following single and multiple dosing of insulin glargine. *Diabetes technology & therapeutics*, 8(2):237–243.

Getty, L., Hamilton-Wessler, M., Ader, M., Dea, M., and Bergman, R. (1998). Biphasic insulin secretion during intravenous glucose tolerance test promotes optimal interstitial insulin profile. *Diabetes*, 47(12):1941.

Gillies, P., Figgitt, D., and Lamb, H. (2000). Insulin glargine. *Drugs*, 59(2):253–260.

Goldberg, P., Sakharova, O., Barrett, P., Falko, L., Roussel, M., Bak, L., Blake-Holmes, D., Marieb, N., and Inzucchi, S. (2004a). Improving glycemic control in the cardiothoracic intensive care unit: clinical experience in two hospital settings. *Journal of cardiothoracic and vascular anesthesia*, 18(6):690–697.

Goldberg, P., Siegel, M., Sherwin, R., Halickman, J., Lee, M., Bailey, V., Lee, S., Dziura, J., and Inzucchi, S. (2004b). Implementation of a safe and effective insulin infusion protocol in a medical intensive care unit. *Diabetes Care*, 27(2):461–467.

Golightly, L., Jones, M., Hamamura, D., Stolpman, N., and McDermott, M. (2006). Management of diabetes mellitus in hospitalized patients: efficiency and effectiveness of sliding-scale insulin therapy. *Pharmacotherapy*, 26(10):1421–1432.

Green, L. (2002). How many hospital beds? *Journal Information*, 39(4).

Griesdale, D. E. G., de Souza, R. J., van Dam, R. M., Heyland, D. K., Cook, D. J., Malhotra, A., Dhaliwal, R., Henderson, W. R., Chittock, D. R., Finfer,

S., and Talmor, D. (2009). Intensive insulin therapy and mortality among critically ill patients: a meta-analysis including NICE-SUGAR study data. *CMAJ*, 180(8):821–7.

Gudbjörnsdóttir, S., Sjöstrand, M., Strindberg, L., Wahren, J., and Lönnroth, P. (2003). Direct measurements of the permeability surface area for insulin and glucose in human skeletal muscle. *The Journal of Clinical Endocrinology and Metabolism*, 88(10):4559–64.

Guerci, B. and Sauvanet, J. P. (2005). Subcutaneous insulin: pharmacokinetic variability and glycemic variability. *Diabetes Metab*, 31(4 Pt 2):4S7–4S24.

Hall-Smith, J., Ball, C., and Coakley, J. (1997). Follow-up services and the development of a clinical nurse specialist in intensive care. *Intensive and Critical Care Nursing*, 13(5):243–248.

Hann, C. E., Chase, J. G., Lin, J., Lotz, T., Doran, C. V., and Shaw, G. M. (2005). Integral-based parameter identification for long-term dynamic verification of a glucose-insulin system model. *Computer Methods and Programs in Biomedicine*, 77(3):259–70.

Hasselbalch, S. G., Knudsen, G. M., Videbaek, C., Pinborg, L. H., Schmidt, J. F., Holm, S., and Paulson, O. B. (1999). No effect of insulin on glucose blood-brain barrier transport and cerebral metabolism in humans. *Diabetes*, 48(10):1915–21.

Hasselbalch, S. G., Madsen, P. L., Hageman, L. P., Olsen, K. S., Justesen, N., Holm, S., and Paulson, O. B. (1996). Changes in cerebral blood flow and carbohydrate metabolism during acute hyperketonemia. *Am J Physiol*, 270(5 Pt 1):E746–51.

Hasselbalch, S. G., Madsen, P. L., Knudsen, G. M., Holm, S., and Paulson, O. B. (1998). Calculation of the FDG lumped constant by simultaneous measurements of global glucose and FDG metabolism in humans. *J Cereb Blood Flow Metab*, 18(2):154–60.

Hathout, E., Fujishige, L., Geach, J., Ischandar, M., Maruo, S., and Mace, J. (2003). Effect of Therapy with Insulin Glargine (Lantus®) on Glycemic Control in Toddlers, Children, and Adolescents with Diabetes. *Diabetes Technology & Therapeutics*, 5(5):801–806.

Hattori, N., Huang, S.-C., Wu, H.-M., Yeh, E., Glenn, T. C., Vespa, P. M., McArthur, D., Phelps, M. E., Hovda, D. A., and Bergsneider, M. (2003). Correlation of regional metabolic rates of glucose with glasgow coma scale after traumatic brain injury. *J Nucl Med*, 44(11):1709–16.

Heinemann, L. (2002). Variability of insulin absorption and insulin action. *Diabetes technology & therapeutics*, 4(5):673–682.

Heinemann, L. (2008). Variability of Insulin Action: Does It Matter? *Insulin*, 3(1):37–45.

Heinemann, L., Linkeschova, R., Rave, K., Hompesch, B., Sedlak, M., and Heise, T. (2000). Time-action profile of the long-acting insulin analog insulin glargine (hoe901) in comparison with those of nph insulin and placebo. *Diabetes Care*, 23(5):644–9.

Heise, T., Bott, S., Rave, K., Dressler, A., and Heinemann, R. R. L. (2002). No evidence for accumulation of insulin glargine (lantus): a multiple injection study in patients with type 1 diabetes. *Diabet Med*, 19(6):490–5.

Heise, T., Nosek, L., Rønn, B., Endahl, L., Heinemann, L., Kapitza, C., and Draeger, E. (2004). Lower within-subject variability of insulin detemir in comparison to NPH insulin and insulin glargine in people with type 1 diabetes. *Diabetes*, 53(6):1614.

Heise, T. and Pieber, T. (2007). Towards peakless, reproducible and long-acting insulins. An assessment of the basal analogues based on isoglycaemic clamp studies. *Diabetes, Obesity and Metabolism*, 9(5):648–659.

Henderson, W. and Finfer, S. (2009). Differences in outcome between the NICE-SUGAR and Leuven trials: possible methodological explanations. *Crit Care Resusc*, 11:175–177.

Hermayer, K., Neal, D., Hushion, T., Irving, M., Arnold, P., Kozlowski, L., Stroud, M., Kerr, F., and Kratz, J. (2007). Outcomes of a cardiothoracic intensive care web-based online intravenous insulin infusion calculator study at a medical university hospital. *Diabetes Technology & Therapeutics*, 9(6):523–534.

Hirsch, I. (2005). Insulin analogues. *New England Journal of Medicine*, 352(2):174–183.

Hirsch, I. (2009). Sliding scale insulin–time to stop sliding. *JAMA*, 301(2):213.

Hirsch, I. and Brownlee, M. (2005). Should minimal blood glucose variability become the gold standard of glycemic control? *J Diabetes Complications*, 19(3):178–81.

Hovorka, R., Canonico, V., Chassin, L., Haueter, U., Massi-Benedetti, M., Federici, M., Pieber, T., Schaller, H., Schaupp, L., Vering, T., et al. (2004a). Nonlinear model predictive control of glucose concentration in subjects with type 1 diabetes. *Physiological measurement*, 25:905.

Hovorka, R., Chassin, L. J., Ellmerer, M., Plank, J., and Wilinska, M. E. (2008). A simulation model of glucose regulation in the critically ill. *Physiological Measurement*, 29(8):959–78.

Hovorka, R., Chassin, L. J., Wilinska, M. E., Canonico, V., Akwi, J. A., Federici, M. O., Massi-Benedetti, M., Hutzli, I., Zaugg, C., Kaufmann, H., Both, M., Vering, T., Schaller, H. C., Schaupp, L., Bodenlenz, M., and Pieber, T. R. (2004b). Closing the loop: the adicol experience. *Diabetes Technology & Therapeutics*, 6(3):307–18.

Hovorka, R., Kremen, J., Blaha, J., Matias, M., Anderlova, K., Bosanska, L., Roubicek, T., Wilinska, M. E., Chassin, L. J., Svacina, S., and Haluzik, M. (2007). Blood glucose control by a model predictive control algorithm with variable sampling rate versus a routine glucose management protocol in cardiac surgery patients: a randomized controlled trial. *The Journal of Clinical Endocrinology and Metabolism*, 92(8):2960–4.

Hovorka, R., Shojaee-Moradie, F., Carroll, P., Chassin, L., Gowrie, I., Jackson, N., Tudor, R., Umpleby, A., and Jones, R. (2002). Partitioning glucose distribution/transport, disposal, and endogenous production during IVGTT. *Am J Physiol Endocrinol Metab*, 282(5):E992–1007.

Insel, P., Liljenquist, J., Tobin, J., Sherwin, R., Watkins, P., Andres, R., and Berman, M. (1975). Insulin control of glucose metabolism in man: a new kinetic analysis. *Journal of Clinical Investigation*, 55(5):1057.

Inzucchi, S. and Rosenstock, J. (2005). Counterpoint: Inpatient glucose management. *Diabetes Care*, 28(4):976.

Irwin, R. and Rippe, J. (2009). *Manual of intensive care medicine*. Lippincott Williams & Wilkins.

Jansson, P., Fowelin, J., Von Schenck, H., Smith, U., and Lönnroth, P. (1993). Measurement by microdialysis of the insulin concentration in subcutaneous interstitial fluid. Importance of the endothelial barrier for insulin. *Diabetes*, 42(10):1469.

Jauslin, P. M., Silber, H. E., Frey, N., Gieschke, R., Simonsson, U. S. H., Jorga, K., and Karlsson, M. O. (2007). An integrated glucose-insulin model to describe oral glucose tolerance test data in type 2 diabetics. *The Journal of Clinical Pharmacology*, 47(10):1244–55.

Jeremitsky, E., Omert, L., Dunham, C., Wilberger, J., and Rodriguez, A. (2005). The impact of hyperglycemia on patients with severe brain injury. *The Journal of trauma*, 58(1):47–50.

Jeschke, M., Klein, D., and Herndon, D. (2004). Insulin treatment improves the systemic inflammatory reaction to severe trauma. *Annals of surgery*, 239(4):553–560.

Jones, H., Coggins, R., Lafuente, J., and De Cossart, L. (1999). Value of a surgical high-dependency unit. *British Journal of Surgery*, 86(12):1578–1582.

Kagansky, N., Levy, S., Rimon, E., Cojocaru, L., Fridman, A., Ozer, Z., and Knobler, H. (2003). Hypoglycemia as a predictor of mortality in hospitalized elderly patients. *Archives of internal medicine*, 163(15):1825.

Kalfon, P. and Preiser, J.-C. (2008). Tight glucose control: should we move from intensive insulin therapy alone to modulation of insulin and nutritional inputs? *Critical Care*, 12(3):156.

Kimberly, M., Vesper, H., Caudill, S., Ethridge, S., Archibold, E., Porter, K., and Myers, G. (2006). Variability among five over-the-counter blood glucose monitors. *Clinica chimica acta*, 364(1-2):292–297.

Klein, O., Lynge, J., Endahl, L., Damholt, B., Nosek, L., and Heise, T. (2007). Albumin-bound basal insulin analogues (insulin detemir and NN344): comparable time-action profiles but less variability than insulin glargine in type 2 diabetes. *Diabetes, Obesity and Metabolism*, 9(3):290–299.

Krajicek, B., Kudva, Y., and Hurley, H. (2005). Potentially important contribution of dextrose used as diluent to hyperglycemia in hospitalized patients. *Diabetes care*, 28(4):981–982.

Krinsley, J. (2003). Association between hyperglycemia and increased hospital mortality in a heterogeneous population of critically ill patients. In *Mayo Clinic Proceedings*, volume 78, pages 1471–1478. Mayo Clinic.

Krinsley, J. and Jones, R. (2006). Cost Analysis of Intensive Glycemic Control in Critically Ill Adult Patients*. *Chest*, 129(3):644.

Krinsley, J. S. (2004). Effect of an intensive glucose management protocol on the mortality of critically ill adult patients. *Mayo Clin Proc*, 79(8):992–1000.

Krishnan, J., Parce, P., Martinez, A., Diette, G., and Brower, R. (2003). Caloric Intake in Medical ICU Patients*. *Chest*, 124(1):297–305.

Laird, A., Miller, P., Kilgo, P., Meredith, J., and Chang, M. (2004). Relationship of early hyperglycemia to mortality in trauma patients. *The Journal of trauma*, 56(5):1058–1062.

Langouche, L., Vanhorebeek, I., Vlasselaers, D., Vander Perre, S., Wouters, P., Skogstrand, K., Hansen, T., and Van den Berghe, G. (2005). Intensive insulin therapy protects the endothelium of critically ill patients. *Journal of Clinical Investigation*, 115(8):2277–2286.

Lantus (2001). Product Information:LANTUS (insulin glargine injection). *Bridgewater,(NJ): Aventis Inc 2001*.

Larsen, M., Rolin, B., Wilken, M., Carr, R., and Svendsen, O. (2002). High-Fat High-Energy Feeding Impairs Fasting Glucose and Increases Fasting Insulin Levels in the Gottingen Minipig results from a pilot study in: Lipids and insulin resistance: The role of fatty acid metabolism and fuel partioning. *Annals of the New York Academy of Sciences*, 967:414–423.

Le Compte, A., Chase, J. G., Lynn, A., Hann, C. E., Shaw, G., Wong, X.-W., and Lin, J. (2009). Blood glucose controller for neonatal intensive care: Virtual trials development and first clinical trials. *Journal of Diabetes Science and Technology*, 3(5):1066–1081.

LeCompte, A. (2009). Modelling the Glucose-Insulin Regulatory System for Glycaemic Control in Neonatal Intensive Care. *PhD Thesis*.

Leeson-Payne, C. and Aitkenhead, A. (1995). A prospective study to assess the demand for a high dependency unit. *Anaesthesia*, 50(5):383–387.

Lehmann, E. (2001). The freeware AIDA interactive educational diabetes simulatorhttp://www. 2aida. org(2) Simulating glycosylated haemoglobin (HbA1c) levels in AIDA v4. 3. *Med Sci Monit*, 7(3):516–525.

Lehmann, E. D., Tarin, C., Bondia, J., Teufel, E., and Deutsch, T. (2009). Incorporating a generic model of subcutaneous insulin absorption into the aida v4 diabetes simulator 3. early plasma insulin determinations. *Journal of Diabetes Science and Technology*, 3(1):109–201.

Lemenuel-diot, A., Laveille, C., Frey, N., Jochemsen, R., and Mallet, A. (2007). Mixture Modeling for the Detection of Subpopulations in a Pharmacokinetic/Pharmacodynamic analysis. *Journal of Pharmacokinetics and Pharmacodynamics*, 34(2):157–181.

Lepore, M., Pampanelli, S., Fanelli, C., Porcellati, F., Bartocci, L., Vincenzo, A. D., Cordoni, C., Costa, E., Brunetti, P., and Bolli, G. B. (2000). Pharmacokinetics and pharmacodynamics of subcutaneous injection of long-acting human insulin analog glargine, nph insulin, and ultralente human insulin and continuous subcutaneous infusion of insulin lispro. *Diabetes*, 49(12):2142–8.

Lewis, K., Kane-Gill, S., Bobek, M., and Dasta, J. (2004). Intensive insulin therapy for critically ill patients. *The Annals of pharmacotherapy*, 38(7):1243.

Lin, J., Lee, D., Chase, J., Shaw, G., Hann, C. E., Lotz, T., and Wong, J. (2006). Stochastic modelling of insulin sensitivity variability in critical care. *Biomedical Signal Processing and Control*, 1(3):229–242.

Lin, J., Lee, D., Chase, J. G., Shaw, G. M., Le Compte, A. J., Lotz, T., Wong, J., Lonergan, T., and Hann, C. E. (2008). Stochastic modelling of insulin sensitivity and adaptive glycemic control for critical care. *Computer Methods and Programs in Biomedicine*, 89(2):141–52.

Lin, J., Razak, N. N., Pretty, C. G., Compte, A. L., Docherty, P., Parente, J. D., Shaw, G. M., Hann, C. E., and Chase, J. G. (2011). A physiological intensive control insulin-nutrition-glucose (icing) model validated in critically ill patients. *Computer Methods and Programs in Biomedicine*.

Lonergan, T., Le Compte, A. J., Willacy, M., Chase, J. G., Shaw, G. M., Wong, X.-W., Lotz, T., Lin, J., and Hann, C. E. (2006a). A pilot study of the SPRINT protocol for tight glycaemic control in critically ill patients. *Diabetes Technology and Therapheutics*, 8(4):449–462.

Lonergan, T., Le Compte, A. J., Willacy, M., Chase, J. G., Shaw, G. M., Wong, X.-W., Lotz, T., Lin, J., and Hann, C. E. (2006b). A simple insulin-nutrition protocol for tight glycemic control in critical illness: development and protocol comparison. *Diabetes Technol Ther*, 8(2):191–206.

Lotz, T. (2007). High resolution clinical model-based assessment of insulin sensitivity. *PhD Thesis, Mechanical Engineering, University of Canterbury, Christchurch, New Zealand*.

Lotz, T., Chase, J. G., McAuley, K., Lee, D., Lin, J., Hann, C. E., and Mann, J. (2006). Transient and steady-state euglycemic clamp validation of a model for glycemic control and insulin sensitivity testing. *Diabetes Technology and Therapeutics*, 8(3):338–46.

Lotz, T., Göltenbott, U., Chase, J. G., Docherty, P., and Hann, C. E. (2009). A minimal C-peptide sampling method to capture peak and total prehepatic insulin secretion in model-based experimental insulin sensitivity studies. *Journal of Diabetes Science and Technology*, 3(4):875–86.

Lotz, T. F., Chase, J. G., McAuley, K. A., Shaw, G. M., Wong, X.-W., Lin, J., Le Compte, A. J., Hann, C. E., and Mann, J. I. (2008). Monte Carlo analysis of a new model-based method for insulin sensitivity testing. *Computer Methods and Programs in Biomedicine*, 89(3):215–25.

Luzio, S., Beck, P., and Owens, D. (2003). Comparison of the subcutaneous absorption of insulin glargine (Lantus®) and NPH insulin in patients with Type 2 diabetes. *Hormone and metabolic research*, 35(7):434–438.

Mackenzie, I., Ingle, S., Zaidi, S., and Buczaski, S. (2005). Tight glycaemic control: a survey of intensive care practice in large English hospitals. *Intensive care medicine*, 31(8):1136–1136.

Mann, E., Pidcoke, H., Salinas, J., Wade, C., Holcomb, J., Wolf, S., Lacara, T., Domagtoy, C., Lickliter, D., Quattrocchi, K., et al. (2007). Accuracy of glucometers should not be assumed. *American Journal of Critical Care*, 16(6):531.

Mari, A. and Valerio, A. (1997). A circulatory model for the estimation of insulin sensitivity. *Control Eng Practice*, 5(12):1747–1752.

Mari, A., Wahren, J., DeFronzo, R. A., and Ferrannini, E. (1994). Glucose absorption and production following oral glucose: comparison of compartmental and arteriovenous-difference methods. *Metab Clin Exp*, 43(11):1419–25.

Marik, P. and Raghavan, M. (2004). Stress-hyperglycemia, insulin and immunomodulation in sepsis. *Intensive care medicine*, 30(5):748–756.

Massi Benedetti, M., Humburg, E., Dressler, A., and Ziemen, M. (2003). A one-year, randomised, multicentre trial comparing insulin glargine with NPH insulin in combination with oral agents in patients with type 2 diabetes. *Hormone and metabolic research*, 35(3):189–196.

McCarthy, A. M. and Elmendorf, J. S. (2007). GLUT4's itinerary in health & disease. *Indian J Med Res*, 125(3):373–88.

McCowen, K., Friel, C., Sternberg, J., Chan, S., Forse, R., Burke, P., and Bistrian, B. (2000). Hypocaloric total parenteral nutrition: effectiveness in prevention of hyperglycemia and infectious complications–a randomized clinical trial. *Crit Care Med*, 28(11):3606–11.

McCowen, K. C., Malhotra, A., and Bistrian, B. R. (2001). Stress induced hyperglycaemia. *Crit Care Clin*, 17:107–124.

McDonald, C., Dunaif, A., and Finegood, D. (2000). Minimal-model estimates of insulin sensitivity are insensitive to errors in glucose effectiveness. *J Clin Endocrinol Metab*, 85(7):2504–2508.

Mesotten, D. and Van den Berghe, G. (2009). Clinical benefits of tight glycaemic control: focus on the intensive care unit. *Best Practice & Research Clinical Anaesthesiology*, 23(4):421–429.

Mevorach, M., Giacca, A., Aharon, Y., Hawkins, M., Shamoon, H., and Rossetti, L. (1998). Regulation of endogenous glucose production by glucose per se is impaired in Type 2 diabetes mellitus. *The Journal of Clinical Investigation*, 102(4):744–753.

Meynaar, I., Dawson, L., Tangkau, P., Salm, E., and Rijks, L. (2007). Introduction and evaluation of a computerised insulin protocol. *Intensive care medicine*, 33(4):591–596.

Mittelman, S. D., Fu, Y.-Y., Rebrin, K., Steil, G., and Bergman, R. N. (1997). Indirect effect of insulin to suppress endogenous glucose production is dominant, even with hyperglucagonemia. *The Journal of Clinical Investigation*, 100(12):3121–30.

Mizock, B. (1995). Alterations in carbohydrate metabolism during stress: a review of the literature. *The American journal of medicine*, 98(1):75–84.

Mizock, B. (2001). Alterations in fuel metabolism in critical illness: hyperglycaemia. *Baillière's best practice & research. Clinical endocrinology & metabolism*, 15(4):533–551.

Moghissi, E. S. (2008). Insulin strategies for managing inpatient and outpatient hyperglycaemia and diabetes. *Clinical Nursing*, 75(6):558–66.

Moghissi, E. S., Korytkowski, M. T., DiNardo, M., Einhorn, D., Hellman, R., Hirsch, I. B., Inzucchi, S. E., Ismail-Beigi, F., Kirkman, M. S., and Umpierrez, G. E. (2009). American Association of Clinical Endocrinologists and American Diabetes Association consensus statement on inpatient glycemic control. *Endocr Practice*, 15(4):353–69.

Monzillo, L. U. and Hamdy, O. (2003). Evaluation of insulin sensitivity in clinical practice and in research settings. *Nutr Rev*, 61(12):397–412.

Moore, E., Mitchell, M., and Chalmers, T. (1959). Variability in absorption of insulin-I131 in normal and diabetic subjects after subcutaneous and intramuscular injection. *Journal of Clinical Investigation*, 38(7):1222.

Moreno, R., Vincent, J., Matos, R., Mendonca, A., Cantraine, F., Thijs, L., Takala, J., Sprung, C., Antonelli, M., Bruining, H., et al. (1999). The use of maximum SOFA score to quantify organ dysfunction/failure in intensive care. Results of a prospective, multicentre study. *Intensive care medicine*, 25(7):686–696.

Mosekilde, E., Jensen, K. S., Binder, C., Pramming, S., and Thorsteinsson, B. (1989). Modeling absorption kinetics of subcutaneous injected soluble insulin. *J Pharmacokinet Biopharm*, 17:67–87.

Murphy, N., Keane, S., Ong, K., Ford-Adams, M., Edge, J., Acerini, C., and Dunger, D. (2003). Randomized cross-over trial of insulin glargine plus lispro or NPH insulin plus regular human insulin in adolescents with type 1 diabetes on intensive insulin regimens. *Diabetes Care*, 26(3):799.

Myburgh, J. and Chittock, D. (2009). Differences in outcome between the NICE-SUGAR and Leuven trials: biological mechanisms of intensive glucose control in critically ill patients. *Crit Care Resusc*, 11:178–179.

Natali, A., Gastaldelli, A., Camastra, S., Sironi, A., Toschi, E., Masoni, A., Ferrannini, E., and Mari, A. (2000). Dose-response characteristics of insulin action on glucose metabolism: a non-steady-state approach. *Am J Physiol Endocrinol Metab*, 278(5):E794–801.

Nathan, D., Cleary, P., Backlund, J., Genuth, S., Lachin, J., Orchard, T., Raskin, P., and Zinman, B. (2005). Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study Research Group. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. *N Engl J Med*, 353(25):2643–2653.

Nucci, G. and Cobelli, C. (2000). Models of subcutaneous insulin kinetics.a critical review. *Comput Methods Programs Biomed*, 62(3):249–57.

Olansky, L., Sam, S., Lober, C., Yared, J., and Hoogwerf, B. (2009). Cleveland Clinic Cardiovascular Intensive Care Unit Insulin Conversion Protocol. *Journal of diabetes science and technology (Online)*, 3(3):478.

Owens, D. R., Coates, P. A., Luzio, S. D., Tinbergen, J. P., and Kurzhals, R. (2000). Pharmacokinetics of 125i-labeled insulin glargine (hoe 901) in healthy men: comparison with nph insulin and the influence of different subcutaneous injection sites. *Diabetes Care*, 23(6):813–9.

Pachler, C., Plank, J., Weinhandl, H., Chassin, L., Wilinska, M., Kulnik, R., Kaufmann, P., Smolle, K., Pilger, E., Pieber, T., et al. (2008). Tight glycaemic control by an automated algorithm with time-variant sampling in medical ICU patients. *Intensive care medicine*, 34(7):1224–1230.

Parker, R. S. and Doyle, F. J. (2001). Control-relevant modeling in drug delivery. *Advanced Drug Delivery Reviews*, 48(2-3):211–28.

Parker, R. S., Doyle, F. J., and Peppas, N. A. (2001). The intravenous route to blood glucose control. *IEEE engineering in medicine and biology magazine: the quarterly magazine of the Engineering in Medicine & Biology Society*, 20(1):65–73.

Patiño, J., de Pimiento, S., Vergara, A., Savino, P., Rodríguez, M., and Escallón, J. (1999). Hypocaloric support in the critically ill. *World journal of surgery*, 23(6):553–559.

Picchini, U., Gaetano, A. D., Panunzi, S., Ditlevsen, S., and Mingrone, G. (2005). A mathematical model of the Euglycemic Hyperinsulinemic Clamp. *Theor Biol Med Model*, 2:44.

Pillonetto, G., Sparacino, G., Magni, P., Bellazzi, R., and Cobelli, C. (2002). Minimal model $S_I = 0$ problem in NIDDM subjects: nonzero Bayesian estimates with credible confidence intervals. *Am J Physiol Endocrinol Metab*, 282(3):E564–573.

Plank, J., Blaha, J., Cordingley, J., Wilinska, M., Chassin, L., Morgan, C., Squire, S., Haluzik, M., Kremen, J., Svacina, S., et al. (2006). Multicentric, randomized, controlled trial to evaluate blood glucose control by the model predictive control algorithm versus routine glucose management protocols in intensive care unit patients. *Diabetes Care*, 29(2):271.

Porcellati, F., Rossetti, P., Pampanelli, S., Fanelli, C., Torlone, E., Scionti, L., Perriello, G., and Bolli, G. (2004). Better long-term glycaemic control with the basal insulin glargine as compared with NPH in patients with Type 1 diabetes mellitus given meal-time lispro insulin. *Diabetic Medicine*, 21(11):1213–1220.

Porcellati, F., Rossetti, P., Ricci, N., Pampanelli, S., Torlone, E., Campos, S., Andreoli, A., Bolli, G., and Fanelli, C. (2007). Pharmacokinetics and pharmacodynamics of the long-acting insulin analog glargine after 1 week of use compared with its first administration in subjects with type 1 diabetes. *Diabetes care*, 30(5):1261.

Poulin, R., Steil, G., Moore, D., Ader, M., and Bergman, R. (1994). Dynamics of glucose production and uptake are more closely related to insulin in hindlimb lymph than in thoracic duct lymph. *Diabetes*, 43(2):180(11).

Preiser, J. (2009). NICE-SUGAR: the end of a sweet dream? *Critical Care*, 13(3):143.

Preiser, J., Devos, P., Ruiz-Santana, S., Mélot, C., Annane, D., Groeneveld, J., Iapichino, G., Leverve, X., Nitenberg, G., Singer, P., et al. (2009). A prospective randomised multi-centre controlled trial on tight glucose control by

intensive insulin therapy in adult intensive care units: the Glucontrol study. *Intensive care medicine*, 35(10):1738–1748.

Preiser, J.-C. and Devos, P. (2007). Clinical experience with tight glucose control by intensive insulin therapy. *Critical Care Medicine*, 35(9 Suppl):S503–7.

Prigeon, R. L., Røder, M. E., Porte, D., and Kahn, S. E. (1996). The effect of insulin dose on the measurement of insulin sensitivity by the minimal model technique. evidence for saturable insulin transport in humans. *The Journal of Clinical Investigation*, 97(2):501–7.

Queale, W., Seidler, A., and Brancati, F. (1997). Glycemic control and sliding scale insulin use in medical inpatients with diabetes mellitus. *Archives of internal medicine*, 157(5):545.

Radziuk, J. (1987). Tracer methods and the metabolic disposal of a carbohydrate load in man. *Diabetes/metabolism reviews*, 3(1):231–267.

Rasio, E., Mack, E., Egdahl, R., and Herrera, M. (1968). Passage of insulin and inulin across vascular membranes in the dog. *Diabetes*, 17(11):668.

Raskin, P., Klaff, L., Bergenstal, R., Hallé, J., Donley, D., and Mecca, T. (2000). A 16-week comparison of the novel insulin analog insulin glargine (HOE 901) and NPH human insulin used with insulin lispro in patients with type 1 diabetes. *Diabetes care*, 23(11):1666.

Ratner, R., Hirsch, I., Neifing, J., Garg, S., Mecca, T., and Wilson, C. (2000). Less hypoglycemia with insulin glargine in intensive insulin therapy for type 1 diabetes. US Study Group of Insulin Glargine in Type 1 Diabetes. *Diabetes care*, 23(5):639.

Rizza, R., Mandarino, L., and Gerich, J. (1981). Dose-response characteristics for effects of insulin on production and utilization of glucose in man. *American Journal of Physiology- Endocrinology And Metabolism*, 240(6):E630.

Rodbard, D. (2007). Optimizing display, analysis, interpretation and utility of self-monitoring of blood glucose (SMBG) data for management of patients with diabetes. *Journal of diabetes science and technology (Online)*, 1(1):62.

Rolan, P. and Molnar, V. (2006). Clinical pharmacokinetics. *The textbook of pharmaceutical medicine*, page 176.

Rood, E., Bosman, R., Van Der Spoel, J., Taylor, P., and Zandstra, D. (2005). Use of a computerized guideline for glucose regulation in the intensive care unit improved both guideline adherence and glucose regulation. *Journal of the American Medical Informatics Association*, 12(2):172–180.

Rosenberg, A., Hofer, T., Hayward, R., Strachan, C., and Watts, C. (2001). Who bounces back? Physiologic and other predictors of intensive care unit readmission. *Critical care medicine*, 29(3):511.

Rosenstock, J., Lorber, D., Gnudi, L., Howard, C., Bilheimer, D., Chang, P., Petrucci, R., Boss, A., and Richardson, P. (2010). Prandial inhaled insulin plus basal insulin glargine versus twice daily biaspart insulin for type 2 diabetes: a multicentre randomised trial. *The Lancet*, 375(9733):2244–2253.

Rosenstock, J., Park, G., and Zimmerman, J. (2000). Basal insulin glargine (HOE 901) versus NPH insulin in patients with type 1 diabetes on multiple daily insulin regimens. *Diabetes Care*, 23(8):1137–1142.

Rosenstock, J., Schwartz, S. L., Clark, C. M., Park, G. D., Donley, D. W., and Edwards, M. B. (2001). Basal insulin therapy in type 2 diabetes: 28-week comparison of insulin glargine (hoe 901) and nph insulin. *Diabetes Care*, 24(4):631–6.

Rossetti, P., Pampanelli, S., Fanelli, C., Porcellati, F., Costa, E., Torlone, E., Scionti, L., and Bolli, G. (2003). Intensive replacement of basal insulin in patients with type 1 diabetes given rapid-acting insulin analog at mealtime. *Diabetes Care*, 26(5):1490.

Ruiz-Velázquez, E., Femat, R., and Campos-Delgado, D. (2004). Blood glucose control for type I diabetes mellitus: A robust tracking H∞ problem. *Control Engineering Practice*, 12:1179–1195.

Saager, L., Collins, G., Burnside, B., Tymkew, H., LINI, Z., Jacobsohn, E., and Avidan, M. (2008). A randomized study in diabetic patients undergoing cardiac surgery comparing computer-guided glucose management with a standard sliding scale protocol. *Journal of cardiothoracic and vascular anesthesia*, 22(3):377–382.

Schnipper, J., Barsky, E., Shaykevich, S., Fitzmaurice, G., and Pendergrass, M. (2006). Inpatient management of diabetes and hyperglycemia among general

medicine patients at a large teaching hospital. *Journal of Hospital Medicine*, 1(3):145–150.

Schober, E., Schoenle, E., Van Dyk, J., and Wernicke-Panten, K. (2002). Comparative trial between insulin glargine and NPH insulin in children and adolescents with type 1 diabetes mellitus. *Journal of pediatric endocrinology & metabolism: JPEM*, 15(4):369.

Scholtz, H. E., Pretorius, S. G., Wessels, D. H., and Becker, R. H. A. (2005). Pharmacokinetic and glucodynamic variability: assessment of insulin glargine, nph insulin and insulin ultralente in healthy volunteers using a euglycaemic clamp technique. *Diabetologia*, 48(10):1988–95.

Schultz, M. J., de Graaff, M. J., Kuiper, M. A., and Spronk, P. E. (2008). The new Surviving Sepsis Campaign recommendations on glucose control should be reconsidered. *Intensive Care Med*, 34(4):779–80.

Schwartz, M. and Porte Jr, D. (2005). Diabetes, obesity, and the brain. *Science*, 307(5708):375.

Scott, M., Bruns, D., Boyd, J., and Sacks, D. (2009). Tight glucose control in the intensive care unit: are glucose meters up to the task? *Clinical chemistry*, 55(1):18.

Shah, P., Vella, A., Basu, A., Basu, R., Schwenk, W. F., and Rizza, R. A. (2000). Lack of suppression of glucagon contributes to postprandial hyperglycemia in subjects with type 2 diabetes mellitus. *The Journal of Clinical Endocrinology and Metabolism*, 85(11):4053–9.

Shimoda, S., Nishida, K., Sakakida, M., Konno, Y., Ichinose, K., Uehara, M., Nowak, T., and Shichiri, M. (1997). Closed-loop subcutaneous insulin infusion algorithm with a short-acting insulin analog for long-term clinical application of a wearable artificial endocrine pancreas. *Frontiers of medical and biological engineering: the international journal of the Japan Society of Medical Electronics and Biological Engineering*, 8(3):197.

Shulman, R., Finney, S. J., O'Sullivan, C., Glynne, P. A., and Greene, R. (2007). Tight glycaemic control: a prospective observational study of a computerised decision-supported intensive insulin therapy protocol. *Critical Care*, 11(4):R75.

Silber, H. E., Jauslin, P. M., Frey, N., Gieschke, R., Simonsson, U. S. H., and Karlsson, M. O. (2007). An integrated model for glucose and insulin regulation in healthy volunteers and type 2 diabetic patients following intravenous glucose provocations. *The Journal of Clinical Pharmacology*, 47(9):1159–71.

Sjöstrand, M., Gudbjörnsdottir, S., Holmäng, A., Lönn, L., Strindberg, L., and Lönnroth, P. (2002). Delayed transcapillary transport of insulin to muscle interstitial fluid in obese subjects. *Diabetes*, 51(9):2742.

Sjöstrand, M., Holmäng, A., and Lönnroth, P. (1999). Measurement of interstitial insulin in human muscle. *Am J Physiol*, 276(1 Pt 1):E151–4.

Sjostrand, M., Holmang, A., Strindberg, L., and Lonnroth, P. (2000). Estimations of muscle interstitial insulin, glucose, and lactate in type 2 diabetic subjects. *Am J Physiol Endocrinol Metab*, 279(5):E1097–103.

Smiley, D. and Umpierrez, G. (2008). Inpatient insulin therapy. *Insulin*, 3(3):152–166.

Søeborg, T., Rasmussen, C., Mosekilde, E., and Colding-Jørgensen, M. (2009). Absorption kinetics of insulin after subcutaneous administration. *European Journal of Pharmaceutical Sciences*, 36(1):78–90.

Sorensen, J. (1985). A physiologic model of glucose metabolism in man and its use to design and assess improved insulin therapies for diabetes.

Sowell, M., Mukhopadhyay, N., Cavazzoni, P., Carlson, C., Mudaliar, S., Chinnapongse, S., Ray, A., Davis, T., Breier, A., Henry, R., et al. (2003). Evaluation of insulin sensitivity in healthy volunteers treated with olanzapine, risperidone, or placebo: a prospective, randomized study using the two-step hyperinsulinemic, euglycemic clamp. *Journal of Clinical Endocrinology & Metabolism*, 88(12):5875.

Strauss, G., Moller, K., Larsen, F., Kondrup, J., and Knudsen, G. M. (2003). Cerebral glucose and oxygen metabolism in patients with fulminant hepatic failure. *Liver Transplantation*, 9(12):1244–1252.

Suhaimi, F., Le Compte, A., Preiser, J., Shaw, G., Massion, P., Radermecker, R., Pretty, C., Lin, J., Desaive, T., and Chase, J. (2010). What Makes Tight Glycemic Control Tight? The Impact of Variability and Nutrition in Two Clinical Studies. *Journal of diabetes science and technology*, 4(2):284.

Swenson, M. (1992). Scarcity in the intensive care unit: Principles of justice for rationing ICU beds* 1. *The American journal of medicine*, 92(5):551–555.

Swinnen, S., Dain, M., Aronson, R., Davies, M., Gerstein, H., Pfeiffer, A., Snoek, F., DeVries, J., Hoekstra, J., and Holleman, F. (2010). A 24-week, randomized, treat-to-target trial comparing initiation of insulin glargine once-daily with insulin detemir twice-daily in patients with type 2 diabetes inadequately controlled on oral glucose-lowering drugs. *Diabetes care*, 33(6):1176.

Takeshita, H., Okuda, Y., and Sari, A. (1972). The effects of ketamine on cerebral circulation and metabolism in man. *Anesthesiology*, 36(1):69–75.

Tappy, L., Berger, M., Schwarz, J. M., McCamish, M., Revelly, J. P., Schneiter, P., Jéquier, E., and Chioléro, R. (1999). Hepatic and peripheral glucose metabolism in intensive care patients receiving continuous high- or low-carbohydrate enteral nutrition. *JPEN Journal of parenteral and enteral nutrition*, 23(5):260–7.

Tarín, C., Teufel, E., Picó, J., Bondia, J., and Pfleiderer, H. (2005). Comprehensive pharmacokinetic model of insulin glargine and other insulin formulations. *IEEE Transactions on Biomedical Engineering*, 52:12.

Thomas, A., Marchant, A., Ogden, M., and Collin, S. (2005). Implementation of a tight glycaemic control protocol using a web-based insulin dose calculator. *Anaesthesia*, 60(11):1093–1100.

Thomaseth, K., Gastaldelli, A., Pavan, A., Berria, R., Glass, L., and DePronzo, R. (2006). Analysis of double tracer glucose kinetics in humans during oral glucose tolerance test. *Modelling and Control in Biomedical Systems 2006*, page 57.

Thomaseth, K., Pavan, A., Berria, R., Glass, L., DeFronzo, R., and Gastaldelli, A. (2008). Model-based assessment of insulin sensitivity of glucose disposal and endogenous glucose production from double-tracer oral glucose tolerance test. *Computer Methods and Programs in Biomedicine*, 89(2):132–40.

Thorburn, A., Litchfield, A., Fabris, S., and Proietto, J. (1995). Abnormal transient rise in hepatic glucose production after oral glucose in non-insulin-dependent diabetic subjects. *Diabetes research and clinical practice*, 28(2):127–135.

Thorell, A., Rooyackers, O., Myrenfors, P., Soop, M., Nygren, J., and Ljungqvist, O. (2004). Intensive insulin treatment in critically ill trauma patients normalizes glucose by reducing endogenous glucose production. *J Clin Endocrinol Metab*, 89(11):5382–6.

Thorsteinsson, B. (1990). Kinetic models for insulin disappearance from plasma in man. *Dan Med Bull*, 37(2):143–53.

Ting, C. and Nanji, A. (1988). Evaluation of the quality of bedside monitoring of the blood glucose level in a teaching hospital. *CMAJ: Canadian Medical Association Journal*, 138(1):23.

Toffolo, G., Campioni, M., Basu, R., Rizza, R., and Cobelli, C. (2006). A minimal model of insulin secretion and kinetics to assess hepatic insulin extraction. *Am J Physiol Endocrinol Metab*, 290(1):E169–E176.

Tonks, K., Jones, G., McGeechan, K., and Campbell, L. (2010). Hyperglycaemia in hospital inpatients: still a sticky situation. *Internal Medicine Journal*, 40(7):521–526.

Trajanoski, Z., Wach, P., Kotanko, P., Ott, A., and Skraba, F. (1993). Pharmacokinetic model for the absorption of subcutaneously injected soluble insulin and monomeric insulin analogs. *Biomed Tech*, 38(9):224–31.

Treggiari, M., Karir, V., Yanez, N., and Weiss, N. (2008). Intensive insulin therapy and mortality in critically ill patients. *Crit Care*, 12(1):R29.

Tudor, R., Hovorka, R., Cavan, D., Meeking, D., Hejlesen, O., and Andreassen, S. (1998). DIAS-NIDDM–a model-based decision support system for insulin dose adjustment in insulin-treated subjects with NIDDM. *Computer methods and programs in biomedicine*, 56(2):175–192.

Turina, M., Fry, D., and Polk Jr, H. (2005). Acute hyperglycemia and the innate immune system: clinical, cellular, and molecular aspects. *Critical care medicine*, 33(7):1624–1633.

Turnheim, K. and Waldhausl, W. (1988). Essentials of insulin pharmacokinetics. *Wien Klin Wochenschr*, 100(3):65–72.

Umpierrez, G. and Maynard, G. (2006). Glycemic chaos (not glycemic control) still the rule for inpatient care. *Journal of Hospital Medicine*, 1(3):141–144.

Umpierrez, G. E., Smiley, D., Zisman, A., Prieto, L. M., Palacio, A., Ceron, M., Puig, A., and Mejia, R. (2007). Randomized study of basal-bolus insulin therapy in the inpatient management of patients with type 2 diabetes (rabbit 2 trial). *Diabetes Care*, 30(9):2181–6.

Utzolino, S., Kaffarnik, M., Keck, T., Berlet, M., and Hopt, U. (2009). Unplanned discharges from a surgical intensive care unit: Readmissions and mortality. *Journal of Critical Care*.

Van Cauter, E., Mestrez, F., Sturis, J., and Polonsky, K. (1992). Estimation of insulin secretion rates from C-peptide levels. comparison of individual and standard kinetic parameters for C-peptide clearance. *Diabetes*, 41(3):368–77.

Van den Berghe, G., Schetz, M., Vlasselaers, D., Hermans, G., Wilmer, A., Bouillon, R., and Mesotten, D. (2009). Intensive insulin therapy in critically ill patients: NICE-SUGAR or Leuven blood glucose target? *Journal of Clinical Endocrinology & Metabolism*, 94(9):3163.

Van Den Berghe, G., Wilmer, A., Hermans, G., Meersseman, W., Wouters, P. J., Milants, I., Wijngaerden, E. V., Bobbaers, H., and Bouillon, R. (2006a). Intensive insulin therapy in the medical ICU. *The New England Journal of Medicine*, 354(5):449–61.

Van Den Berghe, G., Wilmer, A., Milants, I., Wouters, P. J., Bouckaert, B., Bruyninckx, F., Bouillon, R., and Schetz, M. (2006b). Intensive insulin therapy in mixed medical/surgical intensive care units: benefit versus harm. *Diabetes*, 55(11):3151–9.

Van den Berghe, G., Wouters, P., Bouillon, R., Weekers, F., Verwaest, C., Schetz, M., Vlasselaers, D., Ferdinande, P., and Lauwers, P. (2003). Outcome benefit of intensive insulin therapy in the critically ill: Insulin dose versus glycemic control*. *Critical care medicine*, 31(2):359–366.

Van den Berghe, G., Wouters, P., Kesteloot, K., and Hilleman, D. (2006). Analysis of healthcare resource utilization with intensive insulin therapy in critically ill patients*. *Critical care medicine*, 34(3):612.

Van Den Berghe, G., Wouters, P., Weekers, F., Verwaest, C., Bruyninckx, F., Schetz, M., Vlasselaers, D., Ferdinande, P., Lauwers, P., and Bouillon, R. (2001). Intensive insulin therapy in the critically ill patients. *The New England Journal of Medicine*, 345(19):1359–67.

Van Herpe, T., De Moor, B., and Van den Berghe, G. (2009). Towards closed-loop glycaemic control. *Best Practice & Research Clinical Anaesthesiology*, 23(1):69–80.

Van Herpe, T., Espinoza, M., Haverbeke, N., De Moor, B., and Van den Berghe, G. (2007). Glycemia prediction in critically ill patients using an adaptive modeling approach. *Journal of Diabetes Science and Technology*, 1(3):348–356.

Vanhorebeek, I., Langouche, L., and Van den Berghe, G. (2005). Glycemic and nonglycemic effects of insulin: how do they contribute to a better outcome of critical illness? *Current Opinion in Critical Care*, 11(4):304.

Vanhorebeek, I., Langouche, L., and Van Den Berghe, G. (2007). Tight blood glucose control: What is the evidence? *Critical Care Medicine*, 35(Suppl):S496–S502.

Vicini, P., Caumo, A., and Cobelli, C. (1997). The hot IVGTT two-compartment minimal model: indexes of glucose effectiveness and insulin sensitivity. *American Journal of Physiology- Endocrinology And Metabolism*, 273(5):E1024.

Vincent, J., de Mendonca, A., Cantraine, F., Moreno, R., Takala, J., Suter, P., Sprung, C., Colardyn, F., and Blecher, S. (1998). Use of the SOFA score to assess the incidence of organ dysfunction/failure in intensive care units: results of a multicenter, prospective study. *Critical Care Medicine*, 26(11):1793.

Vincent, J., Moreno, R., Takala, J., Willatts, S., De Mendonca, A., Bruining, H., Reinhart, C., Suter, P., and Thijs, L. (1996). The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. *Intensive Care Medicine*, 22(7):707–710.

Vogelzang, M., Zijlstra, F., and Nijsten, M. (2005). Design and implementation of GRIP: a computerized glucose control system at a surgical intensive care unit. *BMC medical informatics and decision making*, 5(1):38.

Wahl, H. (2009). How accurately do we measure blood glucose levels in intensive care unit (ICU) patients? *Best Practice & Research Clinical Anaesthesiology*, 23(4):387–400.

Wang, F., Carabino, J., and Vergara, C. (2003). Insulin glargine: a systematic review of a long-acting insulin analogue. *Clinical therapeutics*, 25(6):1541–1577.

Weekers, F., Giulietti, A., Michalaki, M., Coopmans, W., Van Herck, E., Mathieu, C., and Van den Berghe, G. (2003). Metabolic, endocrine, and immune effects of stress hyperglycemia in a rabbit model of prolonged critical illness. *Endocrinology*, 144(12):5329.

Weissman, C. (1999). Nutrition in the intensive care unit. *Critical Care*, 3(5):R67–R75.

Wesorick, D., O'Malley, C., Rushakoff, R., Larsen, K., and Magee, M. (2008). Management of diabetes and hyperglycemia in the hospital: a practical guide to subcutaneous insulin use in the non-critically ill, adult patient. *J Hosp Med*, 3(5 Suppl):17–28.

Whitehorn, L. J. (2007). A review of the use of insulin protocols to maintain normoglycaemia in high dependency patients. *Clinical Nursing*, 16(1):16–27.

Wiener, R. S., Wiener, D. C., and Larson, R. J. (2008). Benefits and risks of tight glucose control in critically ill adults: a meta-analysis. *JAMA*, 300(8):933–44.

Wild, C. and Narath, M. (2005). Evaluating and planning ICUs: methods and approaches to differentiate between need and demand. *Health Policy*, 71(3):289–301.

Wilinska, M., Chassin, L., and Hovorka, R. (2008). Automated glucose control in the ICU: Effect of nutritional protocol and measurement error. In *Engineering in Medicine and Biology Society, 2006. EMBS'06. 28th Annual International Conference of the IEEE*, pages 67–70. IEEE.

Wong, J., Chase, J. G., Hann, C. E., Shaw, G. M., Lotz, T. F., Lin, J., and Compte, A. J. L. (2008a). A subcutaneous insulin pharmacokinetic model for computer simulation in a diabetes decision support role: Validation and simulation. *Journal of Diabetes Science and Technology*, 2(4):672–680.

Wong, J., Chase, J. G., Hann, C. E., Shaw, G. M., Lotz, T. F., Lin, J., and Le Compte, A. J. (2008b). A subcutaneous insulin pharmacokinetic model for computer simulation in a diabetes decision support role: Model structure and parameter identification. *Journal of Diabetes Science and Technology*, 2(4):658–671.

Wong, X., Chase, J., Shaw, G., Hann, C., Lotz, T., Lin, J., Singh-Levett, I., Hollingsworth, L., Wong, O., and Andreassen, S. (2006a). Model predictive

glycaemic regulation in critical illness using insulin and nutrition input: a pilot study. *Medical engineering & physics*, 28(7):665–681.

Wong, X., Singh-Levett, I., Hollingsworth, L., Shaw, G., Hann, C. E., Lotz, T., Lin, J., Wong, O., and Chase, J. G. (2006b). A novel, model-based insulin and nutrition delivery controller for glycemic regulation in critically ill patients. *Diabetes Technol Ther*, 8(2):174–90.

Wong, X.-W., Chase, J. G., Hann, C. E., Lotz, T. F., Lin, J., Le Compte, A. J., and Shaw, G. M. (2008c). Development of a clinical Type 1 diabetes metabolic system model and in silico simulation tool. *Journal of Diabetes Science and Technology*, 2(3):424–435.

Yang, Y., Hope, I., Ader, M., and Bergman, R. (1994). Importance of transcapillary insulin transport to dynamics of insulin action after intravenous glucose. *American Journal of Physiology- Endocrinology And Metabolism*, 266(1):E17.

Yang, Y., Hope, I., Ader, M., Poulin, R., and Bergman, R. (1992). Dose-response relationship between lymph insulin and glucose uptake reveals enhanced insulin sensitivity of peripheral tissues. *Diabetes*, 41(2):241.