Insulin Sensitivity Tools for Critical Care

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Abstract

Stress induced hyperglycaemia is prevalent in critical care. Since the landmark paper published by Van den Berghe *et al.* (2001) a great deal of attention has been paid to intensive insulin therapy in an ICU setting to combat the adverse effects of elevated glucose levels and poor glycaemic control. Glycaemic control protocols have been extensively developed, tested and validated within an ICU setting. However, little research has been conducted on the effects of a glycaemic control protocol in a less acute ward setting. There are many additional challenges presented in a ward setting, such as the variation in meals and levels of activity between patients, from day to day and throughout the day.

A simple compartment model is used to describe the nature of insulin and glucose metabolism in patients of the Cardiothoracic Ward (CTW). A stochastic model of the fitted insulin sensitivity parameter is generated for this cohort and validated against cohorts of similar characteristics. The stochastic model is then used to run simulations of predictive control on 7 CTW patients, which shows significantly tighter glucose control than what is obtained with regular clinical procedures. However, the rate of severe hypoglycaemia is an unacceptably high 4.2%. The greatest challenge in maintaining tight glycaemic control in such patients is the consumption of meals at irregular times and of inconsistent quantities.

Insulin sensitivity was compared to extensive hourly clinical data of 36 ICU patients. From this data a sepsis score of value 0-4 was generated as gold standard marker of sepsis. Comparing the sepsis score to insulin sensitivity found that insulin sensitivity provides a negative predictive diagnostic for sepsis. High insulin sensitivity of greater than $S_I = 8 \times 10^{-5}$ L mU^{-1} min^{-1} rules out sepsis for the majority of patient hours and may be determined non-invasively in real-time from glycaemic control protocol data. Low insulin sensitivity is not an effective diagnostic, as it can equally mark the presence of sepsis or other conditions.

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Chapter 1

Introduction

The benefits of glycaemic control in hospitalised and ambulatory patients, such as a reduction mortality, morbidity and length of stay has been extensively investigated (Van den Berghe *et al.*, 2001, 2006b,a; Goldberg *et al.*, 2004b,a; Chase *et al.*, 2006c; Clayton *et al.*, 2006; Collier *et al.*, 2005; Garg *et al.*, 2007; Krinsley, 2003a,b, 2004; Langouche *et al.*, 2007; Laver *et al.*, 2004; Plank *et al.*, 2006; Zerr *et al.*, 1997). This research was prompted by Van den Berghe *et al.* (2001) who found a 42% reduction in mortality among a critically ill cohort with intensive insulin therapy (IIT). The benefits found are largely attributed to a reduction in hyperglycaemia. In particular, many studies in critically ill cardiac and cardiothoracic patients have also seen significant improvements in patient outcome using intensive insulin therapy (Goldberg *et al.*, 2004c; Malmberg *et al.*, 1995). However, the methods of maintaining glycaemic control for less acutely ill patients and the benefits from such control have not been fully explored.

This research is aimed at developing insulin sensitivity tools for use in Christchurch Hospital, with particular emphasis on glycaemic control in the less acute wards within the hospital. Christchurch Hospital already has the paper based glycaemic control protocol SPRINT in place as a nearly established protocol in the Intensive Care Unit (ICU) (Chase *et al.*, 2006c; Lonergan *et al.*, 2006b,a), however the 1-2 hourly measurements required to obtain tight glycaemic control would be excessively burdensome within a ward.

The incidence of Type II diabetes is disproportionately high in critical care (). Even so, diabetes is rapidly becoming one of the most common, preventable and manageble diseases, particularly in the developed world (Wild *et al.*, 2004). It has been estimated that 2.8% of the adult population suffered from diabetes in 2000 (Wild *et al.*, 2004) and this is expected to rise (Wild *et al.*, 2004; King *et al.*, 1998). New Zealand is not exempt from this trend and some 68,000 people

were found to have diabetes in 2000 (Wild *et al.*, 2004). Thus, developing means of maintaining good glycaemic control will have increasing importance and in the years to come.

Pharmacokinetic models of the insulin-glucose system have been used to trial, test and devlop both glycaemic control strategies and glucose tolerance tests and clinical trials have shown good correspondence with predicted outcomes (Lonergan *et al.*, 2006b,a; Chase *et al.*, 2006a; Lotz *et al.*, 2006b,a; Lin, 2007). The use of such models is a safe way of investigating control strategies. A validated, accurate and simple model will also be highly beneficial in developing any real time control tools, although presently such technologies are limited by measurement accuracy and ease. However, such models can provide real time estimates of insulin sensitivity data, which could potentially be used to asses patient condition.

Chapter 2

Background

2.1 Metabolism during Illness

The body's main source of energy is glucose, which once sourced from the diet is stored as glycogen. It is circulated through the bloodstream at a concentration typically 4-6 mmol L^{-1}. Under healthy physiological conditions the constant supply of glucose to muscle cells and adipose cells and other cells throughout the body is regulated by the hormone insulin and sourced from glycogen and stored protein.

Insulin is a peptide hormone sythesized and secreted by the β-cells in the islets of langerhans which are located in the pancreas. Insulin promotes glucose uptake and utilization by cells not located in the central nervous system, which has the effect of lowering plasma glucose levels. High insulin levels also promote the storage of glucose as glycogen. Glycogen is stored in all cells, but is found in highest concentrations in the liver and muscle cells. Insulin release is triggered in response to increased blood glucose levels, such as those encountered after consumption of a meal.

When the blood glucose levels fall, such as between meals, the α-cells of the islets of langerhans will produce glucagon, which induces glycogenolysis in order to maintain healthy glucose levels. Glycogenolysis is the process of converting stored glycogen into glucose and takes place in the liver.

In the periods of fasting, glucose supply is maintained by gluconeogenesis and fat oxidation. Gluconeogenesis is the production of glucose from amino acids, lactate and glycerol and takes place primarily in the liver, although the kidneys also contribute approximately 10% of the total output. This process is stimulated by low blood glucose levels and suppressed by high levels of insulin. In a diabetic patient or patient under physiological stress, gluconeogenesis is often overstimulated resulting in hyperglycaemia. Under physiological stress, the

catabolism of lipids and protein as a fuel is also increased. Lipid metabolism is also stimulated by uncontrolled diabetes or prolonged starvation, however, circulating insulin supresses this mechanism.

When the periods between meals are extended, such as in the case of a CTW patient suffering the the effects of treatment or surgery, this mechanism becomes more dominant than normally encountered in everyday life. The use of catechloamines, vasoconstrictors and glucocorticoids also contribute to overstimulation of gluconeogenesis. If fasting is prolonged beyond 2 days, glucose supply to the brain is sourced from the production of hepatic ketone bodies, which then inhibits gluconeogenesis fuelled by muscle tissue (Chiolero *et al.*, 1997).

2.2 Diabetes and Glycaemic Control

There are two primary forms of diabetes, with varying levels of severity. A patient with Type I diabetes has no β-cell function and must inject exogenous insulin in order to maintain glycaemic control, thus the term 'Insulin Dependent Diabetic'. A patient with Type II diabetes displays reduced cellular responsiveness to insulin throughout the body as well as reduced response to heightened levels of insulin. Reduced insulin sensitivity observed in Type II diabetes is most commonly caused by poor diet consisting of a high concentration of carbohydrate (CHO) rich foods or foods with high sugar content. Type II diabetes can typically be managed with healthy eating and exercising habits combined with weight loss, but is rapidly becoming a common disorder throughout developed nations (DPPRG, 2002).

The use of oral hypoglycaemics, such as thiazolidinediones, biguanides or sulfonylureas are used to increase insulin sensitivity of patients exhibiting high resistance to insulin. The use of such medications enables patients with Type II diabetes to reduce or eliminate the need for exogenous insulin. However, a 2002 study found that healthy lifestyle changes in the form of increased physical activity and improved diet resulted in a much larger reduction in the incidence of Type II diabetes than those recieving the oral hypoglycaemic, Metformin (DPPRG, 2002).

Glycaemic control has been recognised as an important part of reducing the serious complications associated with diabetes, such as retinopathy, neuropathy, cardiac dysfunction and reduced resistance to infection. Glycaemic control is commonly measured by levels of Haemoglobin A1c (HbA1c) in the blood, which reflects the concentrations of glucose which have been present over the lifecycle of haemoglobin (approximately 180 days) (Bennett *et al.*, 2007). Healthy levels

of HbA1c are between 4-6%, although many diabetics target a value below 7%. Currently, the World Health Organisation (WHO) does not recognise this as a diagnostic tool for diabetes.

When determining post-prandial insulin doses, a diabetic patient typically estimates the quantity of carbohydrates in the meal to estimate the required insulin input. The ratio of insulin:CHO is dependent on the extent of β-cell impairment, but typically ranges from 1:8-1:32.

It has been suggested that the creation of an artificial pancreas will allow diabetes suffers to maintain healthy blood glucose levels with minimal risk and increased ease (Teixeira and Malin, 2008). However, the control achieveable with such technology remains unsatisfactory, largely due to the absence of reliable a continuous glucose monitor (CGM). A CGM tests glucose levels intermittently using samples from the interstitium, however the error in the measurements is much greater than that found in finger prick measuring equipment (Nichols *et al.*, 2007). Thus, ambulatory patients are currently limited to the use of insulin pumps or manual insulin administration to obtain good glycaemic control.

However, significant advances in glycaemic control for ambulatory diabetes have been made, particularly with the use of insulin glargine. Glargine is a long acting insulin which has no pronounced peak action and a short rise time. It acts continuously over a 24 hour period, thus allowing a single daily dose for basal insulin secretion replacement. Glargine has been found to have similar benefits as neutral protamine Hagedorn (NPH) insulin, although there is evidence that the use of glargine results in lower HbA1c levels and reduced night-time hypoglycaemia than NPH (Wang *et al.*, 2007; Fritsche *et al.*, 2003; Wang *et al.*, 2003; Yki-Jrvinen *et al.*, 2006). The cause of the hypoglycaemia is likely due to the more pronounced peak of NPH, which could also result in higher average glucose levels.

Several studies using the Holman and Turner algorithm **?** for insulin titration (refer to Equation 2.2) have been conducted with and without oral hypoglycaemics **??**. Using this algorithm on Type II diabetics, along with a regular dose of glimepiride (a suflonylurea), Fritsche found that a regular morning dose of glargine significantly reduced HbA1c levels compared to evening doses of glargine or NPH. However, all interventions demonstrated a reduction in fasting blood glucose and HbA1c levels (Fritsche *et al.*, 2003).

$$\text{Insulin Dose} = \frac{G_E - 50}{10}$$

Where G_E is the fasting plasma glucose level in mg dl^{-1}.

Other titration schemes involve similar sliding scale adjustments to insulin dose based on fasting glucose levels (?Riddle *et al.*, 2003; Davies *et al.*, 2005). Studies in which insulin doses are guided by patient or physician/investigator experience rather than by a specific formula have observed similar benefits from targeted glucose control. However, all of these were designed around dose adjustment occuring at frequencies between 2 days and one week. Because the average length of stay of a patient in the CTW is of the order of one week, such systems will not have reached a final balance by the time of discharge. Similarly, they are not dynamic enough to accomodate the rapid changes in patient condition or daily routine which may occur in a ward.

Strange suggests that once basal insulin titration has been conducted for 12 weeks, the optimal basal dose will have been found and then meal boluses should be investigated (Strange, 2007). However, in a CTW environment, patients need targeted glycaemic control in the short term, so while such methods may improve ambulatory diabetic care, such considerations are beyond the scope of this research.

2.3 Insulin and Intensive Insulin Therapy

Stress induced hyperglycemia is prevalent in critical care, and can occur in patients with no history of diabetes (Capes *et al.*, 2000; Van den Berghe *et al.*, 2001; Mizock, 2001; McCowen *et al.*, 2001). Critically ill patients exhibit increased endogenous glucose production, reduced insulin production, and increased insulin resistance (Mizock, 2001; McCowen *et al.*, 2001; Doran, 2004). Excessive enteral feeding of glucose and administration of glucocorticoids can further exacerbate hyperglycemia (Patino *et al.*, 1999; Ahrens *et al.*, 2005; Krishnan *et al.*, 2003).

Hyperglycemia worsens outcomes leading to risk of further complications, particularly sepsis (Bistrian, 2001), myocardial infarction (Capes *et al.*, 2000), and polyneuropathy and multiple organ failure (Van den Berghe *et al.*, 2001) as well as increased length of stay (Garg *et al.*, 2007). Van den Berghe *et al.* (2001, 2003, 2006b) showed that tight glucose control averaging 5.7-6.0 mmol/L reduced ICU mortality 18-45% for patients with greater than 3 days stay. Krinsley (2003b, 2004) showed a 17-29% reduction in mortality with a higher glucose limit of 7.75 mmol/L. These studies detail the clinical significance of maintaining normoglycemia, and indicate that elevated glucose levels outside the target range are associated with poorer outcomes (Krinsley, 2003a; Van den Berghe *et al.*,

2003; Collier *et al.*, 2005). Tight control also minimises rebound hyperglycaemia on discharge to the wards (Krinsley, 2003b) and minimises development of (new) infections due to elevated blood glucose (Krinsley, 2003a, 2004; Goldberg *et al.*, 2004b).

Clinical studies that did not include mortality endpoints include those by Goldberg *et al.* (2004b), Laver *et al.* (2004) and Thomas *et al.* (2005). A comparison of SPRINT to these protocols has been completed using virtual trials and retrospective patient data by Lonergan *et al.* (2006b). This study showed that SPRINT provided tighter control and higher time in glycaemic control bands (Lonergan *et al.*, 2006b).

Malmberg *et al.* (1995) found that a insulin-glucose infusion resulted in a 29% reduction in 1-year mortality among diabetic patients following a myocardial infarction. For patients who had not previously recieved insulin, the reduction in 1-year mortality was 52%.

Adaptive model-based protocols for insulin-mediated glucose control have shown promise, but have limitations with respect to easy implementation and complexity (Ahrens *et al.*, 2005; Krishnan *et al.*, 2003; Bistrian, 2001; Van den Berghe *et al.*, 2003) The SPRINT protocol satisfied the need for a simple and easily implemented means of getting the effectiveness of computerised, model-based protocols into long term clinical testing. SPRINT was developed to mimic effective model-based methods (Van den Berghe *et al.*, 2003, 2006b), and is unique in its use of both insulin and nutrition inputs for tight glycaemic regulation.

Poor glycaemic control is caused reduced ability to maintain safe levels by normal physiological reactions to elevated glucose levels. The physiological stress of surgery or illness may also induce a significant inflammatory response which causes insulin resistance (Virkamaki and Yki-Jarvinen, 1994). Combined with increased endogenous glucose production (Chambrier *et al.*, 2000), the patient may experience significant hyperglycaemia. The reduction of these dangerous glucose levels, as well as the anti-imflammatory effects of insulin, are the most likely reasons for the success of IIT.

Hypoglycaemic events are the biggest risk of insulin therapies. If large doses are administered without regular measurement of glucose levels the patient is put at risk. This is particularly true when dealing with patients who have a pre-existing diabetes as they may not recognise that they have become hypoglycaemic due to repeated exposure to low glucose levels, which builds up a resistance to the symptoms (Boyle *et al.*, 1995).

2.4 Sepsis and Insulin Sensitivity

Sepsis has a mortality rate of 40-50% (Tsiotou *et al.*, 2005; Esteban *et al.*, 2007) and occurs in 11.8% of ICU patients in Australasia (Finfer *et al.*, 2004). Sepsis defined by the presence of two or more symptoms of Systemic Inflammatory Response Syndrome (SIRS) and infection. SIRS is defined by the presence of one or more of the following:

- body temperature greater than 38° or less than 36°
- heart rate greater than 90 beats per minute
- hyperventilation, a respiratory rate greater than 20 min^{-1} or a PaCO_2 of less than 32 mmHg
- a white blood cell count of greater than 120000 cells μl^{-1} or less than 4000 cells μl^{-1}

Severe sepsis is said to be defined by the above criteria for sepsis as well as organ dysfunction, hypoperfusion or hypotension. Severe sepsis becomes classified as septic shock when hypotension remains pronounced (systolic arterial pressure $<$ 90 mmHg or mean arterial pressure (MAP) < 60) in spite of fluid resuscitation. (Tsiotou *et al.*, 2005)

The inflammatory response to such widespread infection causes vasodilation and fever as well as increasing endogenous glucose production. The inflammation is caused by Interleukin-1 (IL-1) and tumor necrosis factor-α (TNF-α). The use of both of these biomarkers has been used as a diagnostic test with limited success. Positive blood cultures however, while definitive, take too long to process to maintain clinical applicability and thus sepsis remains difficult to positively identify with certainty. There is a documented relationship between insulin resisitance (S_I^{-1}) and infection (Virkamaki and Yki-Jarvinen, 1994; Rassias *et al.*, 1999) however the relationship between real time identified insulin sensitivity metrics has not been related to a diagnosis of sepsis. The accurate identification of sepsis is an important clinical problem because the overuse of antibiotics leads to antibiotic resistant bacteria.

2.5 Pharmacokinetic Models

Identifying insulin sensitivity requires capturing the fundamental dynamics of the glucose regulatory system. The minimal model of Bergman (1979; 1981; 1987; 2005) encapsulates the essential insulin-glucose dynamics through the use

of 3 compartments. This model has been adapted to best suit the cohort being considered. Two important variations of the model are discussed here.

2.5.1 ICU Model

Chase *et al.* (2006c); **?** and Lonergan *et al.* (2006b,a) used the system described by Equations 2.1-2.5. This model has been applied to an ICU cohort in Christchurch Hospital with significant success in model-based and paper-based glycaemic control clinical trials. Extensive validation of the model has also been carried out.

$$\dot{G} = -p_G G - \frac{S_I(G+G_E)Q}{1+\alpha_G Q} + P(t) \quad (2.1)$$

$$\dot{Q} = -kQ + kI \quad (2.2)$$

$$\dot{I} = -\frac{nI}{1+\alpha_I I} + \frac{u_{ex}}{V} + \frac{I_B e^{-u_{ex}}}{V} \quad (2.3)$$

$$P(t_i < t < t_{i+1}) = \bar{P}_{i+1} + (\bar{P}_i - \bar{P}_{i+1})e^{-k_{pd}(t-t_i)} \; where \; \bar{P}_{i+1} < \bar{P}_i \quad (2.4)$$

$$P(t_i < t < t_{i+1}) = \bar{P}_{i+1} + (\bar{P}_i - \bar{P}_{i+1})e^{-k_{pr}(t-t_i)} \; where \; \bar{P}_{i+1} > \bar{P}_i \quad (2.5)$$

Where $G(t)$ [mmol/L] is the plasma glucose above an equilibrium level, and $I(t)$ [mmol/L] is the plasma insulin resulting from exogenous insulin input, $u_{ex}(t)$ [mU/min]. The effect of previously infused insulin being utilised over time is represented by $Q(t)$ [mU/L], with k [1/min] accounting for the effective life of insulin in the system. Patient endogenous glucose clearance and insulin sensitivity are p_G [1/min] and S_I [L/(mU.min)], respectively. The parameter V [L] is the insulin distribution volume and n [1/min] is the constant first order decay rate for insulin from plasma. Total plasma glucose input is denoted $P(t)$ [mmol/(L.min)]. Endogenous insulin production is given by I_B [mU/min]. Michaelis-Menten functions are used to model saturation, with α_I [L/mU] used for the saturation of plasma insulin disappearance, and α_G [L/mU] for the saturation of insulin-dependent glucose clearance. k_{pr} and k_{pd} are the effective half lives of glucose transport from gut to plasma for both increasing and decreasing feed rates respectively, and $\bar{P}_i$ and $\bar{P}_{i+1}$ are the steps in enteral glucose feed rates. Generally, $k, k_{pr}, k_{pd}, n, \alpha_G, \alpha_I$ and V are set to generic population values.

2.5.2 Ambulatory Diabetic Model

Ambulatory diabetics recieve a wide variety of insulins through the subcutaneous route. Wong (**?**2008; 2008) developed a five compartment model which describes

the action of many of these insulins following administration and their decomposition into hexameric and dimeric/monomeric state. The insulins considered in this model are:

- RI - a short acting insulin
- MI - a short acting insulin
- NPH - an intermediate acting insulin
- lente - an intermediate acting insulin
- ultralente - a long acting insulin
- glargine - a long acting insulin

Equations 2.6-2.14 define the absorption kinetics.

$$\dot{x}_i(t) = -(k_3 + k_{d,i})x_i(t) + k_2 x_{dm}(t) \tag{2.6}$$

$$\dot{x}_h(t) = -(k_1 + k_d)x_h(t) + k_{crys,NPH}c_{NPH}(t) + k_{crys,len}c_{len}(t) + u_{h,RH}(t)... + u_{h,NPH}(t) + u_{h,len} \tag{2.7}$$

$$\dot{x}_{dm}(t) = -(k_2 + k_d)x_{dm}(t) + k_1 x_h(t) + k_{1,ulen}x_{h,ulen}(t) + k_{1,gla}x_{h,gla}(t) + u_{mono}(t)... + u_{m,RHt}(t) + u_{m,NPH}(t) + u_{m,len}(t) + u_{m,ulen}(t) + u_{m,gla}(t) \tag{2.8}$$

$$\dot{c}_{NPH}(t) = -k_{crys,NPH}c_{NPH}(t) + u_{c,NPH}(t) \tag{2.9}$$

$$\dot{c}_{len}(t) = -k_{crys,len}c_{len}(t) + u_{c,len}(t) \tag{2.10}$$

$$\dot{x}_{h,ulen}(t) = -(k_{1,ulen} + k_d)x_{h,ulen}(t) + k_{crys,ulen}c_{ulen}(t) + u_{h,ulen}(t) \tag{2.11}$$

$$\dot{c}_{ulen}(t) = -k_{crys,ulen}c_{ulen}(t) + u_{c,ulen}(t) \tag{2.12}$$

$$\dot{x}_{h,gla}(t) = -(k_{1,gla} + k_d)x_{h,gla}(t) + min(k_{prep,gla}p_{gla}(t), r_{dis,max}) + u_{h,gla}(t) \tag{2.13}$$

$$\dot{p}_{gla}(t) = -min(k_{prep,gla}p_{gla}(t), r_{dis,max}) + u_{p,gla}(t) \tag{2.14}$$

Where:

x_i is mass in the interstitium compartment [mU]
x_h is mass in the hexameric compartment [mU]
$x_{h,ulen}$ is mass in the ultralente hexameric compartment [mU]
$x_{h,gla}$ is mass in the glargine hexameric compartment [mU]
x_{dm} is mass in the dimer/monomer compartment [mU]
c_{NPH} is mass in the NPH crystalline protamine compartment [mU]
c_{len} is mass in the lente crystalline zinc compartment [mU]
p_{gla} is mass in the glargine precipitate compartment [mU]
k_1 is hexamer dissociation rate [min^{-1}]

$k_{1,ulen}$ is ultralente hexamer dissociation rate [min^{-1}]
$k_{1,gla}$ is glargine hexamer dissociation rate [min^{-1}]
k_2 is dimeric/monomeric insulin transport into interstitium [min^{-1}]
k_3 is interstitium insulin transport rate into plasma [min^{-1}]
$k_{d,i}$ is rate of loss from interstitium [min^{-1}]
k_d is rate of diffusive loss from hexameric and dimeric/monomeric state compartments [min^{-1}]
$k_{prep,gla}$ is glargine precipitate dissolution rate [min^{-1}]
$k_{crys,len}$ is lente zinc crystalline dissolution rate [min^{-1}]
$k_{crys,ulen}$ is ultralente zinc crystalline dissolution rate [min^{-1}]
$k_{crys,NPH}$ is NPH protamine crystalline dissolution rate [min^{-1}]
$r_{dis,max}$ is maximum glargine preciptate dissolution rate [mU min^{-1}]
u_h is RI hexamer state insulin input [mU min^{-1}]
$u_{h,NPH}$ is NPH hexamer state insulin input [mU min^{-1}]
$u_{h,len}$ is lente hexamer state insulin input [mU min^{-1}]
$u_{h,ulen}$ is ultralente hexamer state insulin input [mU min^{-1}]
$u_{h,gla}$ is glargine hexamer state insulin input [mU min^{-1}]
u_{mono} is MI dimer/monomer state insulin input [mU min^{-1}]
$u_{m,RH}$ is RI dimer/monomer state insulin input [mU min^{-1}]
$u_{m,NPH}$ is NPH dimer/monomer state insulin input [mU min^{-1}]
$u_{m,len}$ is lente dimer/monomer state insulin input [mU min^{-1}]
$u_{m,ulen}$ is ultralente dimer/monomer state insulin input [mU min^{-1}]
$u_{m,gla}$ is glargine dimer/monomer state insulin input [mU min^{-1}]

The model above has been validated against various pharmacokinetic studies finding good correspondence between almost all predicted peak values and target data (**?**Wong *et al.*, 2008; Wong, 2008).

2.5.3 Parameter Identification using the Integral Fitting Method

The integral fitting method of Hann *et al.* (2005) has been extensively used for parameter identification of long term pharmacokinetic models (Lonergan *et al.*, 2006a; **?**). The integral fitting method is convex and generates a linear system to be solved. An analysis of the error introduced into the method by approximating the glucose curve as a piecewise linear profile (refer to Equation 2.15) found that no additonal error is introduced by the fitting process. This is shown by

Equations 2.16 and 2.17, which are the two patient specific terms of the error term introduced. As shown, both are of the order δ (a measure of the best possible fit) which is not affected by the glucose data approximation. Note that this analysis is for the application of the method to the ICU model, where both S_I and p_G are fitted parameters.

$$0 \leq |\epsilon(t)| \leq \delta \; where \; G(t)_{T,real} = G(t)_{T,approx} + \epsilon(t) \tag{2.15}$$

$$\left| \frac{p_G \delta(t - t_0)}{p_G \int_{t_0}^{t} G_{T,real}(t)dt} \right| < \frac{\delta(t - t_0)}{\int_{t_0}^{t} 1dt} = \delta \; where \; G_{T,real} = 1 \tag{2.16}$$

$$\left| \frac{S_I \delta(t - t_0)}{S_I \int_{t_0}^{t} G_{T,real}(t)\bar{Q}(t)dt} \right| < \frac{\delta \int_{t_0}^{t} \bar{Q}(t)}{\int_{t_0}^{t} \bar{Q}(t)dt} = \delta \; where \; G_{T,real} = 1 \tag{2.17}$$

$$\tag{2.18}$$

2.5.4 Stochastic Modelling

Lin *et al.* (2008) used a stochastic model to describe the characteristics of an ICU population. Because S_I is a Markov variable, the probability of $S_{I,n+1} = y$ is defined by the previous state, S_I, n, as shown in Equation 2.19.

$$p(S_{I,n+1} = y | S_{I,n} = x) \quad = \quad \frac{p(S_{I,n} = x, S_{I,n+1} = y)}{p(S_{I,n} = x}) \tag{2.19}$$

The probabilities required in Equation 2.19 are defined by the available clinical data, using Equation 2.20.

$$p(x, y) \quad = \quad \frac{1}{n} \sum_{i=1}^{n} \frac{\phi(x; x_i, \sigma_{x_i}^2)}{p_{x_i}} \frac{\phi(y; y_i, \sigma_{y_i}^2)}{p_{y_i}} \tag{2.20}$$

$$p_{x_i} \quad = \quad \int_0^{\infty} \phi(x; x_i, \sigma_{x_i}^2) \tag{2.21}$$

$$p_{y_i} \quad = \quad \int_0^{\infty} \phi(y; y_i, \sigma_{y_i}^2) \tag{2.22}$$

Where x_i and y_i represent the $S_{I,n}$ and $S_{I,n+1}$ pairs in the clinical data. The $\phi(x; x_i, \sigma_{x_i}^2)$ term represents a non-negative normal probability distribution function centered at x_i and similarly for y_i. Integrating Equation 2.20 gives Equation 2.23.

$$p(x) = \int p(x,y)dy = \frac{1}{n}\sum_{i=1}^{n}\frac{\phi(x;x_i,\sigma^2_{x_i})}{p_{x_i}} \tag{2.23}$$

Thus, Equation 2.19 can be written as shown in Equations 2.24 and 2.25.

$$p(S_{I,n+1} = y|S_{I,n} = x) = \sum_{i=1}^{n}\omega_i(x)\frac{\phi(x;x_i,\sigma^2_{x_i})}{p_{x_i}} \tag{2.24}$$

$$\omega_i(x) = \frac{\frac{\phi(x;x_i,\sigma^2_{x_i})}{p_{x_i}}}{\sum_{j=1}^{n}\frac{\phi(x;x_j,\sigma^2_{x_j})}{p_{x_j}}} \tag{2.25}$$

Chapter 3

Cohort Data

3.1 CTW Patient Data

Glycaemic control data from patients experiencing hyperglycaemia in the CTW of Christchurch Hospital in the year 2007 was gathered for this study. Patients in the CTW typically have a one week turnaround and there are 10 beds. Ethics approval from the South Island Regional Ethics Committee was obtained for this research.

Obtaining glycaemic control data for patients in the CTW presented significant challenges. Only patients recieving insulin were of interest because these are patients that have experienced poor glucose control and thus reflect the target population for new glycaemic control strategies. In addition, patients not recieving exogenous insulin cannot be as accurately modelled as those who are due to the unknown endogenous metabolic response to such inputs. Without exogenous insulin, all glucose regulation is performed by endogenous production of insulin and glucose,and its endogenous clearance of the same. These processes cannot be accurately modelled without further, high density, clinical data, such as C-peptide levels, over time that are not available in this case.

The primary difficulty in data collection was accurately determining the selected patients' carbohydrate intake. Patients in the CTW eat hospital meals, as well as food brought in from outside of the hospital. Generally, no detailed record of food consumed is kept. To enable a study cohort to be modlled, nurses in the CTW kept a record of hospital meals ordered and the proportion consumed for those patients recieving insulin. Using nutritional data from Christchurch Hospital, the carbohydrate value of patient meals could be calculated and adjusted to the portion eaten.

However, several errors are inherent in this method. There is a discretisation error as the proportion consumed was only recorded as 0%, 25%, 50% 75% or

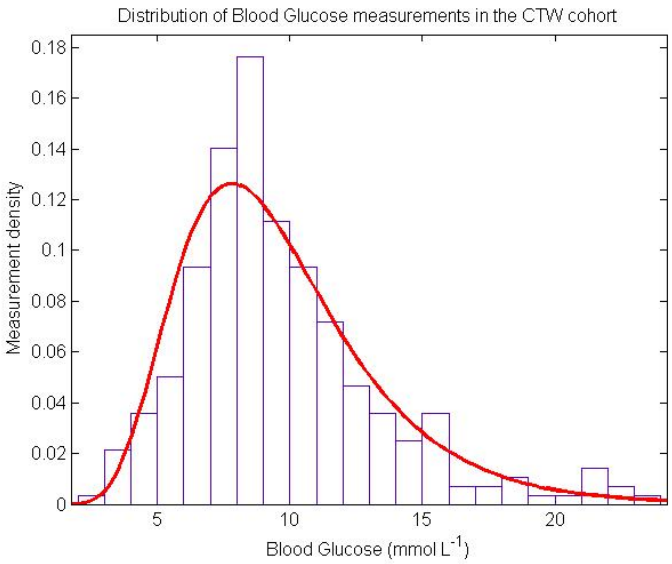


Figure 3.1 Distribution of blood glucose measurements from all 7 patients of the CTW cohort. The fitted probability density function assumes a lognormal distribution

100%. There is also a degree of subjective judgement involved in recording a proportion consumed, which may vary between nurses. Finally, the proportion consumed does not take into account which particular foods in a meal were consumed. For example, if 50% of a meal was consumed, this does not necessarily mean that 50% of carbohydrates in that meal was consumed. A patient may select the carbohydrate rich foods, or avoid those foods depending on tastes.

Finally, errors in the documentation process were also present. Difficulties occured with meal times being ommitted from recorded data. If such cases ocurred in isolation and the rest of the data was of high quality, an estimate of the time of consumption could be made based on regular meal times and glycaemic data. Where data measurements were largely vague or inaccurate, the entire data set for that period had to be excluded, further limiting the amount of useable data.

Figure 3.1 shows the blood glucose data for the CTW cohort. There is a high mean value and mode, which is indicative of the fact that the patients included are those who require glycaemic control. The data does not necessarily cover a patient's entire stay in the CTW, but represents different stages of the recovery process. The quality of data available dictated the periods that have been selected for investigation was not dependent on the time spent in the CTW. Periods of no insulin administration were omitted. However, these omitted periods are not reflected in any of the statistics presented.

3.1.1 Cohort Statistics

A total of 7 sets of patient data were of sufficient quality to be used in this study, comprising a total of 278 blood glucose measurements over 744 hours (approximately 1 measurement every 2.6 hours). After some sections of poor data quality were removed, the remaining number of patient hours was 692 which included 269 glucose measurements (approximately 1 measurement every 2.6 hours). The summary statistics for this cohort are shown in Tables 3.1 and 3.2. Full cohort details are shown in Table 3.3.

	Mean	IQR[1]	SD[2]
Length of Data Series	98.9	63.8-113.0	47.5
Age	69.4	65.0-75.3	7.9
Sex (% Male)	71	-	-

[1] Inter-quartile range
[2] Standard deviation

Table 3.1 Summary statistics of CTW patient data

Median Blood Glucose during stay (mmol L^{-1})	8.9
Blood Glucose standard deviation (mmol L^{-1})	3.8
BG readings below 4 mmol L^{-1} (%)	2.2
BG readings above 6 mmol L^{-1} (%)	88.5
BG readings above 7 mmol L^{-1} (%)	79.9
BG readings above 7.75 mmol L^{-1} (%)	69.1
BG readings above 10 mmol L^{-1} (%)	37.2

Table 3.2 Summary statistics of CTW patient glycaemic control data

The ratio between number of measurements and hours of data varies significantly between patients. High data density is ideal because it allows identification of higher frequency changes in insulin sensitivity over time and thus gives a better approximation to the likely true patient behaviour. Large insulin doses also enable more accurate fits. Overall, the cohort also has entirely diagnosed diabetes which is one likely reason for the generally greater measurement frequency.

It is important to remember that the cohort includes only CTW patients experiencing glycaemic control problems and does not represent typical CTW characteristics overall. However, the patients included in the cohort are those who would likely benefit from any control technologies that are developed. Thus it is created for protocol design, rather than representing a specific unit.

Patient 7 had a period of 34 hours in which no meal data is available. It is uncertain whether no meal was eaten during this time or if data was not recorded,

	Pt 1	Pt 2	Pt 3	Pt 4	Pt 5	Pt 6	Pt 7
Age	65	73	82	59	65/66	66	76
Sex	M	M	M	M	F	F	M
Weight (kg)	74	90.5	110	91.65	79.4	77.2	72.05
Length of data (hours)	98	100.5	116	54.5	90	188	42
Number of glucose measurements	44	70	21	10	45	66	13
Median Blood Glucose (mmol L^{-1})*	9.0	11.5	7.1	8.7	5.1	6.0	10.4
Standard Deviation (mmol L^{-1})*	0.4	0.5	0.4	0.3	0.3	0.3	0.3
Blood Glucose range (mmol L^{-1})	3.1-18.3	3.8-23.6	2-10.2	6-14.4	4.3-14	4.8-17.3	6.6-15.9
Insulin Types	MI, RH & IV	RH & IV	NPH	Penmix 30	IV	MI, NPH & IV	RH
Diabetes status	Type II	Medicated Type II	Newly diagnosed Type II	Type II	Type II	Type II	Type II

*Statistics from a lognormal distribution

Table 3.3 CTW cohort data

however the latter case is most likely based on the data. For this reason, the last 54 hours of data was removed from the study. The data in Tables 3.1-3.3 reflects this ommission.

Using the methods and model described in Chapter 4, an S_I profile was fit for the entire set of data available, including the last 54 hours for Patient 7. The errors in this fit due to reaching imposed upper and lower limits on S_I were then corrected for by fitting a new glucose input curve. This curve closely follows the modelled glucose input from the CHO content of CTW meals, with three notable exceptions marked by arrows in Figure 3.2.

The first is during the middle of the 34 hour period missing meal data where it is highly likely that a meal or two was eaten during this time, shown by the two peaks of modelled glucose input. This conclusionappeals to common sense, which dictates that no patient that had been eating regular meals would refuse food for a period of 34 hours and then resume regular eating habits the next day. The presence of two insulin administrations during this period also support this theory.

The second discrepancy lies in the slightly elevated levels of fitted glucose input when compared to modelled meal intakes. Because the level of elevation is reasonably constant, and is maintained between meals, it likely reflects an elevated level of EGP. This elevation is likely caused by slightly excessive levels over normal of the increased physiological stress and catecholamine activity that is typical after cardiac surgery.

The final unexpected peak in modelled glucose for Patient 7 appears at the end of the data collection period. Data for one breakfast meal of 35.2g of CHO was available for this patient, but the time of consumption and some quantities consumed were ommitted so this meal was left out of the data set. However, the time of the unknown glucose input does not correspond to a breakfast meal and it is therefore likely that this meal was consumed at the end of the data collection period, where there is a final unexpected peak in modelled glucose intake appears.

3.2 Ambulatory Diabetic Patient Data

Due to the limited patient turnover in the CTW alternative soures of relevant glycaemic control data were utilised. Ambulatory diabetic individuals present many similar characteristics of CTW patients and a cohort of such patients was already available from the research of Wong et al (**?**). Additionally, data from the Automated Insulin Dosage Advisor (AIDA) online[2](Lehmann and Deutsch, 1993)

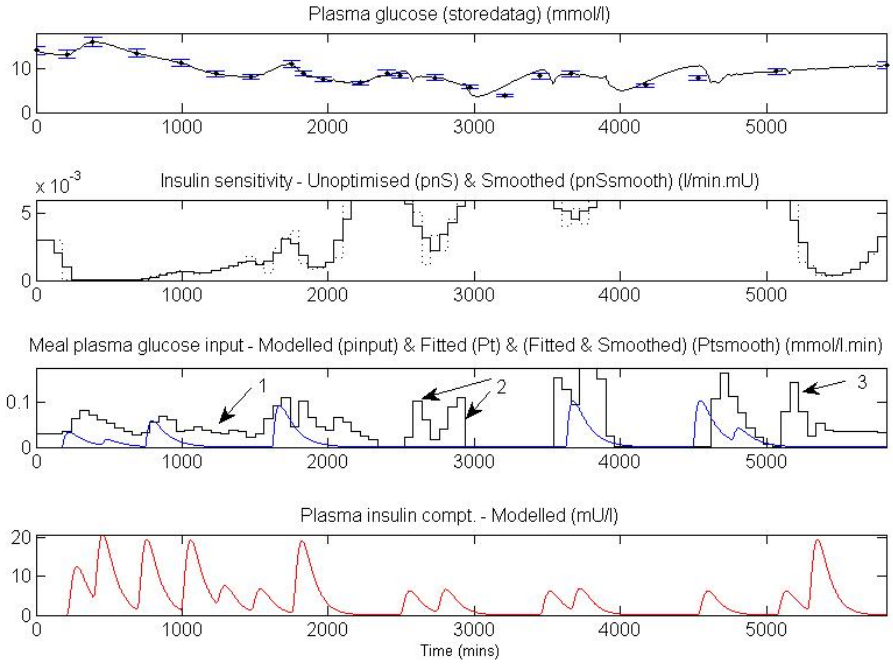


Figure 3.2 Fitted S_I profile of Patient 7 with error correction using fitted glucose intake

test cases was utilised and considered part of the ambulatory diabetic patient group. Both sets of patients exhibit significant diurnal rhythms. However, it is unknown whether CTW patients exhibit similar rhythms.

Ambulatory diabetics frequently encounter problems with glycaemic control, particularly in response to the variable nature of meals and exercise. In the CTW setting, sustained exercise is not encountered, but the problems with post-prandial glycaemic control are very similar, as is the overall physiological stress. Patients in the CTW are also sometimes newly diagnosed with Type II diabetes, which is identified or highlighted by hyperglycaemia seen during their hospital stay. In other cases, it is possible that glycaemic control problems are early warning signs of the onset of Type II diabetes or simply caused by the stress of their condition. In either case, the cohort of ambulatory diabetic patients provides additional hours of clinical data relevant to glycaemic control of less acutely ill patients. For much of this research, the ambulatory diabetic cohort is considered independently of the CTW cohort to detect any significant variances in behaviour or characteristics. In the absence of significant variance, the chorts can be considered simultaneously in developing tools for a more general ward cohort.

3.2.1 Cohort Statistics

A summary of the cohort statistics is shown in Table 3.4. The overall data illustrates a hyperglycaemic cohort. In particular, the 20.6% over 10 mmol L^{-1} indicate a significant level of variability in control.

Median Blood Glucose during stay (mmol L^{-1})	6.9
Blood Glucose interquartile range (mmol L^{-1})	5.0-9.4
BG readings below 4 mmol L^{-1} (%)	12.6
BG readings above 6 mmol L^{-1} (%)	61.7
BG readings above 7 mmol L^{-1} (%)	47.9
BG readings above 7.75 mmol L^{-1} (%)	40.9
BG readings above 10 mmol L^{-1} (%)	20.6

Table 3.4 Summary statistics of ambulatory diabetic patient data

3.3 ICU Patient Data

Extensive glycaemic conrol data for 394 patients admitted to Christchurch Hospital ICU between 2001 and 2007 is available for this study. Much of this data is from patients that were placed on the SPRINT protocol between 2005 and 2007. All glucose readings in these patients were taken using a Glucocard^{TM} test strip. Enteral nutrition consisted primarily of Diabetic Resource, although Glucerna, Jevity, NovoSource and several other feed types were used at various times throughout the study. The common use of enteral feeds in the ICU gives easily quantifiable CHO intake values, reducing the overall error in the insulin sensitivity fits.

However, enteral nutrition is rarely encountered in the wards and thus this data provides little insight into the characteristics of meal metabolism and glycaemic management. Similarly, the heightened degree of illness in ICU patients compared with the ward patients means that overall metabolism and insulin sensitivity profiles are likely to vary significantly, as would the underlying causes of hyperglycaemia. For these reasons, a general ICU cohort is not applicable to a study of glycaemic control in the wards.

Given these points, the transition of ICU patients from a critically ill state to a less acute state that leads to admission to a ward is of particular interest. This transition frequently coincides with less exogenous insulin dependence due to a reduction in stress-induced endogenous glucose production and increasing endogenous insulin production. Therefore, patients require a less intensive in-

sulin regime. The mechanics of making this transition safely have been largely neglected within most hospitals. To examine the patient characteristics found during this transition period, the last 36 hours data of of all ICU patients discharged to a ward are examined, which consisted of 131 patients from the original SPRINT cohort of 394. These 36 hours of data could represent the last 36 hours in the ICU or the last 36 hours of insulin administration in the ICU. Of this group, 87% of the data included patients still recieving enteral nutrition. The remaining 13% of patient hours had no meal data available.

Also of interest from this 394 patient cohort is the use of insulin sensitivity metrics to identify sepsis. In order to correlate hour by hour S_I profiles to a patient's sepsis status, further clinical data was required. The collection of this additional clinical data was very time consuming and thus only conducted on 36 patients that were identified by experienced clinical staff and blood culture results as having had sepsis during their ICU stay. These patients were also selected from the 394 patient cohort and thus all had sufficient glycaemic control data density to provide good insulin sensitivity fits. In addition to the existing glycaemic control data, extensive hour-by-hour clinical data of the sepsis cohort was gathered. This data had information on the following:

- Heart rate
- Blood pressure
- Respiration rate
- Temperature
- FiO_2
- Fluid balance
- Glasgow Coma Scale (GCS) score

Aditionallly, any atrial fibrilation was noted, as well as the use of any of the following drugs:

- Antibiotics
- Vasopressin
- Adrenaline
- Noradrenaline
- Dobutamine

From this information, conclusions about the specific times of sepsis can be drawn.

3.3.1 Cohort Statistics

The statistics for the final 36 hours of the stable ICU cohort is shown in Table 3.5. It is likely that this ICU cohort underestimates the presence of hyperglycaemia due to the majority of the cohort being on the SPRINT protocol during their ICU stay. However, the insulin sensitivity profiles are still likely to reflect a broadly similar metabolic status to those patients entering the CTW, particularly in the situation where glycaemic control protocols are in use before admission (eg. during surgery, ICU patients transitioning to the less acute wards).

Sex (% male)	74.7
Mean age (years)	58.9
Mean APACHE II	
Median length of SPRINT use	
Median Blood Glucose during stay (mmol L^{-1})	5.8
Blood Glucose interquartile range (mmol L^{-1})	5.1-6.6
BG readings below 4 mmol L^{-1} (%)	3.0
BG readings above 6 mmol L^{-1} (%)	40.5
BG readings above 7 mmol L^{-1} (%)	15.2
BG readings above 7.75 mmol L^{-1} (%)	7.8
BG readings above 10 mmol L^{-1} (%)	1.7

Table 3.5 Cohort Statistics for the ICU patients included in this study

The statistics for the 36 patient sepsis subcohort is shown in Table 3.6. This data set also indicates a tightly controlled cohort. However, it is also more hyperglycaemic than the cohort of Table 3.5, as might be expected.

Sex (% male)	
Mean age (years)	
Mean APACHE II	
Median length of SPRINT use	101
Median Blood Glucose during stay (mmol L^{-1})	6.0
Blood Glucose interquartile range (mmol L^{-1})	5.3-6.8
BG readings below 4 mmol L^{-1} (%)	2.4
BG readings above 6 mmol L^{-1} (%)	49.3
BG readings above 7 mmol L^{-1} (%)	20.1
BG readings above 7.75 mmol L^{-1} (%)	10.9
BG readings above 10 mmol L^{-1} (%)	2.1

Table 3.6 Cohort statistics for patients potentially having experienced sepsis

Chapter 4

Modelling and Parameter Identification

4.1 Model Structure

The final form of the model used is given in Equations 4.1-4.5. In Equation 4.3, X is given the value found by Equation 2.6 in the subcutaneous insulin model described in Section 2.5.2. A description of all other parameters and a discussion of their numerical determination is included in Section 4.2.

$$\dot{G_T} = -p_G G_T - \frac{S_I G_T Q}{1 + \alpha_G Q} + P(t) + EGP \tag{4.1}$$

$$\dot{Q} = kI - kQ \tag{4.2}$$

$$\dot{I} = \frac{-nI}{1 + \alpha_I I} + \frac{k_2 X}{V_i} + \frac{u(t)}{V_i} + \frac{I_B}{V_i} \tag{4.3}$$

$$\dot{S} = k_3 S + u_{CHO}(t) \tag{4.4}$$

$$\dot{T} = min(k_4 T, a_{max}) + k_5 S \tag{4.5}$$

$$P(t) = \frac{min(k_4 T, a_{max})}{V_p} \tag{4.6}$$

Where:

G_T is blood glucose [mmol L^{-1}]

p_G is endogenous glucose clearance [min^{-1}]

S_I is insulin sensitivity [L mU^{-1} min^{-1}]

Q is utilised insulin [mU]

α_G is the Michaelis-Menton constant for insulin mediated glucose clearance [L mU^{-1}]

$P(t)$ is plasma glucose input [mmol L^{-1} min^{-1}]

EGP is endogenous glucose production [mmol L^{-1} min^{-1}]

k is the effective life of insulin [min^{-1}]
I is plasma insulin [mU]
n is the insulin decay rate from the plasma [min^{-1}]
α_I is the Michaelis Menton constant for plasma insulin clearance [L mU^{-1}]
k_2 is the rate of transport of insulin from the intersitium into plasma [min^{-1}]
X is insulin from the interstitium [mU min^{-1}]
$u(t)$ is the exogenous insulin inputs [mU min^{-1}]
V_i is the distribution volume of insulin [L]
I_B is endogenous insulin secretion [mU min^{-1}]
S is the CHO content of the stomach [g]
T is the CHO content of the ileum [g]
u_{CHO} is the CHO content of meals consumed [g min^{-1}]
k_3 is the CHO gastric emptying rate [min^{-1}]
k_4 is the CHO gut absorption rate [min^{-1}]
a_{max} is the maximum gut CHO absorption rate [g min^{-1}]
V_p is glucose plasma distribution volume [L]

4.2 Parameter Values

The minimal model proposed by Bergman *et al.* (1979, 1981, 1987) describes the dominant effects in glucose-insulin kinetics. This model has since been modified to suit the particular characteristics of different populations (Bergman, 2005). The study of critically ill patients in Christchurch Hospital's ICU from 2001-2008 used the model described in Section 2.5.1 by Equations 2.1 - 2.5. The primary driving factor identified in such patients is the insulin sensitivity which is proportional to $\frac{feed}{glucose \times insulin}$ when glucose is at a steady state.

4.2.1 Insulin Sensitivity

Insulin sensitivity is a lumped parameter describing the combined effects of insulin on glucose uptake, which is the primary function of insulin. Under normal physiological functioning, the presence of insulin stimulates the cell walls enabling glucose to pass through to be processed by mitochondria. When the effect of insulin is diminished, a patient is said to be insulin resistant, which is equivalent to a low insulin sensitivity.

Insulin sensitivity has been shown to vary significantly throughout the day

and during the course of illness (Wilinska *et al.*, 2003; Langouche *et al.*, 2007). It is the driving parameter behind glucose changes and thus likely to be the key to achieving good glycaemic control. S_I is fitted as a piecewise constant parameter, varying hourly. It is limited to values of 1×10^{-5} and 6×10^{-3} L mU^{-1} min^{-1}, which extends significantly higher than most reported ranges (Bettini *et al.*, 1995; Doran, 2004), but as will be demonstrated in Section **??**, the modelled value does not typically extend beyond 2×10^{-3} L mU^{-1} min^{-1}, which is within the range reported by McDonald *et al.* (2000).

4.2.2 Endogenous Glucose Production

In order to more accurately capture the true time varying profiles of insulin sensitivity in a critically ill patient the model given in Equations 2.1-2.3 were modified to include an endogenous glucose production (EGP) term, Equation 2.1 is thus replaced by Equation 4.1 of the ICU model in Section 2.5.1.

The use of the EGP term allows the removal of the G_E term to give glucose dynamics, where $G_T = G + G_E$. These changes allow for greater accuracy in determining S_I profiles by eliminating the use of equilibrium glucose which is unknown and must therefore be estimated by statistical means. The G_E term was best estimated by a 12-hourly average of G, which allows some uptake of insulin sensitivity dynamics into this term, which would be particularly true in patients exhibiting diurnal cycles such as ambulatory diabetics or less critically ill patients. By eliminating this periodic re-estimation, the insulin sensitivity found by the model will more accurately represent true patient dynamics and is also more physiologically accurate than G_E.

EGP is held at a constant 3 mg min^{-1}, which is within the reported range (Chambrier *et al.*, 2000; Mittelman *et al.*, 1997; Singhal *et al.*, 2002; Dalla Man *et al.*, 2007). It is at the higher end of the range found by Chambrier *et al.* (2000) for both septic and control patients, but the standard deviation was much higher in septic patients than the control and consequently no statistically significant difference between the groups was observed. Thus, EGP is considered constant for all patients, whether or not they had sepsis. The value of 3 mg min^{-1} was selected to provide minimum time of modelled S_I on imposed upper or lower limits.

It should be noted that the physiological EGP rate has high interpatient variability and depends on a variety of factors, such as physiological stress, nutrition levels and glucose levels. The effect of stress is likely to be minimal as all pa-

tients in each cohort is under similar levels of physiological stress, however, with ambulatory diabetic patients, such stress levels could vary significantly during the course of a day as well as from patient to patient. However, a varying EGP rate would mathematically uptake S_I variation and so a constant rate for each patient must be chosen. Similarly, when patients consuming regular meals are considered, it is likely that EGP would be supressed immediately following meal consumption which usually induce periods of elevated glucose levels due to the diabetic nature of the chort. However, this effect is not modelled and thus it is possible that insulin secretion will be overestimated during such periods, or insulin sensitivity may be overestimated during such periods.

4.2.3 Central Nervous System Uptake

The central nervous system is biologically insulated from low blood glucose levels since, unlike other cells in the body, insulin is not needed for glucose uptake. This allows a constant uptake of glucose into the cells of the CNS essentially regardless of glucose levels in the blood. The only exception to this is extreme hypoglycaemic incidents (below approximately 2 mmol L^{-1}) at which point the patient experiences dizziness and loss of consciousness (Guyton and Hall, 2000). The physical symptoms of such lowered glucose levels can reduce with repeated exposures to such glycaemic levels, however the ultimate outcome of death is still death if the hypoglycaemia is left untreated. The changes in glucose metabolism during such severe hypoglycaemic incidents is, however, beyond the scope of this research and thus CNS uptake is considered to have a constant effect on glucose levels over time.

Since CNS glucose uptake is not insulin mediated it cannot be included in the systemic uptake term in Equation 4.1. It has the mathematical effect of reducing the EGP of the body, although this should not be mistaken for a physiological effect. However, for purposes of this study, the EGP term is considered to denote the overall effect of non-glucose dependent parameters on change in blood glucose.

4.2.4 Glucose Clearance

The rate of glucose clearance from the plasma by non-insulin stimulated means is modelled by the use of a lumped fractional clearance rate, p_G. This term originates from the original 3-compartment model of Bergman 1981. Studies suggest that the effect of variability in p_G over time is minimal in comparison to S_I. For this reason, p_G is considered a constant over time for each patient,

although interpatient variability is allowed for in the CTW cohort. The final p_G values are limited between 0.002 and 0.02 min^{-1}, which largely covers the range found in clinical studies (Avogaro *et al.*, 1989; Bergman *et al.*, 1981; Bettini *et al.*, 1995; Cobelli *et al.*, 1999; Furler *et al.*, 1985; McDonald *et al.*, 2000; Pillonetto *et al.*, 2002; **?**).

4.2.5 Endogenous Insulin Secretion

In moving focus from critically ill ICU patients to the less acute wards such as the CTW, endogenous insulin secretion(EIS) becomes a more prominent feature. This is evidenced by post-prandial peaks in insulin sensitivity when fitted using the model described in Equations 2.1-2.3. An example of such a fit is shown in Figure 4.1. The majority of meal inputs, as shown in the $P(t)$ curve induces a peak in insulin sensitivity for between 1-4 hours after the initial carbohydrate input.

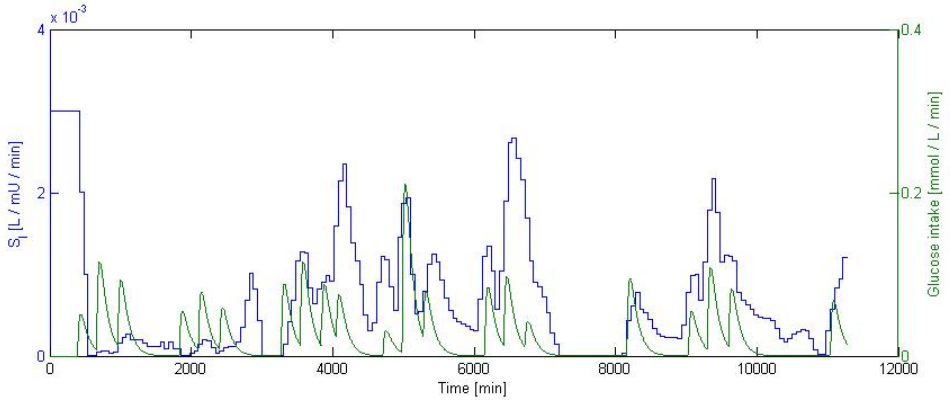


Figure 4.1 An example of a patients S_I profile compared to modelled glucose intake with no endogenous insulin secretion

Since S_I is fitted hourly, it is likely that this compensation for EIS misses the first peak phase of insulin secretion which usually last for approximately 10 minutes before reducing and then re-elevating for 2-3 hours following a meal (Guyton and Hall, 2000; Pratley and Weyer, 2001). However, it is also possible that this first phase secretion is absent due to the impairment of beta cell response inherent in the nature of diabetes. A comparison between a healthy post-prandial insulin response and that of a patient with Type II diabetes is shown in Figure 4.2. Note that a patient with Type I diabetes would exhibit negligible levels of insulin.

An upper limit of endogenous insulin secretion is imposed to maintain physiological accuracy. A limit of 10 U hr^{-1} is imposed on all insulin secretion rates.

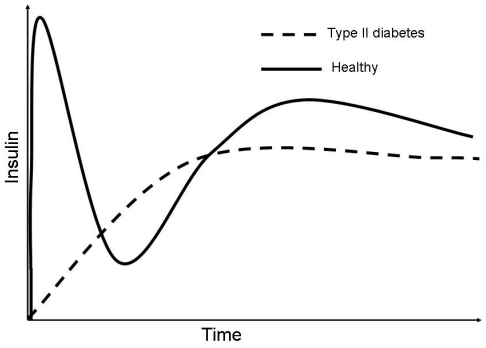


Figure 4.2 A qualitative comparison between the endogenous insulin secretion profiles of a healthy patient and one with Type II diabetes in response to a meal. Note that the first phase response of a healthy patient is completely missed by the patient with Type II diabetes.

This value lies on the upper range for of insulin secretion rates in obese patients derived from a two-compartment model based on C-peptide measurements (Polonsky *et al.*, 1988) and is almost twice that found by a study in healthy subjects during glucose infusion(Porksen *et al.*, 1997). While not all patients in the cohort are obese, it is likely that some will fall into this category, thus it is necessary that the upper limit allows for this. At all other times, basal insulin secretion is considered negligible.

Hyperglycaemia in the CTW was more commonly observed in patients with a history of diabetes and it is therefore likely that the cause is in failure of natural glucose control systems exacerbated by stress than solely stress-induced hyperglycaemia. Coupled with the lower insulin doses encountered in the CTW, this implies that insulin secretion is likely to be less significantly suppressed in such patients.

Modelling the arrival of endogenous insulin secretions (EIS) into the plasma allows basal replacement therapy to be modelled where the reduced endogenous function is allowed to manage post-prandial glucose rises. Basal replacement therapy for Type II diabetics has been investigated as a control strategy by numerous studies as summarised in Section 2.2.

It is well documented that exogenous insulin suppresses the secretion of endogenous insulin. This was taken into account by the $e^{-u(t)}$ factor of I_B in the ICU model, where I_B was assumed constant. However, the supression of EIS is assumed to be complete at all times except for 3 hours after a meal. It is assumed that after meals, EIS in a Type II diabetic is not suppressed by exogenous insulin in any levels that would be encountered in a practical situation. If EIS

is not suppressed to the extent assumed, the effect would be overestimation of insulin inputs, which would result in higher glucose levels than desired. However, underestimating I_B could result in an insulin overdose, causing hypoglycaemic events. Therefore, the inclusion of EIS in initial pilot trials is the safest option and accounting for EIS suppression might be developed after initial clinical trials.

It is important to note that the secretion rates calculated are the rates of secreted insulin that arrives in the plasma, not the rate of secretion by the β-cells. Approximately 50% of the insulin secreted by β-cells is cleared by the liver before taking effect on cellular glucose uptake. However, the aim of this research is to accurately model the dynamics between glucose and exogenous insulin rather than endogenous insulin dynamics and therefore the exact values rate insulin secretion and extraction are not required and would simply add unnecessary complexity to the model.

4.2.6 Subcutaneous Insulin

Wong *et al.* (2008); Wong (2008) modelled the effect of various types of insulin used in ambulatory diabetic patient management. While only IV insulin and insulin glargine are investigated for use in this study, much of the data available is from patients using a wide variety of insulin types. Thus the arrival of these insulins into the plasma needs to be modelled. This is achieved by the use of a subcutaneous insulin model described in Section 2.5.2.

4.3 Parameter Identification

4.3.1 Population Constants

The value of all population constants used are given in Table 4.3.1.

4.3.2 Fitted Parameters

Both insulin sensitivity (S_I) and endogenous insulin secretion (I_B) are considered variables in this model and thus both parameters must be fitted. Insulin sensitivity is assumed piecewise constant over each hour, whereas insulin secretion is constant over 10 minute periods. The model given in Section 4.1, which is used for the CTW patients thus includes a nonlinear term, $S_I G_t Q_{eff}$ in Equation 4.1, to the system to be solved. Nonlinear solution methods present a significant computational burden, which reduces the available number of paitient hours that

Parameter	Value
α_G	0.015 L mU^{-1}
α_I	0.0017 L mU^{-1}
EGP	1.16 mmol L^{-1} min^{-1}
n	0.16 min^{-1}
k	0.0099 min^{-1}
k_2	0.0649 min^{-1}
k_3	0.0388 min^{-1}
k_4	0.0097 min^{-1}
a_{max}	1.1
V_p	22% of bodymass
V_i	15% of bodymass

Table 4.1 Constant model parameters used

can be considered. Therefore, the fitting is not solved as a simultaneous system, but rather as a sequential series of S_I profiles, with Q_{eff} resolved for 3 hours following the meal periods, assuming a constant S_I. It has been shown (Wilinska *et al.*, 2004; la Fleur, 2003; la Fleur *et al.*, 2001) that insulin sensitivity varies significantly over a day and therefore it is not expected that insulin sensitivity would remain constant over the 3 hours following a meal. However, a constant S_I is required to identify endogenous insulin secretion.

Data is divided into periods for fitting, where each period goes from 3 hours following the last meal (or the first available data point) up to 3 hours following the next meal. If another meal is eaten within the final three hours, then S_I becomes variable again 3 hours following the last meal. Once each section has been solved, S_I is refitted over the whole time period to correct any error which arises from needing negative I_B values, which are not physiologically possible.

Integrating Equation 4.1 over a time period gives:

$$\int_t^{t+x} \dot{G}dt = G_{t+x} - G_t = -p_G \int_t^{t+x} Gdt - S_I \int_t^{t+x} GQdt + \int_t^{t+x} \frac{P(t) + EGP}{V} dt \quad (4.7)$$

In Equation 4.7, x is 10 when S_I is being fitted and 1 when I_B is being fitted. Thus, there are 6 and equations for S_I and I_B respectively when solving the system, which is of the form: $[A] \begin{pmatrix} S_I \\ Q \end{pmatrix} = \underline{b}$. Such a system can be solved by the method of least squares.

Once the system has been solved, $(t)Q(t)$ can be found since S_{I,t_n-3} is known. Differentiating the last 18 elements of the solution vector then gives the GQ

product over time and thus Q_{eff} (and hence Q) can be found. From known Q the $\dot{Q}$ equation can be integrated written in terms of $\int Idt$ using the same method as above. The integrated Equation 4.2 is given in Equation 4.8. From this equation, a system of the form $[k]\,(_I) = \underline{Q}$ can be written and solved.

$$\int_t^{t+1} \dot{Q}dt = Q_{t+1} - Q_t = -k\int_t^{t+1} Qdt + k\int_t^{t+1} Idt \tag{4.8}$$

Finally, from this solution, $\int I_B dt$ can be fitted to the $\dot{I}$ equation using known insulin inputs. Equation 4.3 is shown in its integrated form in Equation **??**. The solution to the resulting system is the desired 18×1 solution vector of endogenous insulin secretion. The linear least squares solution for I_B is bound to be positive.

$$\int_t^{t+1} \dot{I}dt = I_{t+1} - I_t = -n\int_t^{t+1} \frac{I}{1+\alpha_I I}dt + \frac{1}{V}\int_t^{t+1} u(t)dt + \frac{1}{V}\int_t^{t+1} I_B dt \tag{4.9}$$

The fit values of I_B should approximate the expected profile of insulin secretion, shown in Figure 4.2. It is possible to fit a curve through these secretion rates found to reflect this profile and use this curve for the insulin secretion model, however due to the small changes in rate that occur over 10 minutes, with the occasional exception of an acute spike in the initial stage, it is likely that this would not affect the accuracy of the fits obtained.

An example of a patient fitted using this method is shown in Figure 4.3. The shaded regions indicate time during which S_I is held constant and I_B is fitted. It can be seen that the period of I_B fitting is sometimes longer than three hours, which occurs when a patient consumes a meal within 3 hours of the last. In this case, S_I is held constant for the duration of the meals and becomes variable again 3 hours after the final meal.

An extensive validation study of this model is yet to be carried out. C-peptide data would need to be available to confirm the EIS rates fitted using the methods described above. Similarly, continued data collection in relevant patient cohorts will assist in validating the model, particularly if insulin is administered throughout the patients stay.

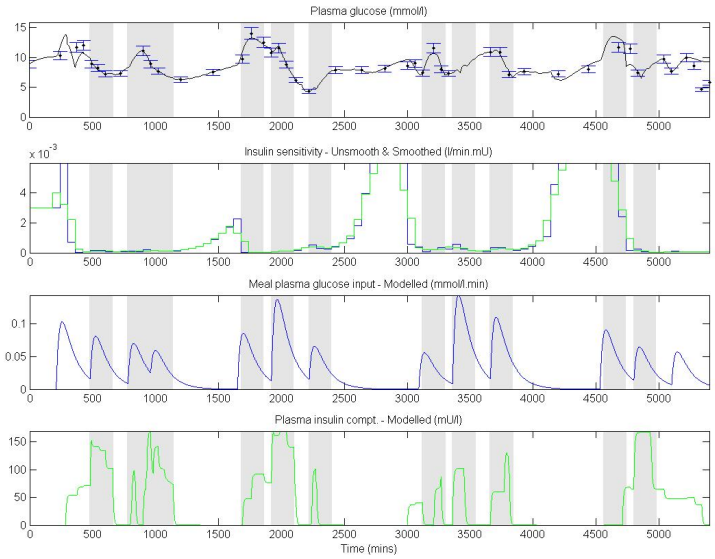


Figure 4.3 Fitted and modelled data for CTW patient 5

Chapter 5

Stochastic Modelling

The improvement of glycaemic control with increased measurement and intervention adjustment frequency is well established. However, in many settings, the increased burden on clinical staff introduced by such glycaemic control protocols is restrictive (Mackenzie *et al.*, 2005; Aragon, 2006). Thus, minimising the frequency of adjustment or measurement in glucose control strategies is of paramount importance to attain maximum effectiveness for minimal impact on clinical burden. In this chapter, stochastic modelling methods are employed to generate a virtual patient cohort that reflects the physiology of patients encountered in less acute wards with lower nurse:patient ratios. These profiles can then be used in control utilizing 1-3 hourly measurements to optimize clinical burden in the overall result.

5.1 Methodology

To predict the effect of a treatment protocol on a population, understanding insulin-glucose dynamics alone is insufficient. Time varying profiles of patient specific parameters are required to simulate how any therapies interact with these progressions over time. However, to achieve good correspondence between simulation and clinical results many hundreds of hours of clinical data are required, which takes time and resources to collect. Stochastic modelling enables understanding of population characteristics as a probabilistic model using Markov chains.

It is physiologically expected and well recorded that current insulin sensitivity of a patient is related to insulin sensitivity after one hour. Given that future insulin sensitivity can be viewed as a conditional progression from a present insulin sensitivity state, it can be modelled using Markov chains. Lin (2007) developed a stochastic model of insulin sensitivities of critically ill patients using

a cohort of 394 ICU patients from Christchurch Hospital using 2-dimensional kernel density estimation.

Such predictive measures reduce the heightened risk of hypoglycaemic episodes in patients recieving intensive insulin therapy (Chase *et al.*, 2007). The model is defined by confidence bands based on clinically observed parameter variations. Using Monte Carlo methods, statistically accurate S_I profiles can be generated, thus creating a 'Virtual Patient'. Validation against 23,324 hours of clinical SPRINT data has shown an excellent correspondence in control algorithm results on Virtual Patients (Lin *et al.*, 2008; Chase *et al.*, 2007).

The probabilistic model generated will determine the most likely insulin sensitivity to follow a given present value for a subset of patients. The probability of each outcome for a given present value is determined by the fitted clinical data. It is assumed that insulin sensitivity is dependent only on its previous hourly value. Clinically, this assumption holds true because patients generally experience changes in their metabolism that are caused by unmodelled external factors, such as a worsening of the admission condition. However, there is evidence that insulin sensitivity generally progresses during a patients stay (Langouche *et al.*, 2007).

This should not affect the validity of the Markovian assumption for the application of the model to the control problem since it is not trends over long periods of time that affect a patient's need for insulin or glucose, but rather over 2-3 hour periods. The control inputs need to be able to respond to the higher frequency changes in insulin sensitivity. However, if data included long periods of stay, the Markovian property assumption may become invalid.

Two dimensional kernel density estimation of S_I is generated from the data described in Section 5.2. The conditional probability of each outcome is calculated by the probability of the sequence of data as determined by the observed frequency in clinical data and normalised by the probability of the initial condition. Since S_I values are continuous a discretisation must be made to calculate these probabilities. For the models presented in this thesis, S_I is discretised with a resolution of 6×10^{-5} L mU^{-1} min^{-1}. The probability density function is such that the integral of the probability curve between 1×10^{-6} and 6×10^{-3} L mU^{-1} min^{-1} is equal to one. Thus, a slice along the $S_{I,t}$-axis of the generated density functions gives the distribution of likelihood of the subsequent S_I reading for a given current S_I. The joint probability density function is weighted by the probability of $S_{I,t} = x$ so that the most likely S_I values have highest density values. The normalisation is such that the integral of the surface is equal to one.

5.2 Probability Model

Using the methods of Lin *et al.* (2006, 2008) as described in Section 2.5.4, a two dimensional kernel estimation function was generated using the subset of 394 patients admitted to the Christchurch Hospital ICU during the years 2001-2007 and experienced hyperglycaemia during their ICU stay. Details of this subset are given in Section 3.3. Patients from this cohort were chosen to isolate more stable ICU patients which would closely resemble the characteristics of a patient found in the CTW. This was achieved by selecting patients that were discharged to the ward and examining the last 36 hours of their ICU stay. In total, 4104 hours of patient data pairs were available for the model generation, collected from 130 patients of the 394 cohort. The difference between the expected number of hours (130 patients $\times$ 36 hours) is due to some of the 130 patient stays being shorter than 36 hours, or at least the period of glycaemic data available did not exceed 36 hours.

It is expected that the glycaemic control data of ward patients is fundamentally different to that of ICU patients. ICU patients are more critically ill and recieve larger doses of insulin which is entirely intravenous (IV). However, it is not uncommon for patients to recieve IV insulin as part of the SPRINT protocol and need to transition to subcutaneous insulin. This transition needs to be examined also. For this purpose, the last 36 hours of ICU patient data of patients discharged to a ward following their ICU stay were examined. This is the period most closely resembling the physiological characteristics of a patient in the ward, although nutrition and insulin therapies will be significantly different once a patient is in the ward. These differences necessitate the use of additional insulin compartments to describe the action of the range of insulin therapies encountered.

All of these patients were on the SPRINT protocol during the stable period that was isolated and 87% of patients were on the SPRINT protocol for insulin administration alone. That is, 13% of patient hours considered were collected from patients consuming regular, unregulated meals, which is also a characteristic of patients in the CTW. However, data on the meals consumed is not available and thus no compensatory measures such as endogenous insulin secretion spikes are considered.

The insulin sensitivity pair distribution is shown in Figure 5.1 along with the confidence intervals. The probability densities generated for this cohort of data are shown in Figure 5.2 and Figure 5.3. The density of data available for insulin sensitivities greater than 3×10^{-3} mU L^{-1} min^{-1} is very low as shown in

Figure 5.1. Therefore, there is poor model quality for insulin sensitivities greater than this, expressed as an irregular and highly asymmetric surface. Overall, the amount of data available is likely insufficient to generate a model which will accurately represent the characteristics of a patient in the CTW, as would be expected from the results of Lin *et al.* (2008, 2006) which observed convergence after 1200 patient hours with a smaller domain of possible S_I values.

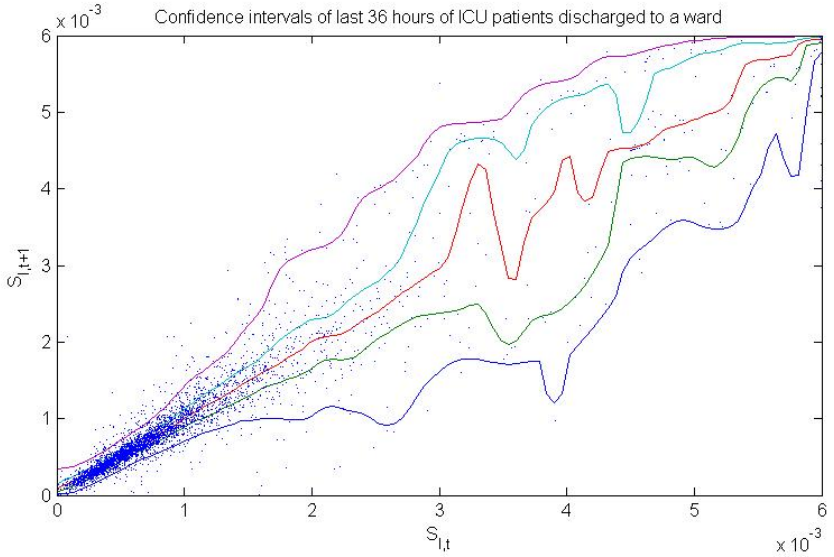


Figure 5.1 Confidence intervals for $S_{I,t+1}$ values for stable ICU cohort

The S_I data used in the model creation uses 3 point smoothing, however in order to maintain clinical applicability the smoothing was done using the last 3 S_I values rather than using future values, as would normally be done. This type of smoothing has the potential to introduce a lag in a controller's response to changes in glucose levels, but would also prevent a controller overreacting to a spike in percieved S_I reading due to a contaminated sample or similar error. This type of retrospective smoothing could be easily implemented into a clinical setting and therefore the use of smoothing does not adversely affect the useability of the results. Smoothing has the effect of tightening the probability distributions towards the line $S_{I,t} = S_{I,t+1}$ as can be seen in comparing (a) and (b) of Figure 5.2. The high frequency noise that is removed by smoothing is unlikely to be physiologically accurate as variation in S_I has been shown to vary diurnally (la Fleur, 2003; la Fleur *et al.*, 2001).

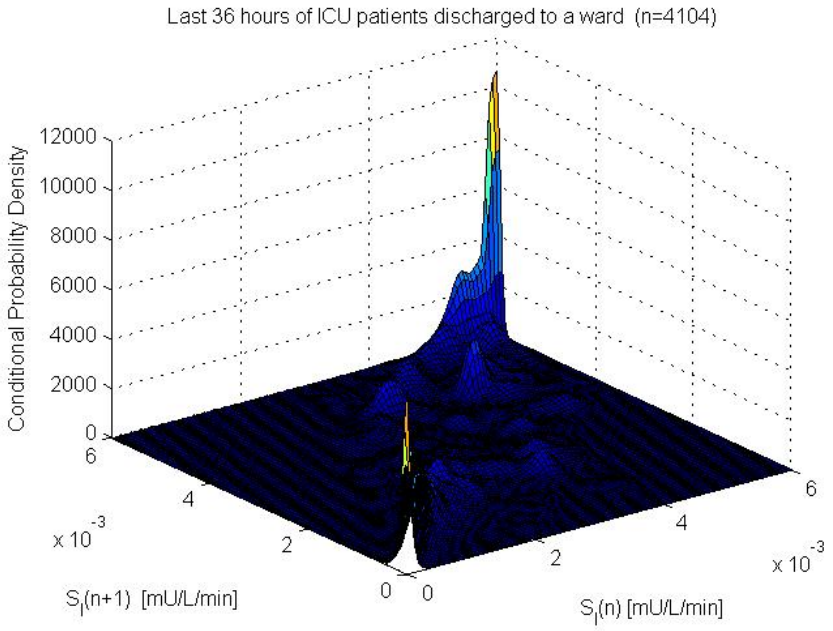


Figure 5.2 Probability density function for ICU patients

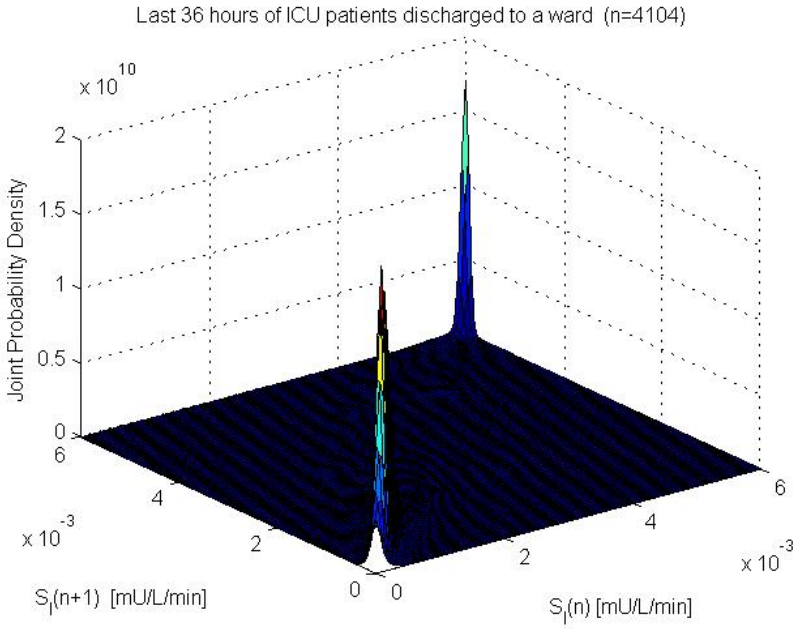
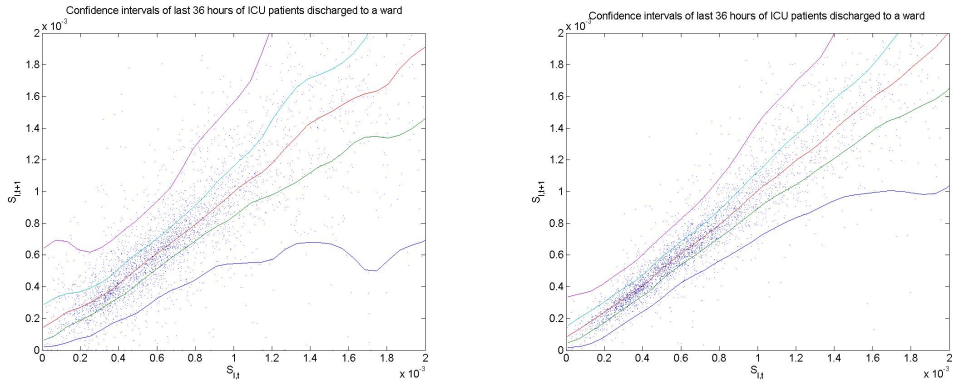


Figure 5.3 Joint probability density function for ICU patients



(a) No smoothing (b) 3 point smoothing

Figure 5.4 The effect of smoothing on lower section of insulin sensitivity distributions

5.2.1 Validation

5.2.1.1 Data Inclusion

Table 5.1 shows the model for the same patients, but using increased or decreased periods of data inclusion. Comparing the data between these groups shows that the period of inclusion does not significantly affect the model developed for random sample sets of 1000 values. The p-values for Table 5.1 are calculated using the Kolmogorov-Smirnov test, which compares the two sample sets and tests the hypothesis that the data values are drawn from the same distribution. Thus, the results indicate the desired similarity in this case.

Hours prior to discharge	Hours of Data	P-value*
12	1577	0.78
24	2919	0.43
36	4104	0.85
48	5224	-

*P values comparing the distribution from 48 hours of inclusion to the stated number of hours inclusion

Table 5.1 Comparison of insulin sensitivity distributions for varying hours prior to discharge included

There is a high density of readings at the imposed lower limits of S_I in the ICU cohort. The lower limit of S_I (1×10^{-6} L mU^{-1} min^{-1}) is frequently found during periods of time when a patient is given no insulin. If patients with a period of more than 6 hours without insulin are excluded from the model, the probability distributions show lower densities at these limiting values, as can be seen by comparing Figures 5.1 and 5.5. However, increased asymmetry and

irregularities increase due to the reduced quantity of data available, particularly at S_I above 2×10^{-3} L mU^{-1} min^{-1}.

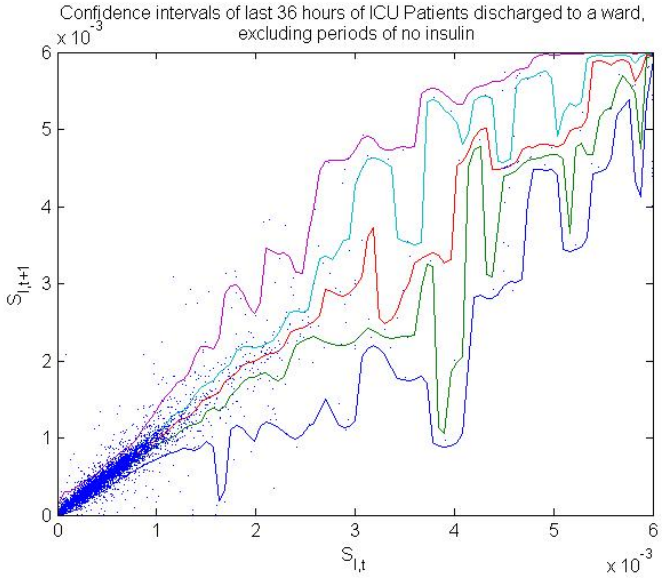


Figure 5.5 Confidence intervals for $S_{I,t+1}$ values for stable ICU cohort, excluding periods without insulin dosing

5.2.1.2 Random Walk compared to Clinical Data

To test the validity of assumption of S_I as a Markov variable, the results from a random walk of 2 and 3 hours is compared to the confidence intervals expected from clinical data. The results of this analysis are shown in Table 5.2. Table 5.2 indicates that while the 90% confidence interval gives a good bound on the clinical data, the model significantly overestimates the variability in the 50% confidence interval creating a narrower peaked distribution. The key aspect is that the data distribution on either side of the median remains relatively constant. A large trend to one side would indicate time dependent directed progression of clinical data that is unmodelled in this case. There is a large change in the 50% confidence interval at 2 hour predictions, but as all other elements are largely equal, it is likely the result of some set of outliers in the data.

5.2.1.3 Comparison to other data

In addition to the ICU patient data, the 7 CTW patient fitted profiles were examined. This time of hourly varying S_I constituted 88.4% of patient time over the given cohort. For the remaining 11.6% of patient time, EIS was fitted and S_I held constant. Variance in S_I during this time is considered after I_B has

	1 hour	2 hours	3 hours
50% Confidence Interval	62.2%	68.2%	62.6%
90% Confidence Interval	91.8%	91.0%	89.7%
Number of Patients Above 50th percentile	57.1%	50.9%	51.5%
Number of Patients Below 50th percentile	42.9%	48.1%	48.5%

Table 5.2 Proportion of clinical ICU $S_{I,t}$ and $S_{I,t+2,3}$ pairs falling between model generated from a 2 and 3 hour random walk

been fitted and therefore these periods are thus still able to be included in the stochastic model. To omit the S_I values during this time would bias the model towards times during which meals are not eaten.

Finally, data from 10 Ambulatory Diabetic patients was utilized to compare S_I distributions. It is expected that these patients will exhibit higher S_I values than the CTW or ICU patients because they are otherwise healthy subjects. However, this data provides a comparison to ensure that the modified fitting method employed on CTW patients is not causing any significant changes between the groups.

A comparison of the stochastic model generated to a similar model generated by the limited amount of clinical data specific to the problem is summarised below. The clinical data is then compared to the stochastic model created and the results are shown in Table 5.3.

	1 hour	2 hours	3 hours
50% Confidence Interval	47.9%	49.8%	45.2%
90% Confidence Interval	79.4%	81.4%	78.2%

Table 5.3 Incidence of $S_{I,t}$ and $S_{I,t+1}$ pairs from CTW patients within ICU patient confidence intervals

Figures 5.6-5.7 shows the distribution of $S_{I,t+1}$ for each group. In all cases, Lin *et al.* (2006, 2008) found that with approximately 1200 patient hours of data, model convergence was observed, when compared with a similar model from 23,000 patient hours. However, the range of possible S_I readings was limited from 1×10^{-5} L mU^{-1} min^{-1} to 1.2×10^{-3} L mU^{-1} min^{-1} and in the models generated for the CTW and ambulatory cohorts, the model uses an increased range of 1×10^{-5} L mU^{-1} min^{-1} to 6×10^{-3} L mU^{-1} min^{-1}. It is therefore likely that more data will be required to obtain an equally reliable model.

Figures 5.6 and 5.7 show the confidence intervals for available data from the CTW and ambulatory diabetic patients respectively. However, in both cases, the

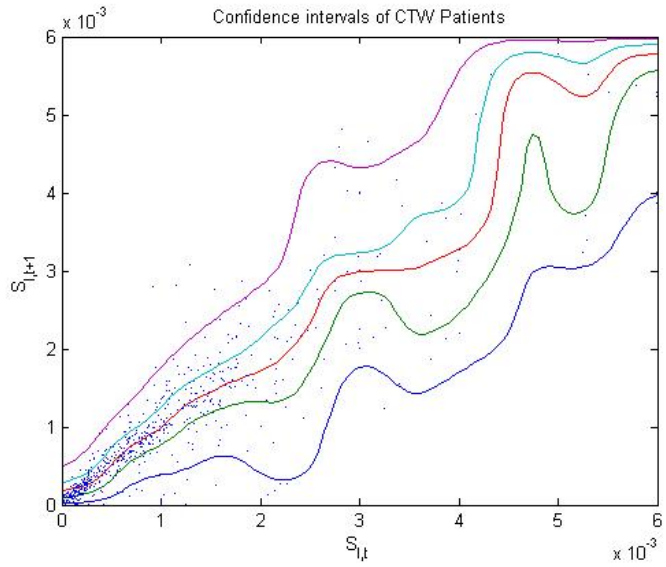


Figure 5.6 Confidence intervals for $S_{I,t+1}$ values for CTW cohort

number of hours available is low (600 hours combined) compared to that for the ICU cohort model (over 4000). Hence, its reliability may be less and variability greater.

It is clear that there is a greater relative density of low S_I in the CTW cohort than the ICU patients, likely due to the presence of diabetes in all patients included in the study. The CTW patients showed greater density of data in the higher S_I range than the ambulatory diabetics. This result is likely because the CTW cohort has a subset of diabetic patients, but also includes patients experiencing glycaemic control problems without any previous history of diabetes. Therefore, it is possible that some CTW patients' hyperglycaemia is not due to insulin resistance, but due to increased stress-related gluconeogenesis brought on by their condition or surgery. The CTW patients also show significantly higher variance, which could be expected due to their changing condition.

5.2.1.4 Model Convergence

To determine if sufficient data is available to produce reliable model results a model convergence study was carried out. The convergence study is conducted on the stable ICU cohort as it has the greatest amount of data available. Following the method of Lin 2007, the patients are divided into four equal groups and a model is built from 3 of the 4 data sets. The remaining data set can then be compared to the modelled confidence intervals and the proportion of data lying between these bounds can be compared. The statistics for each group are

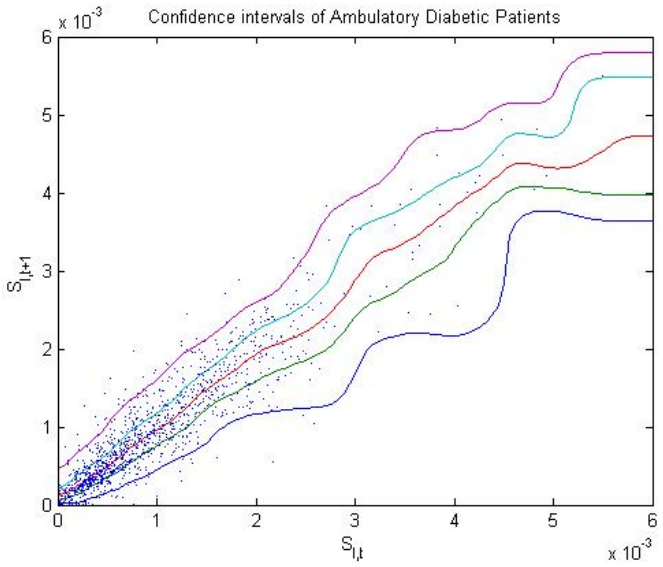


Figure 5.7 Confidence intervals for $S_{I,t+1}$ values for Ambulatory Diabetic cohort

summarised in Table 5.4.

The results of the study are summarised in Table 5.5 and there is some significant variance between the sets of patients and the final combined result. This outcome indicates that additional data may be required for model convergence. In light of this, it is expected that the CTW model with much less data will also require further clinical results before a satisfactory stochastic model can be developed.

Group	APACHE II	Age	Gender (% Male)	LOS[a] (Days)	Mean BG (mmol L^{-1})*
1	19.7	56.3	73.3	13.6	5.7
2	18.2	60.1	75.1	8.8	6.2
3	20.3	61.5	75.1	11.0	5.2
4	19.8	57.9	74.5	12.2	6.0

[a] Length of stay
* $p < 0.05$

Table 5.4 Average statistics for data groups used in convergence study

It is interesting to note that the predicted confidence intervals are consistently conservative, particularly the 50% confidence bounds. This behaviour has been observed by other studies (?Lin *et al.*, 2008, 2006). This result may be due to the variance estimator employed, and could potentially be corrected by bias-variance trade-off. Interestingly, the pontentially more useful 90% bounds are

Excluded Test Group	Percentage of Data falling between the 50% confidence interval	Percentage of Data falling between the 90% confidence interval
1	60.1	91.4
2	57.5	90.2
3	66.5	92.4
4	66.3	94.6
-	61.2	92.1

Table 5.5 Proportion of $S_{I,t+1}$ values falling between predicted confidence bounds in convergence study over 5 test groups

more accurate indicating a mismatch between the clinical data and assumed distributions.

Chapter 6

Glycaemic Control Protocols

Glycaemic control has been shown to reduce mortality, sepsis and other negative outcomes in critically ill patients. It has also been recognised as an important factor in managing diabetes in ambulatory patients. The methods of attaining normoglycaemia in such a variety of patient parameters and lifestyles have however proved far more elusive. Lonergan *et al.* (2006b) produced the paper based SPRINT protocol for use in critically ill patients, particularly those on enteral feed. This protocol increased patient time between 4.4-6.1 mmol L^{-1} from 30% to 53.9% (**?**). However, SPRINT requires measurements every 1-2 hours, which is a large clinical burden. Alternative strategies based on the principle of SPRINT but employing the use of long-acting insulin or predictive measures could potentially make tight glycaemic control accessible in a ward setting.

6.1 SPRINT in the Wards

6.1.1 SPRINT with Insulin Infusions

SPRINT is a nearly established protocol in Christchurch Hospital ICU. However, the ICU has a 1:1 nurse to patient ratio, allowing for the extra burden that SPRINT places on clinical staff. The frequent blood glucose readings and insulin/feed adjustments (1-2 hourly) and hourly bolus administrations are likely to become overly cumbersome within a ward setting where nurse to patient ratios are closer to 1:3 or worse. Therefore, measurement periods of 1-3 hours are more likely to achieve practical success in clinical implementation. For this purpose, insulin infusions are also likely to be better suited. Infusions require less time to complete protocol related tasks and would likely need adjustment less frequently once stability is attained. The greatest risk of this approach is that of hypoglycaemia, which may result from infusions being allowed to run over the specified

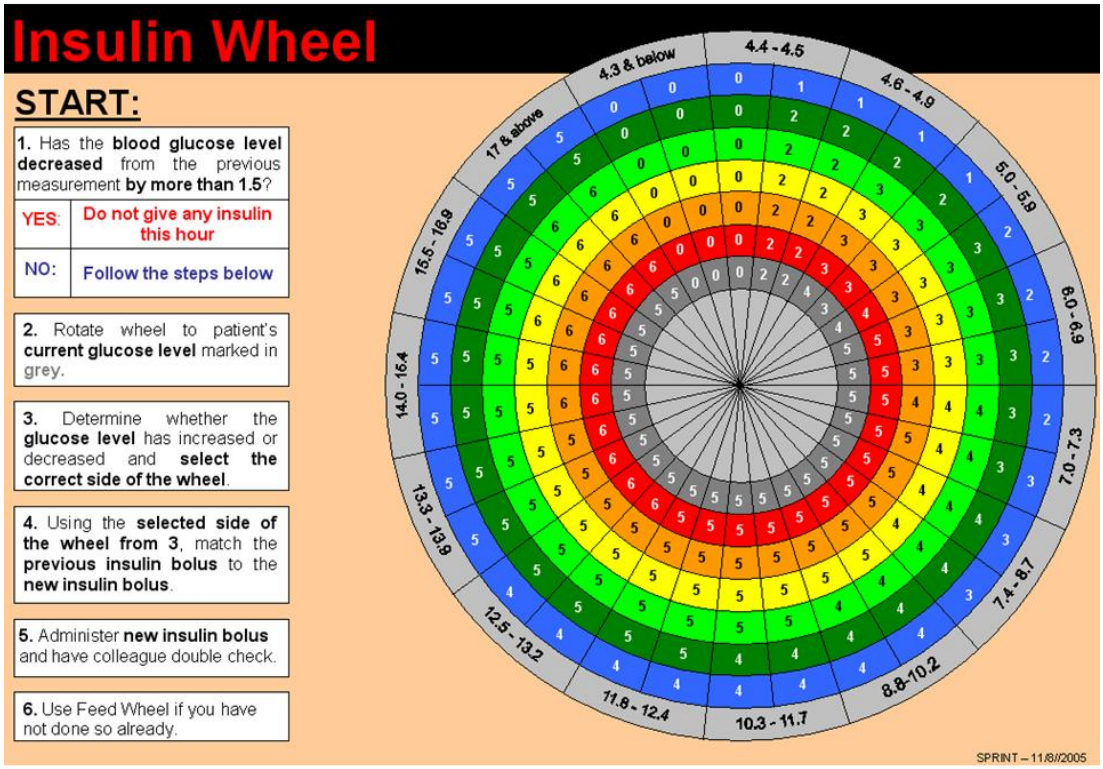


Figure 6.1 The SPRINT insulin wheel

time period.

SPRINT is an adaptive glycaemic control protocol that responds to changes in glucose (derivative control) by adjusting feed and insulin doses. Because SPRINT is well established in Christchurch Hospital's ICU a similar control system would be easier to clinically implement in the wards than other novel approaches. CTW patients are not enterally fed and thus all nutrition comes from meals consumed at irregular intervals over the course of a day, followed by nightime fasting. Simulations were run on CTW and ambulatory diabetic patients using the SPRINT insulin wheel only (see Figure 6.1) to determine IV insulin infusions. Meals were not modified or controlled in any way, as would be expected in a clinical setting.

The simulations showed very poor glycaemic control with a very high incidence of hypoglycaemia. These results are potentially dangerous and unacceptable for clinical practice. The summary statistics for the response of the cohort to this algorithm is shown in Table 6.1.

In particular, hypoglycaemia was common following meals and during long fasting periods, such as during night. SPRINT was also slow to mitigate the high blood glucose levels observed following large carbohydrate intakes. These

results are actually to be expected, as SPRINT was designed for patients receiving relatively constant glucose inputs and required adjustment of the feed rates based on glucose levels. Since the glucose intake (in the form of meals) in CTW patients are more like impulses than constant forces on the system, SPRINT cannot adjust to the rapid changes in glucose levels and insulin requirements. In addition, assuming constant nutrition means that it is equally slow to shut off insulin between irregular CTW meals.

It is not clear if the model employed is overestimating a patients postprandial response to insulin infusions, but highly likely. Insulin sensitivity generally peaks around meal times, as described in Section 4.2.5. If this effect is not physiologically real and instead represents a modelling error due to the omission of endogenous insulin secrection then the hypoglycaemia incidence rate will be overstated.

To check the extent of this possible modeling error, identical simulations were run using the modified model described by Equations 4.1-4.3 which include a fitted I_B. The summary statistics for these simulations are shown in Table 6.1. It is important to note that the model employed in these simulations has not undergone validation for the CTW cohort or similar group. Thus, the protocols proposed below could potentially be underestimating insulin sensitivity during endogenous insulin secretion. If this is the case, then the response to insulin inputs would be much larger than expected and could thus induce a hypoglycaemic incident.

The inclusion of EIS does mean that a portion of the required insulin to allow uptake of the glucose input into the cells is provided by the body's physiological responses to elevated levels. If this portion of insulin recommended is counted as part of the SPRINT input, then it would help counteract the effects of underestimating insulin sensitivity while using SPRINT, as EIS is the uptake of modeled insulin sensitivity dynamics when insulin sensitivity is frozen.

6.1.2 Modifications to SPRINT

The results of the CTW cohort being controlled by the SPRINT insulin wheel (Figure 6.1) are summarised in Table 6.1. The results show a high level of hypoglycaemia and little success in maintaining blood glucose levels in a desireable 4-7 mmol L $^{-1}$ band.

The response of SPRINT to changes in blood glucose are agressive in terms of insulin dose adjustments. SPRINT is able to deliver a high dose of insulin

in response to blood glucose spikes without significantly increasing the risk of hypoglycaemia as feed levels in the ICU can be increased on the next hour if a large drop of blood glucose is observed. In contrast, in the wards, this response is not available because of the nature of nutrition recieved by the patient.

Similarly, the Insulin Wheel is not designed to respond to large carbohydrate intakes that result in blood glucose spikes. A spike in glucose in an ICU patient represents either an erroneous measurement or a change in patient condition. Thus, SPRINT needs to respond to this change by adjusting baseline doses gradually until equilibrium is achieved. Clearly this response is not appropriate to postprandial blood glucose behaviour. To address these issues, several modifications were made to the SPRINT insulin wheel and/or its use, as described below.

6.1.2.1 Reducing Insulin Dose

SPRINT is generally too aggressive in reducing glucose for CTW cohorts, with little safeguard against hypoglycaemia as the feed is not modulated. Therefore, simulations were run that administered the recommended SPRINT dose as an infusion, less 1 U hr^{-1}. The results of these simulations are shown in Table 6.1 and are compared to the unmodified SPRINT results for the same cohort.

	SPRINT		SPRINT reduced by 1 U hr^{-1}	
Fit Parameter(s):	S_I	S_I and I_B	S_I	S_I and I_B
Time between 4.0-6.1 mmol L^{-1}	37.3%	35.4%	36.8%	33.6%
Time between 4.0-7.0 mmol L^{-1}	47.1%	49.7%	49.2%	46.7%
Time between 4.0-7.75 mmol L^{-1}	54.0%	57.0%	56.2%	56.6%
Time above 6 mmol L^{-1}	39.2%	48.0%	45.3%	52.2%
Time below 4 mmol L^{-1}	24.4%	17.4%	19.2%	15.7%
Time below 2.5 mmol L^{-1}	10.0%	6.6%	6.6%	5.1%
Time below 2.2 mmol L^{-1}	3.5%	1.5%	1.8%	1.3%
Mean Blood Glucose (mmol L^{-1})	6.2	6.6	6.5	6.8
Standard Deviation (mmol L^{-1})	3.2	3.2	3.2	3.2

Table 6.1 Simulation results for SPRINT and SPRINT reduced by 1 U hr^{-1}

Table 6.1 clearly indicates that while the incidence of hypoglycaemic episodes is greatly reduced by reducing the SPRINT infusion, it is at the cost of an increase in hyperglycaemia. It appears that this change merely shifted the glucose distribution toward the higher blood glucose region, while losing some tightness of control. This outcome is also illustrated by Figure 6.2.

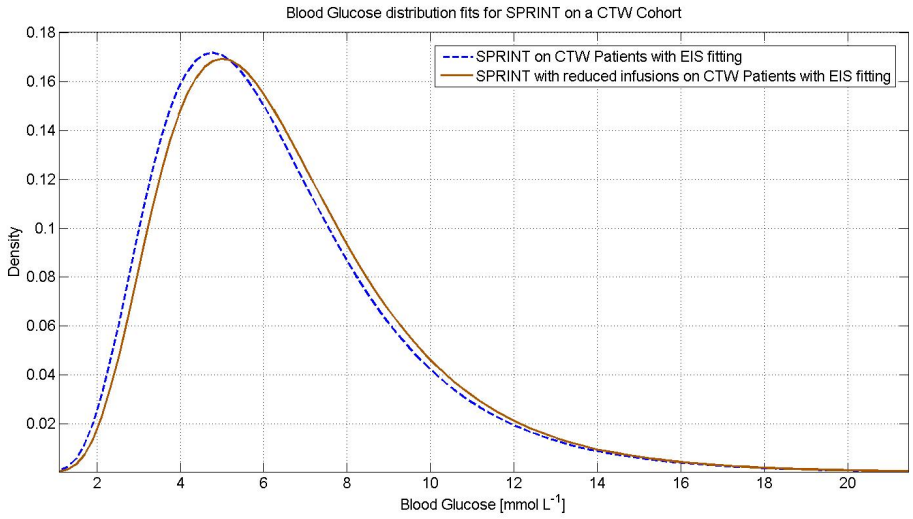


Figure 6.2 Blood glucose readings distribution for SPRINT and two modifications

6.1.3 Meal Dependent Boluses

Emulating the principles of 'Carb Counting' (Section 2.2), a strategy to include meal boluses into the SPRINT protocol was investigated. The number of carbohydrates consumed in a meal was used as a guide to the IV insulin bolus administered. The use of similar principles has been investigated by several studies (Raslov *et al.*, 2004; Perriello *et al.*, 2005; Dailey *et al.*, 2004; **?**), although rapid acting subcutaneous insulins were used instead of IV insulin. Meal boluses were to be administered to a patient one and sometimes also two hours after consuming a meal, their size based on the carbohydrate content of what was eaten and in some cases, the time of the day. Using two meal boluses instead of one allows for a conservative choice to be made in the first instance and then correction of an inadequate bolus at the second, if required, without prolonged hyperglycaemia. The results for these simulations are given in Tables 6.2 and Figure ctwvsbolus. A constant 1 U hr−1 IV infusion was present at all times, except for when glucose levels fell below 5 mmol L^{-1}.

This approach should remedy the problem with slow response to blood glucose peaks that SPRINT inherently entails. However, because such large doses are being administered in bolus form, a much higher risk of hypoglycaemia may be present. While in some cases, boluses deliver good reduction in postprandial glucose spikes, others reach dangerously low blood glucose rates. It is important to note that the model employed here is not validated in these low glucose readings of less than 2 mmol L^{-1} and thus figures below this value are likely indicative

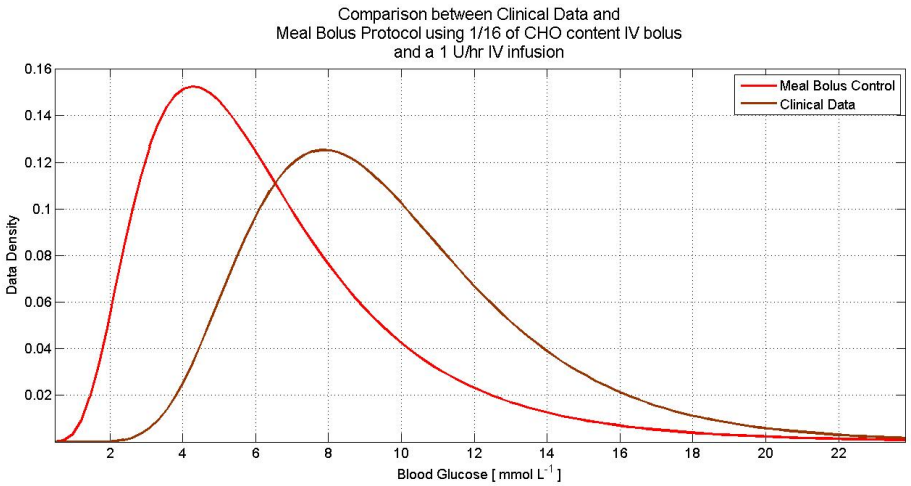


Figure 6.3 A comparison between the glucose distributions of CTW clinical data and predictive control results. Fits assume a lognormal distribution.

only. It is likely that glucose levels this low would cause severe phsyical symptoms, which would alert clinical staff to the situation. Levels this low should also induce an increase in EGP, which is not modelled directly due to the high difficulty in quantifying such an effect given inter-patient variability.

Bolus at 1 hr: Bolus at 2 hrs:	CHO/8 -	CHO/16 -	CHO/32 -	CHO/32 CHO/64
Time between 4.0-6.1 mmol L^{-1}	34.2%	35.0%	33.6	34.3%
Time between 4.0-7.0 mmol L^{-1}	45.4%	45.3%	44.6	44.8%
Time between 4.0-7.75 mmol L^{-1}	52.6%	53.6%	53.1	53.4%
Time above 6 mmol L^{-1}	45.1%	46.7%	49.3%	46.6%
Time below 4 mmol L^{-1}	22.3%	19.4%	18.8%	20.1%
Time below 2.5 mmol L^{-1}	10.3%	9.2%	8.8%	9.4%
Time below 2.2 mmol L^{-1}	5.8%	5.2%	4.9%	4.6%
Mean Blood Glucose (mmol L^{-1})	6.3	6.8	6.6	6.5%
Standard Deviation (mmol L^{-1})	3.9	3.7	3.7	3.6%

Table 6.2 Simulation results for protocols using meal dependent boluses. All dosing ratios include a constant 1 U hr^{-1} IV infusion, except for when glucose below 5 mmol L^{-1} is measured

6.1.4 Basal Insulin Replacement Strategies

Glargine mimics the basal insulin secretion of a healthy pancreas and lasts for approximately 24 hours. It exhibits no peak action and therefore is not a substitute for post-prandial insulin secretion, which (if required) must be replaced

with a bolus of short acting insulin or with endogenous function. For this reason, glargine administration trials are run only on the insulin sensitivity profiles that include EIS. Glargine has often been used in conjunction with oral hypoglycaemics and insulin dose is usually adjusted over a period of weeks to ensure good equilibrium. However, patients in the CTW require targeted glycaemic control over a period of a few days, so the titration of glargine must be relatively rapid.

Daily glargine dose adjustments for the Treat-to-Target protocol (Riddle *et al.*, 2003) are given in Table 6.3. All patients start on a 10U dose, which is then adjusted daily. Meal boluses of $\frac{CHO}{16}$ are preserved for one simulation. Simulation results are summarised in Table 6.4 for this approach.

Morning Fasting Glucose (mmol L^{-1})	Dose Adjustment
≥ 10	+8U
7.8 - 10	+6U
6.7 - 7.8	+4U
5.6 - 6.7	+2U
≤ 5.6	-

Table 6.3 Glargine dose titration for Treat-to-Target protocol

	Meal Bolus	No Bolus
Time between 4.0-6.1 mmol L^{-1}	37.3%	12.1%
Time between 4.0-7.0 mmol L^{-1}	47.1%	23.4%
Time between 4.0-7.75 mmol L^{-1}	54.0%	33.0%
Time above 6 mmol L^{-1}	39.2%	82.4%
Time below 4 mmol L^{-1}	24.4%	5.9%
Time below 2.5 mmol L^{-1}	10.0%	2.5%
Time below 2.2 mmol L^{-1}	3.5%	1.4%
Mean Blood Glucose (mmol L^{-1})		8.9
Standard Deviation (mmol L^{-1})		3.9

Table 6.4 Simulation results for glargine based protocol

The results in Table 6.4 suggest that insulin glargine is not appropriate for control of CTW patients. While the glucose levels do normalise after several days of treatment (see Figure 6.4), the initial period sees little to no improvement over the actual clinical results (shown as a dashed line).

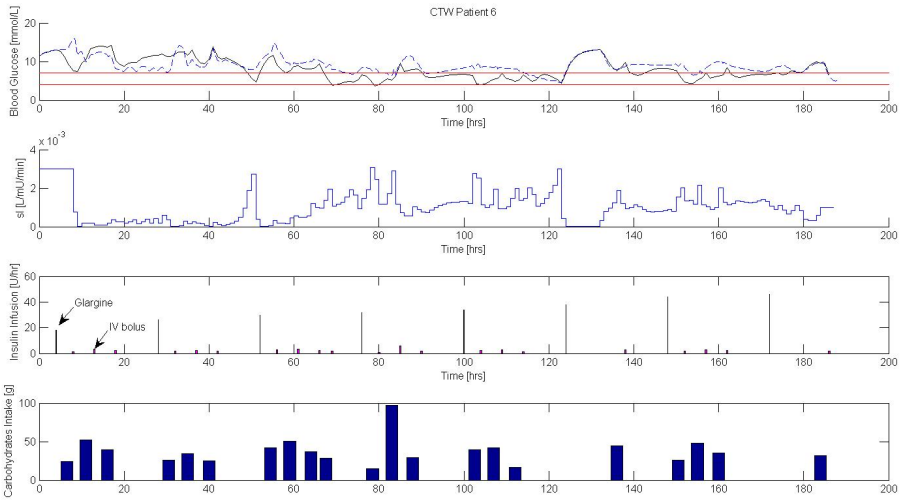


Figure 6.4 An example of a CTW patient on the Treat-to-Target protocol

6.2 Predictive Control

Predictive control has been used by **??** to effectively control glucose in intensive care. Similar principles can be applied to less critically ill patients in order to determine the effectiveness of glycaemic control methods at less frequent measurement and intervention intervals. The model used for prediction is shown in Figure 5.3. The first S_I value is predicted based on the 50th percentile of the stochastic model of the appropriate cohort. The second is based on the initial S_I reading, but from the model's 50th percentile after two hours and the same for the third. Thus, the predictions are all made based on data that is only acquired every third hour. Thus, the uncertainty grows with time, as seen by the 50% and 90% confidence bands. An example of these growing confidence bands are shown in Figure 6.5.

The target to be achieved greatly affects the performance of the controller. Performance is altered by varying insulin infusions from between 0 and 10 U hr^{-1} with resolution of 0.5 U hr^{-1}. To prevent unacceptable levels of hypoglycaemia, a target can be set that keeps the 5th percentile above 4 mmol L^{-1}, however, when confidence bands are large, this necessarily requires a large probability of hyperglycaemia. Thus, for this study, a target of 5 mmol L^{-1} or a reduction of 1.5 mmol L^{-1} hr^{-1} is set, with no constraints on the lower confidence bands.

To examine the effect of measurement frequency, predictive control is run based on 1,2 or 3 hourly measurements. The glycaemic control results are shown

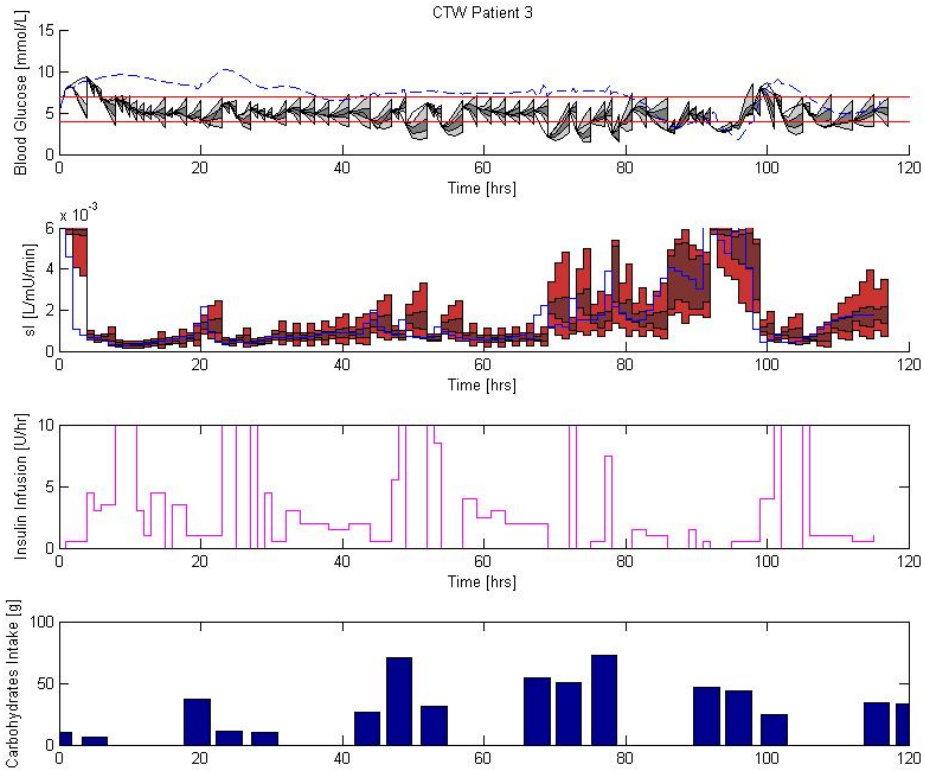
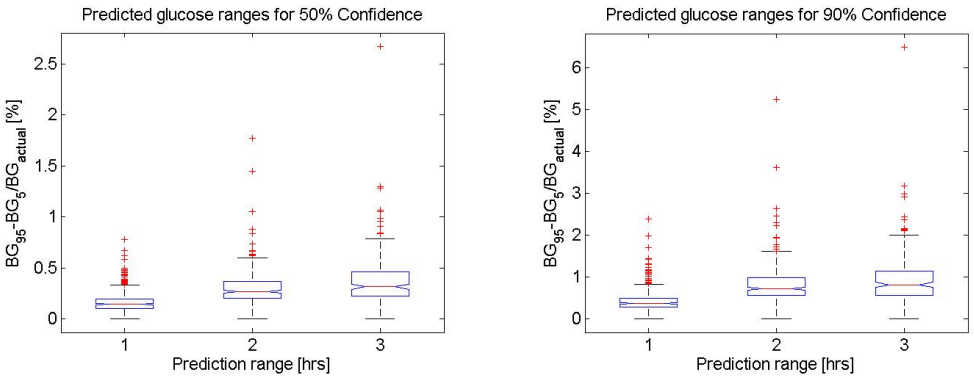


Figure 6.5 An example of the growth of confidence bands over time. In the blood glucose graph, the dotted line represents the fitted clinical outcome over the time considered. The 50% and 90% confidence bands of blood glucose are shown in dark grey and light grey respectively. The modelled glucose profile is shown by the solid line. The red lines indicate the ideal blood glucose range. For the insulin sensitivity graph, the actual fitted S_I profile is shown in a solid blue line while the 50% and 90% confidence intervals in S_I are shown in dark red and red respectively. The insulin infusion graph indicates the insulin dose administered and the carbohydrate intake graph indicates the time and carbohydrate content of meals

in Table 6.5. To summarise the results in Table 6.5, Figure 6.2 shows the blood glucose range of the 90% confidence interval and its growth over time for this cohort. It is clear that while 1 hour prediction is easy to target due to such small variance, 2 and 3 hourly prediction contains much more uncertainty and is thus a potentially riskier process.

Measurement Frequency:	1	2	3
Time between 4.0-6.1 mmol L^{-1}	46.1%	36.2%	36.4%
Time between 4.0-7.0 mmol L^{-1}	54.5%	42.5%	46.6%
Time between 4.0-7.75 mmol L^{-1}	59.9%	50.0%	52.5%
Time above 6 mmol L^{-1}	36.4%	45.9%	42.8%
Time below 4 mmol L^{-1}	18.5%	19.0%	21.6%
Time below 2.5 mmol L^{-1}	8.7%	6.8%	5.6%
Time below 2.2 mmol L^{-1}	3.4%	2.3%	6.4%
Mean Blood Glucose (mmol L^{-1})	6.1	6.8	6.4
Standard Deviation (mmol L^{-1})	3.1	3.6	3.6

Table 6.5 Simulation results for predictive insulin based protocol



(a) 50% confidence range growth (b) 90% confidence range growth

Figure 6.6 The growth in prediction range over 3 hours

6.2.1 Variable Timing

Upon close examination of Figure 6.2 it is clear that there are some periods during which 3 hourly predictions do maintain good correspondence with the actual observed progressions. It is these periods that we wish to isolate in variable timing methods to reduce the burden of glycaemic control on clinical staff. Because some probability bands become much larger over the two hourly measurements, a variable timing scheme is tested. This approach requires a measurement to be

Timing Options:	1-2 hourly	2-3 hourly	1-2-3 hourly
Time between 4.0-6.1 mmol L^{-1}	37.3%	36.8%	35.7%
Time between 4.0-7.0 mmol L^{-1}	48.9%	45.3%	47.7%
Time between 4.0-7.75 mmol L^{-1}	55.6%	50.6%	54.1%
Time above 6 mmol L^{-1}	39.2%	49.7%	50.8%
Time below 4 mmol L^{-1}	24.4%	14.8%	14.9%
Time below 2.5 mmol L^{-1}	5.3%	5.8%	4.2%
Time below 2.2 mmol L^{-1}	1.6%	1.6%	1.7%
Mean Blood Glucose (mmol L^{-1})	6.8	6.5	6.9
Standard Deviation (mmol L^{-1})	3.3	3.2	3.3
Time of 1 hourly measurements	47.5%	-	47.6%
Time of 2 hourly measurements	52.6%	73.7%	27.3%
Time of 3 hourly measurements	-	26.3%	25.3%

Table 6.6 Simulation results for variable timing schemes using a large allowable band of 3 mmol L^{-1}

taken when the probability bands become 'too large' (here defined as 3 mmol L^{-1}) or after the maximum period of time between measurements. The target used is 5 mmol L^{-1}, as used previously.

The results for this approach show significant improvement and reduce the clinical burden during times when uncertainty in patient response is low. A comparison between the 1-2-3 hourly measurement control and the existing CTW clinical practice data is shown in Figure 6.7. Table 6.6 also summarizes the results. In all cases, hypoglycaemia and control are much improved over prior, more rigid approaches to control.

6.3 Discussion

The simulations using a simple insulin sensitivity fit appear to indicate that EIS needs to be taken into account when modeling CTW patient behaviour. The majority of the major hypoglycaemic events that occurred are due to large doses of insulin being given in response to a post-prandial spike (or in anticipation of such), which occur simultaneously alongside sharp increases in S_I. It was explained in Section 4.2.5 that the presence of EIS would be manifested in the current model as an increasing S_I and it is hypothesised that this modelling error is the cause of this anomoly. However, even when consideration of EIS is made, basal replacement strategies alone are inadequate to control hyperglycaemia in the cohorts studied here, which have a greater diabetes focus.

Clearly some clinical validation of the above results is required to ensure that

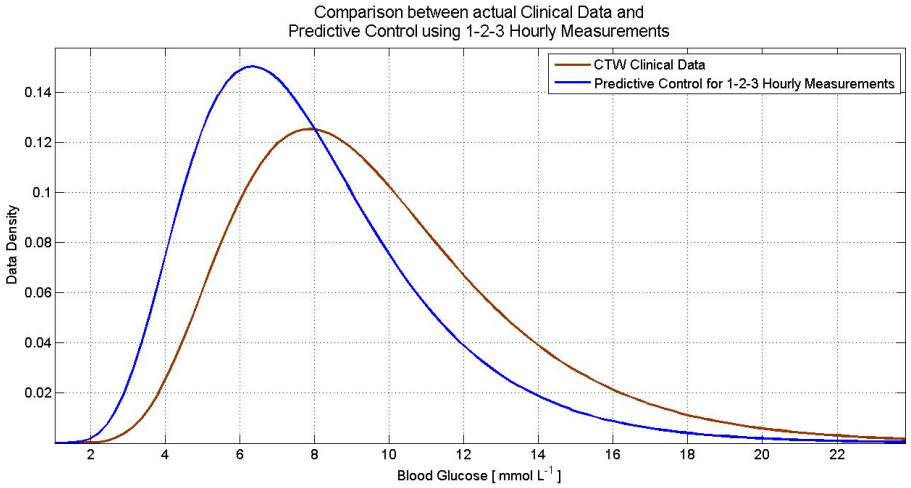


Figure 6.7 A comparison between the glucose distributions of CTW clinical data and predictive control results. Fits assume a lognormal distribution.

the inclusion of EIS is capturing the essential dynamics of the patients' glucose system. However, these results do provide a working model for the development of clinical trials. The initial results indicate that improved insulin therapies in a ward setting are possible using predictive control and could potentially improve clinical outcomes for less acutely ill ward patients. However, further studies will have to be completed to create a user-friendly and paper based version of the protocol.

Predictive control shows the most promise as a control strategy, but also requires the most resources. Thus, a look up table based protocol should be developed from the results presented here. The creation of lookup tables can be assisted by the use of virtual patients to ensure coverage of all likely scenarios. The results from predictive control simulations also show that 3 hourly measurements are possible. However, the removal of 1 hourly measurements from the protocol altogether result in significant loss of tight control. It is likely that 50% of measurements with one hour frequency would be too clinically burdensome in a less acute ward setting. Thus, the acceptable bands may need to be widened or reduced performance accepted if tight control is to be obtained.

From all of the results presented, it is clear that the tight glycaemic control achieved by SPRINT in the ICU cannot be readily emulated for similar or Type I diabetes focused cohorts in a ward setting. The inability to achieve these results is largely due to the consumption of meals, which are varied in timing and quantity. However, predictive control strategies do show some reduciton of hyperglycaemia as well as a tighter glucose distribution accross the CTW cohort than is currently

achieved clinically.

Chapter 7

Sepsis Diagnosis

Severe sepsis and septic shock has a high incidence rate and high mortality rate in an ICU (Angus *et al.*, 2001; Carrigan *et al.*, 2004; Dellinger *et al.*, 2004). The cost of treating sepsis and of additional bed hours required in sepsis patients is reported to be $16.7 billion dollars in the United States (Angus *et al.*, 2001). Insulin control protocols have been widely used to tightly control blood glucose values (Chase *et al.*, 2006b; Lonergan *et al.*, 2006a; Goldberg *et al.*, 2004b,c; Krinsley, 2003b; Chase *et al.*, 2006a; Van den Berghe *et al.*, 2006b, 2001), which has shown to result in a reduction in the incidence of sepsis (Van den Berghe *et al.*, 2001).

Diagnosis of sepsis presents many challenges in a clinical setting. A positive culture should precede the use of antibiotics (Dellinger *et al.*, 2004). However, blood culture results take 24-48 hours, or longer, to process (Carrigan *et al.*, 2004). More rapid diagnosis can be achieved using a variety of biomarkers. Procalcitonin (PCT) has been extensively investigated as such a tool, with specificity values ranging from slighter better than random (55%) to almost perfect (88%). Tang *et al.* (2007) reviewed 18 such studies and found a mean specificity of 71%, with the upper limit of the 95% confidence interval reaching only 76% (lower limit of 67%). Balci *et al.* (2003) found PCT was the only marker that had a strong negative predictive value (NPV) of 90%, as well as an 89% positive predictive value (PPV). IL-8 was a distant second to these values, with a PPV of 53% and NPV of 69% (Balci *et al.*, 2003), however Harbarth *et al.* (2001) report a much higher PPV of 80% and 79% for IL-6. Other biomarkers investigated as a diagnostic by Balci include TNFα, CRP, IL-6 and PCT, with even lower diagnostic values (Balci *et al.*, 2003).

Another problem in sepsis diagnosis is the differentiation between sepsis and SIRS. For this purpose, studies have found that the diagnostic value of CRP

is greatly increased if it is considered in conjunction with C3a or to a lesser extent C4 (immune system proteins) (Sungurtekin *et al.*, 2006). However, for all tests, a minimum lag time of typically 2-3 hours is still present (Carrigan *et al.*, 2004). Therefore, other signs must be investigated to assist in making the most timely diagnosis and potentially starting appropriate treatments, such as fluid resuscitation, and vasopressor and inotrope use. The earlier these interventions are correctly applied, the better the mortality outcome (Bridges and Dukes, 2005; Rivers *et al.*, 2001). Rivers *et al.* (2001) found that early goal-directed treatment of sepsis reduced mortality from 46.5% to 30.5%.

The negative effect of sepsis on insulin sensitivity and glucose metabolism is well documented (Agwunobi *et al.*, 2000; Chambrier *et al.*, 2000; Rusavy *et al.*, 2005). However, the mechanisms by which these changes take place are not fully understood. It has been suggested that sepsis induces a significant counterregulatory hormone response, causing the reduction in insulin sensitivity

Insulin sensitivity can be found using lumped parameter compartment models that have had extensive clinical validation in critical care (Lonergan *et al.*, 2006a; Chase *et al.*, 2006a; Wong *et al.*, 2006; Chase *et al.*, 2005; Lonergan *et al.*, 2006b; Shaw *et al.*, 2006). In such models, varying insulin sensitivity is the driving dynamic. Alternatively, glycaemic control protocols usually provide some measure of insulin sensitivity in real time. An example of one such protocol is SPRINT, which regulates enteral nutrition rates and insulin boluses (Chase *et al.*, 2006b; Lonergan *et al.*, 2006a,b). Enteral nutrition and insulin are modulated according to the patient's current blood glucose level and the change in blood glucose level as well as prior hour interventions, and an insulin sensitivity metric may also be derived from these input data. This insulin sensitivity information whether model based or estimated from intervention data is available without additional invasive procedures, outside of those required for glucose control.

7.1 Methods

Using the cohort described in Section 3.3 - a subset of 30 patients who potentially had sepsis during their hospital stay - comprehensive hour-by-hour clinical data was examined to isolate the time and duration of sepsis. Every hour a value for S_I was identified creating a patient-specific and time varying profile.

	Sepsis Patients	Non Sepsis Patients	Total
Number of Patients	30	113	143
Total Hours	6,744	19,709	26,453
Number of Hours in which $\dot{G_T} = 0$	2,036	5,493	7,529

Table 7.1 Summary of patient hours in each subset of the ICU cohort

7.1.1 Sepsis Score

From the clinical data, a sepsis classification score (ss) was generated for each hour of the patients stay that strictly follows the American College of Chest Physicians/Society of Critical Care Medicine guideline definitions of 1992 and 2003 (ACCP, 1992; Mitchell M. Levy *et al.*, 2003). The criteria for the sepsis score (ss) are defined in Tables 7.2-7.4. The organ failure criteria scoring in Table 7.3 uses the most relevant elements of the definitions for the Sepsis-related Organ Failure Assessment (SOFA) score (Vincent *et al.*, 1996). The sepsis score thus includes Systemic Inflammatory Response Score (SIRS) and SOFA organ failure criteria, as well as including factors for treatments indicated in sepsis. Thus, it provides better correlation than any single criterion (Mitchell M. Levy *et al.*, 2003).

This sepsis score is similar to that used by Clayton *et al.* (2006), where a SIRS of 3 or more was required alongside an infection or one of:

1. WBCs in a normally sterile body fluid
2. Perforated viscus
3. Radiographic evidence of pneumonia with purulent sputum production
4. Strong clinical evidence of an infection without an identified pathogen.

The combination of hour-by-hour signs of infection along with a definitive diagnosis of infection at some point during the patient's stay is the key factor in developing a useful sepsis score for this study. While sepsis is not a discrete process, but rather a continuum of severity of infection, in order to generate an ROC, some gold standard diagnosis must be assumed. To identify a clear signal, only the most severe and clear cut instances of sepsis should be required. Thus, the requirement of a positive culture ensures that sepsis was present at some point during the patient stay while the use of hour by hour signs pinpoint the precise times at which sepsis was most severe.

In Table 7.2 a tick indicates a necessary criterion and all necessary criteria

Sepsis Score		Definition					
		SIRS ≥ 2	Infection during stay	Organ Failure ≥ 1	Fluid Resuscitation	Inotrope Use	High Inotrope Use [a]
0	Normal						
1	Sepsis						
2	Severe Sepsis						
3	Septic Shock						
4	Refractory Septic Shock						

[a] Adrenaline or Noradrenaline > 0.2 mg min $^{-1}$ kg^{-1}

Table 7.2 Sepsis Score criteria

must be present to attain the indicated score. For example, a patient only on fluid therapy resuscitation would attain a sepsis score of 0. For this study, the gold standard diagnosis of sepsis is a sepsis score of 3 or more. This ss=3 value corresponds to a SIRS score of 2 or more, an organ failure score of 1 or greater, fluid resuscitationtherapy and inotropic therapyinotrope use of any amount all at the time of investigation, and an infection during the patient's ICU stay. Tables 7.3 and 7.4 define the organ failure and SIRS scores utilized in this overall score.

Score	System	Criteria	
+1	Cardiovascular	MAP OR need for inotropes	≤ 60 mmHg
+1	Respiratory	PaO_2/FiO_2	≤ 250 mmHg/mmHg ≤ 200 mmHg/mmHg with pneumonia
+1	Renal	Urine Output	< 0.5 mL/kg/hr
+1	Blood	Platelets	< 80 OR 50% drop in 3 days

Table 7.3 Organ Failure criteria

For this 30 patient sepsis cohort, the mean APACHE II score was 22 with a range of 7-40. The mean length of stay was 11.7 days with a range of 0.7-59 days. The mean sepsis score for this subset was 0.5 throughout their stay. However, 45 patient hours had a sepsis score of 3 or higher at some point in their stay.

Score	Criteria	
+1	Temperature	$\leq 36°$ C $\geq 38°$ C
+1	Heart Rate	≥ 90 min^{-1}
+1	Respiratory Rate OR $PaCO_2$	≥ 20 min^{-1} ≤ 32 mm Hg
+1	White Blood Cell Count	$\leq 4 \times 10^9$ L^{-1} $\geq 12 \times 10^9$ L^{-1} OR presence of $> 10\%$ granulocytes

Table 7.4 SIRS criteria

7.1.2 Reciever Operating Characteristic

The definition of categorisation of all possible test outcomes is given in Table 7.5. The ratios of positive results are defined in Equations 7.1-7.4.

		Patients with Sepsis	
		True	False
Patients with low* insulin sensitivity	True	True Positive (TP)	False Positive (FP)
	False	False Negative (FN)	True Negative (TN)

* Low is defined as being below a cutoff value

Table 7.5 Definitions of test outcome used in the ROC generation

$$sensitivity = \frac{TP}{TP + FN} \tag{7.1}$$

$$specificity = \frac{TN}{TN + FP} \tag{7.2}$$

$$Positive\ Predictive\ Value = \frac{TP}{TP + FP} \tag{7.3}$$

$$Negative\ Predictive\ Value = \frac{TN}{TN + FN} \tag{7.4}$$

From the sepsis score information, a Receiver Operating Characteristic (ROC) curve was drawn for the 30 patients using the model-based insulin sensitivity, (S_I) as the marker, and a sepsis score of $ss = 3$ as the diagnostic. An ROC curve plots the sensitivity of a diagnostic test against 1-specificity, which is equivalent to the true positive rate plotted against the false positive rate, for all possible cutoff values. A completely random test is represented as a line at 45 degrees to each axis, representing an additional false positive result for each false negative result eliminated. A perfect test (100% specificity and 100% sensitivity) is a vertical

line up the sensitivity axis at 1-specificity=0 and then a horizontal line along the 1-specificity axis, allowing selection of a cutoff with a zero false positive rate and a zero false negative rate. An example of each of these extreme cases is shown in Figure 7.1. It is expected that real diagnostic tests lie between these two lines indicating the presence of some false positives and some false negatives. The choice of cutoff is usually that which is furtherest from the diagnonal axes, and thus minimises the sum of both false results.

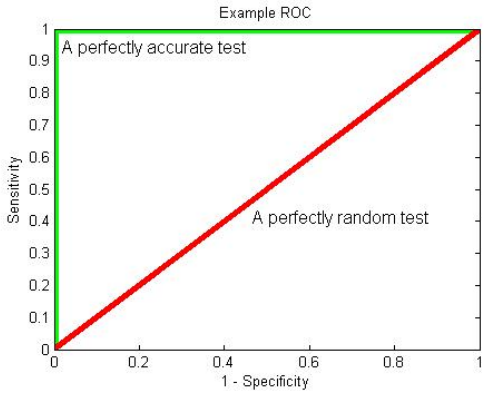


Figure 7.1 An example of an ROC with a perfectly accurate test (sensitivity=1, specificity=1) and a random test (sensitivity=0.5, specificity=0.5)

7.1.3 Simple Insulin Sensitivity

The generate ROC curve is compared to the estimated insulin sensitivity identified by the SPRINT protocol, referred to as simple insulin sensitivity or SS_I. This approximated insulin sensitivity is evaluated only at times that the change in glucose is less than the measurement error of 7% (Arkray, 2001) (ie. $\dot{G} = 0$). The formula for SS_I is given by Equation 7.5 and the derivation of this term is shown below. Starting from Equation 4.1 and setting $\dot{G} = 0$ gives:

$$0 = -p_G G - S_I Q_{,eff} G + P(t) + EGP$$

Then, assuming endogenous glucose clearance and production is small first equation above becomes:

$$0 = -S_I Q_{,eff} G + P(t)$$

The final assumption made is that $Q_{,eff}$ is entirely influenced by exogenous inputs and thus has no saturation effects. This assumption implies that the effect of insulin administered previously is small compared to the current insulin input, which means that SS_I will be a more accurate measure of insulin sensitivity

during large exogenous insulin inputs. Finally, simple algebraic rearrangement results in the following definition:

$$S_I = \frac{P(t)}{Q_{,eff}G}$$

This definition is an approximated S_I value when glucose is in a steady state. We can then write the metric identified, as shown in Equation 7.5.

$$SS_I = \frac{60P(t)}{I(t)G} \tag{7.5}$$

In evaluating this metric, when blood glucose is not available at any hour, the last reading taken is used. The number of patient hours that satisfy the $\dot{G} = 0$ criteria are shown in Table 7.1.

Alternatively, the combined estimated effect of EGP and CNS could be added to the $P(t)$ factor. However, this choice would serve only to scale the curve unless patient specific values were availale. The implications of the curve are calibrated by empirical data and thus this process would unnecessarily add complexity to the calculation of SS_I, as no additional diagnostic power would be gained.

7.2 Results

Figure 7.2 and Table 7.6 shows the insulin sensitivity distributions for 130 patients compared with APACHE II score, discretising the patient set into 9 groups of APACHE II scores. Note that the remaining 13 patients are not included in the APACHE II score groups due to unavailable APACHE II score data. None of these 13 were in the 30 patient sepsis cohort. Figure 7.2 shows the high density of low S_I readings found in all groups with APACHE II greater than 6.

The ROC curve for model-based S_I data from 6744 patient hours is shown in Figure 7.3. The sensitivity of the insulin sensitivity test was found to be 77.8% and the specificity, 82.2%. The positive predictive value was 2.8% and the negative predictive value was 99.8%. The cutoff value for this test was an S_I of 8×10^{-5} L mU^{-1} min^{-1}. Over 85% of the 26,453 identified insulin sensitivity values for the general ICU cohort (143 patients, with and without sepsis) were above the 8×10^{-5} L mU^{-1} min^{-1} cutoff.

Over 85% of the time, an ICU patient's insulin sensitivity will be above the cutoff point of 8×10^{-5} L mU^{-1} min^{-1} as found from fitting the 26,453 hours of the 143 general overall ICU patient cohort employed.

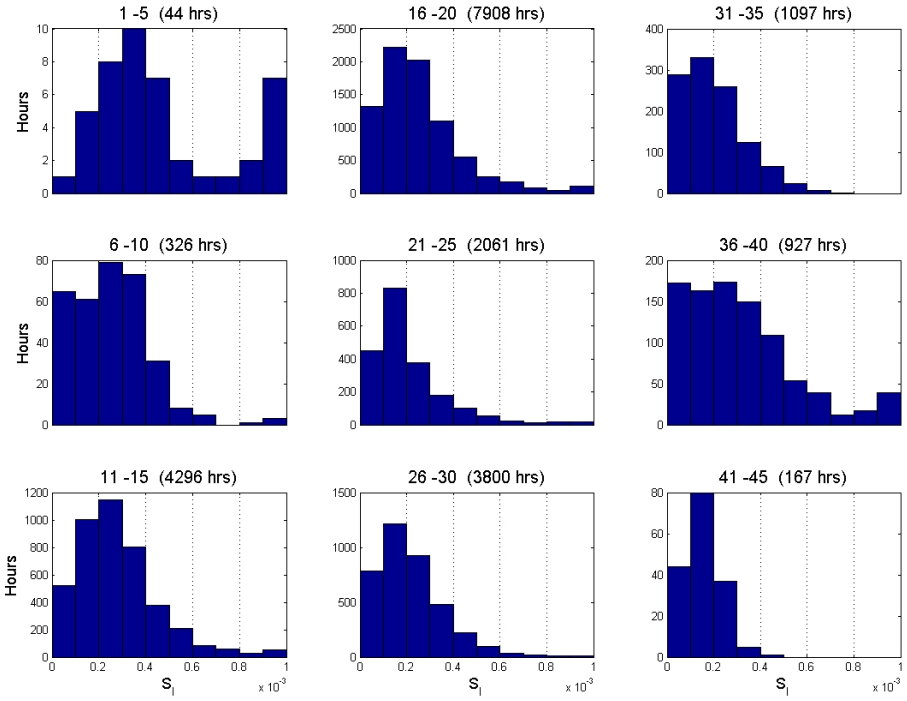


Figure 7.2 Insulin Sensitivity (S_I) distributions of ICU patients grouped by APACHE II scores

Insulin sensitivity distributions were compared with APACHE II score, discretising the patient set into 9 groups of APACHE II scores. The results for 130 patients are shown in Figure 2 and Table 7.6. Note that the remaining 13 patients are not included in the APACHE II score groups due to unavailable APACHE II score data. None of these 13 were in the 30 patient sepsis cohort.

The SS_I ROC curve for the applicable 2036 patient hours that $\dot{G} = 0$ is shown in Figure 7.4. The sensitivity of the insulin sensitivity test was found to be 68.8% and the specificity, 81.7%. The positive predictive value was 2.9% and the negative predictive value was 99.7%. The cutoff value for this test was an SSI of 2.8×10^{-4} L mU^{-1}, which is approximately 3 times higher than that for S_I in Figure 12. For 82.7% of the time, an ICU patient's simple insulin sensitivity (SS_I) will be above this cutoff point of 2.8×10^{-4} L mU^{-1} as found from the 7529 hours of the 143 general ICU patient cohort (28% of 26,453 available hours). This 82.7% result is similar to the result for S_I over the full time period.

APACHE II score range	Percentage of time below cutoff
1 - 5	2.3
6 - 10	15.3
11 - 15	8.7
16 - 20	12.7
21 - 25	14.8
26 - 30	15.3
31 - 35	20
36 - 40	15.3
41 - 45	19.8

Table 7.6 Time spent below $S_I = 8 \times 10^{-5}$ L mU^{-1} min^{-1}, the cutoff value for $ss \geq 3$

7.3 Discussion

Absence of sepsis shows a strong correlation with a higher S_I. The ROC shown in Figure 7.3 indicates that insulin sensitivity can exclude a sepsis diagnosis far more accurately than it can make one. Specifically, 87% of the time in this ICU cohort it is 99.8% certain that a patient does not have sepsis ($ss = 2$) due to a modeled insulin sensitivity of greater than 8×10^{-5} L mU^{-1} min^{-1}.

However, as a positive predictor, insulin sensitivity is not applicable. Figure 7.2 shows that with increasing APACHE II scores, the lognormal distribution of SI tends to lower S_I values (Kruskal-Wallis Test $p<0.05$). This result indicates that not only sepsis, but other severe illness and effects could be responsible for a low SI value in a critically ill patient, causing a high number of false positives. This result explains the low positive predictive value of either insulin sensitivity metric (S_I or SS_I).

The SS_I was an inferior predictor to the model based S_I profiles, but the negative predictive value was still very high offering the possibility of ruling out sepsis in 82.7% of patient hours. However, with additional data the cut-off point identified by the ROC may move significantly, but these predictive values should only change slightly. A limiting factor in this analysis is that only 16 septic patient patient hours with sepsis, out of 2036 patient hours, were available for this part of the study. This limited quantity of data is due to the requirements of non-zero feed enteral nutrition and insulin input and negligible changes in blood glucose for Equation 7.5. Overall, only approximately 30% of patient hours (30.2% of patient hours in the sepsis cohort and 32% in the complete cohort) were available to compute SSI and 32% in the complete cohort, creating a potential further

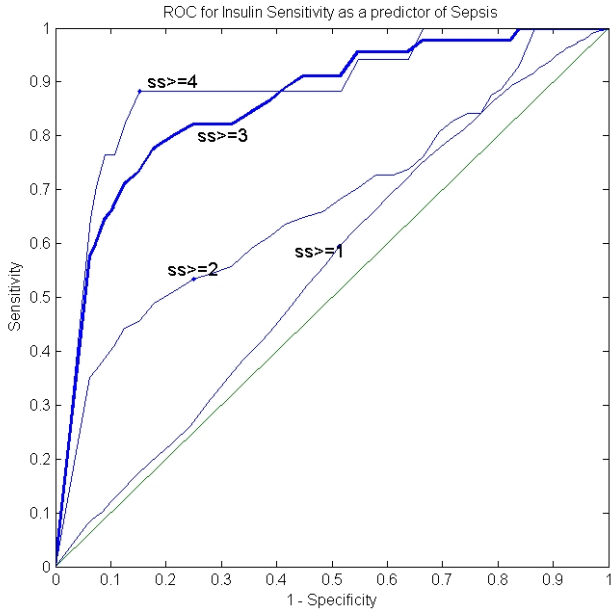


Figure 7.3 ROC of Modeled Insulin Sensitivity (S_I) as a predictor of Sepsis ($ss \geq 3$)

limitation for the simpler metric.

While the sensitivity of the test remained relatively unchanged for SS_I versus S_I, the specificity dropped greatly due to a large increase in the number of false positives. This result can be partly explained by the protocol's reduced resolution. However, it is possible that another effect is due to the pool of data being reduced by the requirement that change in measured glucose is less than 7% of previous measurement (measurement error). Constant blood glucose is more likely to be found in more stable patients who are generally less likely to have sepsisbe septic. This unintended filtering in using the simplified SSI metric increases the proportion of patients with low baseline insulin sensitivity, to patients with sepsis induced low insulin sensitivity. In particular, 40% of septic hours with sepsis in the sepsis cohort were eliminated by the criterion. This filtering also causes the discretised appearance of the ROC curve, by reducing the number of available data points, particularly periods of sepsis.

However, the 1 U hr^{-1} insulin requirement for the estimated metric is not as restrictive in an ICU as in a less acute ward setting. A 1 U hr^{-1} or greater insulin dosage is frequently called for in glycaemic control protocols and is often sustained for prolonged periods of a patients' hyperglycaemic stay. Similarly, patients will typically not spend significant periods of time fasting in an ICU. For this study, only enteral feed nutrition was considered as oral and parenteral

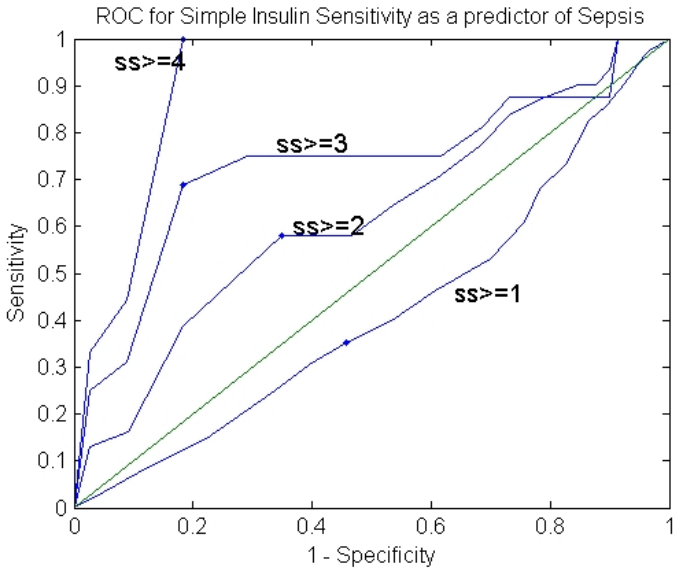


Figure 7.4 ROC of Insulin Sensitivity (SS_I) evaluated in real time as a predictor of Sepsis

feed nutrition were not used.

The advantage of SS_I as a predictor is that it can be very easily evaluated in real time with only a pocket calculator. Hence, a clinician can obtain useful information about a patient's condition without invasive, computationally intensive or time consuming tests. While the simple method introduces additional uncertainty by reduced resolution, as well as offering limited availability, the reduction in computational effort could justify its use over a model based approach if the computational resources were not available (eg. A PDA with program). A growing trend toward computation driven protocols is occurring which could lead towards the regular use of a modeled S_I value (Chase *et al.*, 2006a; Plank *et al.*, 2006; Shulman *et al.*, 2007; Thomas *et al.*, 2005).

Figure 4 shows the correlation between model S_I and SS_I. The R^2 value for the relationship is 0.68. This stronger correlation supports the similarity between the findings of the S_I and SS_I diagnostics, despite the small amount of sepsis hours available for the latter. This comparison between insulin sensitivities is for 7529 hours of the general ICU cohort of 143 patients. The comparison includes times when blood glucose values are changing by less than 7% and when insulin received is greater than 1 U hr^{-1}. The latter constraint is applied to include only times when EGP is sufficiently suppressed. If the requirement is extended to those times at which a patient receives 1.5 U hr^{-1} of insulin, the R^2 value increases to 0.78 by eliminating the outliers as shown. Additionally, the model SI fit limits the values to 1×10^{-5} L mU^{-1} $min^{-1} = S_I = 1 \times 10^{-3}$ L mU^{-1} min^{-1},

whereas SS_I is unrestricted in value. These different limits have also reduced the correlation between S_I and SS_I.

With the discretised nature of the gold standard sepsis definition used ($ss = 3$), it is clear that some error must be present in the gold standard used in the derivation of the ROC curves. This error may limit the reliability of the results. However, with limited blood culture and biomarker data available due to the retrospective nature of the study, this error was unavoidable.

Patients who have Type I or Type II diabetes are excluded from this study. If these patients were to be included it is likely that the sensitivity and predictive value would be even lower than at present since these patients will present with insulin resistance (at least, in Type II diabetics). The prevalence of Type II diabetes is high and disproportionately so in an ICU (King *et al.*, 1998; Umpierrez *et al.*, 2002), and is expected that Type II diabetics will have longer hospital stays due to increased insulin resistance, further limiting the clinical applications of this study.

Figure 7.5 shows an example of ss over time in comparison with S_I. The shaded areas represent a diagnosis of sepsis according to the respective parameters. It can be seen that during the initial 48 hours of the patients stay, S_I is very low and ss peaks multiple times during this period. At all other times, ss is 1 or less, and S_I rarely falls below the cutoff value.

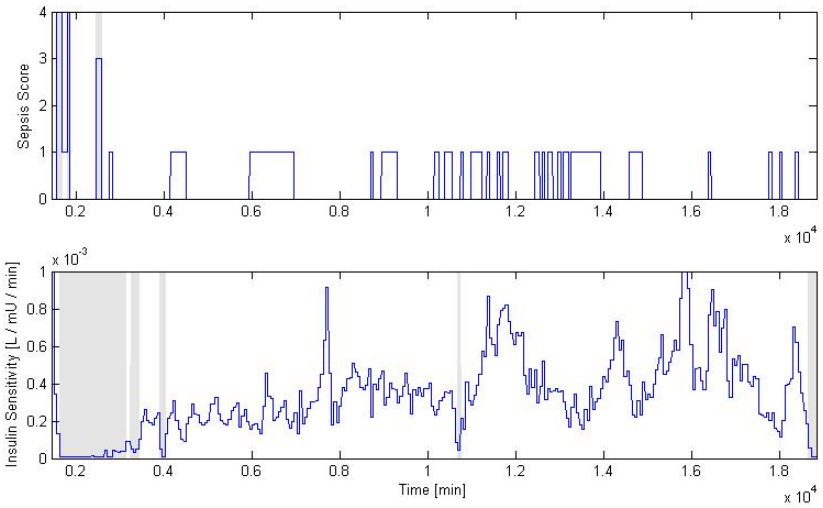


Figure 7.5 An example of ss and S_I variance over time

Chapter 8

Conclusions

This study has presented the variable nature of patient's glycaemic stability in a less acute ward. Modifications to a standard ICU model have been made to identify the limited endogenous insulin secretion that such patients are likely to display in response to consumption of a meal. This model has not been validated.

From the glycaemic data of 7 CTW patients a stochastic model was generated and validated against a subcohort of 131 stable ICU patients. Model convergence was not observed, most likely due to the increased range of insulin sensitivity observed. This stochastic model was used in predictive control for varied and lengthened intervention periods. The amount of data available which is

The simulation results on 7 CTW patients reveal that glycaemic levels in the ward cannot be adequately controlled by a SPRINT based system, nor by meal boluses. Due to the highly variable nature of insulin sensitivity, which is affected by such a wide range of factors, no accurate delivery of insulin dose is possible without considering the progression of the probability bounds and using predictive control strategies. However, while the simulation results illustrate tighter control than what was clinically obtained during the patients' stay, there is a unacceptably high rate of hypoglycaemia (4% below 2.5 mmol L^{-1}). It is uncertain if such high hypoglycaemic episodes Even so, glycaemic variability (and thus uncertainty) was found to increase with increasing time between measurements, limiting the success of predictive control. Thus, it is likely that in order to provide glycaemic control to a ward in a safe and time-efficient manner some compromise on performance in hyperglycaemia reduction will have to be made.

Insulin sensitivity was found to be a good diagnostic marker of the absence of sepsis in an ICU cohort - high insulin sensitivity can rule out the presence of sepsis in a critically-ill non-diabetic patient for the majority of their stay. Sepsis is ruled out when modelled insulin sensitivity is above $S_I = 8 \times 10^{-5}$ L mU^{-1}.

This condition is met for 85% of all patient hours in this general ICU setting. Insulin sensitivity below 8×10^{-5} L mU^{-1} min^{-1} can be due to either sepsis or other underlying conditions. The accuracy and flexibility of model based insulin sensitivity gives better reliability as a diagnostic for sepsis. However, insulin sensitivity can be reasonably accurately evaluated using estimated methods in real time by using glycaemic control protocol data. These estimated values provide similar negative predictive values. This study shows the potential of insulin sensitivity as a diagnostic metric for sepsis when used as a negative predictor, however it will also require a larger validation study including more complete blood culture data to fully validate it for clinical use.

Chapter 9

Future Work

This paper has presented a framework for investigating the introduction of a glycaemic control strategy into less acute wards. While, no satisfactory means of avoiding the risk of hypoglycaemia has been found, there are some benefits to be gained from the results found.

Additional data of patients from the less acute wards would greatly assist the understanding of typical population characteristics. If more data was available to the generation of the stochastic model, greater reliability would be evident in predictive control. Similarly, simulation of glycaemic control on a larger cohort might give better estimates of how a general ward population would respond to any treatment strategies.

No validation of the model used in this study has been conducted. It is possible that the model is overestimating hypoglycaemic episodes since the increase in EGP that should arise from low glucose levels is not modelled. Clinical trials using a much less agressive means of control, such as the Treat-to-Target protocol utilising glargine and no meal boluses would indicate if such incidences are being overestimated without risking patient safety. If the results of such trials allow for the consideration of increasing EGP then this mechanism can be easily included in the model and greater control obtained from the increased reliability. However, it would be unwise to trial a protocol using variable EGP without further validation when it is clear from the results presented that neglecting the variance indicates that severe hypoglycaemia would result.

There are some unexplored avenues in control strategy which may also justify further investigation. The target set in predictive control significantly affects the outcome, as expected. Thus, experimentation with different targets may yield a more clinically viable control strategy. Similarly, insulin could be limited when the 5% confidence band falls below 4 mmol L^{-1}.

Meal boluses are typically very effective in the management of diabetes, however a rigid protocol has shown little success in this research. Possibly this is due to a lack of patient specific doses. That is, insulin sensitivity is not taken into account when determining the bolus, only the blood glucose level. Similarly, no progression of patient condition is allowed for. Thus, developing a more flexible and responsive controller of meal boluses many significantly reduce the post-prandial peaks of blood glucose.

There are many aspects of regular meal consumption that have not been investigated here, particularly in relation to predictive control. The consumption of meals should be included in the predictions using expected values of glucose rise and fall from a meals. Similarly, some estimate of the likely endogenous insulin secretions should improve the viability of glycaemic control. Such estimates of EIS will need to be patient specific to account for the significant variance in β-cell function observed in the varying levels diabetes or insulin-resistance.

Some analysis of the effect of errors in meal estimates is also essential to developing a working protocol. Such sensitivity analyses would give greater protection against hypoglycaemic incidences in the event of miscalculation of carbohydrate intakes.

This study has presented insulin sensitivity models and tools for use in a clinical setting based upon critically ill and less acutely ill patients. The diagnostic value of insulin sensitivity measures may be further improved by better sepsis criteria. At present, the discretisation of a gold standard diagnosis of sepsis indicates that sepsis is rapidly switching between presence and absence on an hourly basis. Smoothing of sepsis score data or improved logical criteria for a diagnosis may prevent this and identify periods rather than hours during which sepsis is present. With this improved accuracy, the positive predictive value of S_I and SS_I is likely to improve and a new cutoff value will be found.

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