

Elsevier Editorial System(tm) for Biomedical Signal Processing and Control

Manuscript Draft

Manuscript Number: BSPC-D-05-00018R2

Title: Model-based Glycaemic Control in Critical Care - A review of the state of the possible

Article Type: Review Article

Section/Category:

Keywords: Critical Care, Hyperglycemia, Insulin, Nutrition, Control, Dynamic Systems, Modeling

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Manuscript Region of Origin:

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However, clinical results are highly variable and there is little agreement on what levels of performance can be achieved and how to achieve them. A typical clinical solution is to use ad-hoc protocols based primarily on experience, where large amounts of insulin, up to 50U/hr, are titrated against glucose measurements variably taken every 1-4 hours. When combined with the unpredictable and sudden metabolic changes that

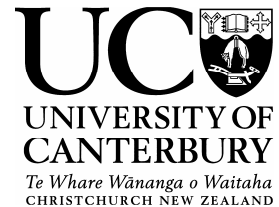
characterise this aspect of critical illness and/or clinical changes in nutritional support, this approach results in highly variable blood glucose levels. The overall result is sustained periods of hyper- or hypo- glycaemia, characterised by oscillations between these states, which can adversely affect clinical outcomes and mortality. The situation is exacerbated by exogenous nutritional support regimes with high dextrose content. Hence, there is an emerging, strong need for the more rigorous analysis and methods that model-based control methods bring to this type of problem.

This paper reviews the state of the clinical and model-based control systems approach to the problem of managing hyperglycaemia in critical care, emphasising emerging methods and results. The overall goal is to present the fundamental problem and associated science and technologies involved. Thus, it is less a discussion of specific advantageous approaches than a presentation of the different factors that impact the problem and the different approaches taken to address them in the limited clinical engineering research done to date. These discussions are presented in the context of current and emerging clinical studies, both model-based and empirical protocol driven. Analogies to the Type 1 diabetes mellitus control problem are also noted where relevant and significant. Hence, it is more overview than specific analysis, where the overall conclusion is that there are many opportunities and unanswered questions remaining on which model-based control research can have significant clinical impact.

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Re: Submission Declarations for Biomedical Signal Processing and Control (BSPC).

Prof Allen,

30 November 2005

This letter is to declare that the material in our review article submission "*Model-based Glycaemic Control in Critical Care – A state of the possible review*" is original and unpublished in any other source. We agree that the paper, should it be accepted, will be the copyright of Elsevier and the journal.

Regards,

A handwritten signature in black ink, appearing to read 'J. Geoffrey Chase'. The signature is written in a cursive style with a large initial 'J'.

J. Geoffrey Chase (for all the authors)

Model-based Glycaemic Control in Critical Care – A review of the state of the possible

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Financial Support:
Canterbury Intensive Care Research and Education Trust
Tertiary Education Commission Te Amorangi Matauranga Matua

Keywords:
Critical Care, Hyperglycemia, Control, Models, Blood Glucose, Insulin, Review

Abstract

Hyperglycaemia is prevalent in critical care, as patients experience stress-induced hyperglycaemia, even with no history of diabetes. Hyperglycaemia in critical care is not largely benign, as once thought, and it has a deleterious effect on outcome. Recent studies have shown that tight glucose regulation to average levels from 6.1-7.75 mmol/L can reduce mortality 25-43%, while also significantly reducing other negative clinical outcomes.

However, clinical results are highly variable and there is little agreement on what levels of performance can be achieved and how to achieve them. A typical clinical solution is to use ad-hoc protocols based primarily on experience, where large amounts of insulin, up to 50U/hr, are titrated against glucose measurements variably taken every 1-4 hours. When combined with the unpredictable and sudden metabolic changes that characterise this aspect of critical illness and/or clinical changes in nutritional support, this approach results in highly variable blood glucose levels. The overall result is sustained periods of hyper- or hypo- glycaemia, characterised by oscillations between these states, which can adversely affect clinical outcomes and mortality. The situation is exacerbated by exogenous nutritional support regimes with high dextrose content. Hence, there is an emerging, strong need for the more rigorous analysis and methods that model-based control methods bring to this type of problem.

This paper reviews the state of the clinical and model-based control systems approach to the problem of managing hyperglycaemia in critical care, emphasising emerging methods and results. The overall goal is to present the fundamental problem and associated science and technologies involved. Thus, it is less a discussion of specific advantageous approaches than a presentation of the different factors that impact the problem and the different approaches taken to address them in the limited clinical engineering research done to date. These discussions are presented in the context of current and emerging clinical studies, both model-based and empirical protocol driven. Analogies to the Type 1 diabetes mellitus control problem are also noted where relevant and significant. Hence, it is more overview than specific analysis, where the overall conclusion is that there are many opportunities and unanswered questions remaining on which model-based control research can have significant clinical impact.

1.0 Introduction and Problem Definition

Critically ill patients often experience stress-induced hyperglycaemia and high insulin resistance, even with no prior diabetes [1-5]. The increased counter-regulatory hormone and cytokine response stimulates endogenous glucose production and increases effective insulin resistance. Absolute and relative insulin deficiency and steroid-based therapies are further causes. Studies also indicate that high glucose content nutritional support regimes result in excess glucose [6-9]. More recently, reductions in enteral nutrition [9-11] or its carbohydrate content [6] led to reductions in glycaemic levels. Similarly, the reduced use of dextrose as a diluent in intravenous medication [12], resulted in reductions in glycaemia. Both changes have been shown to alleviate the impact of the hyperglycaemic counter-regulatory response that drives this problem [3, 4, 13, 14].

Although hyperglycaemia can be a marker of severity of illness and is associated with mortality, it is also associated with increases in other negative clinical outcomes, including severe infection [15], sepsis and septic shock [16-19], myocardial infarction [1], as well as polyneuropathy and multiple-organ failure [2, 20]. In each of these cases or patient subgroups, lower glucose levels were associated with reduced mortality and/or complications. Similar studies have associated early hyperglycaemia with mortality in trauma patients [21-23]. Finally, there is also evidence of significant reductions in need for dialysis, bacteremia and number of blood transfusions with aggressive blood glucose control using intensive insulin therapy [2, 24, 25].

There are two landmark studies that have observed and defined this problem and the impact of tight control on mortality and other clinical outcomes. First, van den Berghe et al [2, 24] showed that tight blood glucose control to less than 6.1mmol/L reduced cardiac surgical ICU patient mortality by up to 45% in a randomised controlled trial. Krinsley [25, 26] reported a 17-29% total reduction in mortality over a wider, more critically ill, ICU population with a higher glucose limit of 7.75mmol/L, however this study was a comparison to a matched cohort of retrospective data with enough patients to show statistical power for the intervention. The exact reasons for the reductions in mortality and other clinical outcomes is not fully known, but has been extensively analysed in these and other works [2, 20, 24-34].

Both van den Berghe et al [2, 24] and Krinsley [25, 26] used ad-hoc protocols that did not employ models or control theory, and relied only on exogenous (intravenous) insulin intervention to reduce blood glucose levels. The main differentiators of these two landmark studies are the glycaemic limit used and the level of critical illness of the cohorts, as measured by APACHE II score. In particular, Krinsley studied a broader, more representative critical care cohort with a much greater level of critical illness, reporting an average APACHE II score of 16.9 (IQR: 13-24). Due perhaps to the severity of illness of their cohort, a higher titration limit and goal was established. In contrast, van den Berghe et al reported a much lower median APACHE II score of 9 (IQR: 6-13), in combination with their much lower glycaemic target limit.

Thus, two important results can be drawn from these initial clinical studies. First, tighter control with lower glycaemic limits appears to offer increased benefit in terms of reduced mortality and reductions in other measurable negative clinical outcomes.

Second, the level of critical illness is generally proportional to observed hyperglycaemia and insulin resistance [24, 28, 35-38], which will result in a decreased ability to reduce blood glucose with insulin alone for more critically ill cohorts. However, neither study addressed issues such as blood glucose variability, time within a desired glycaemic band, nor other typical control system oriented performance metrics that would help further clarify the requirements for tight glycaemic control. It is these two conclusions and the other unanswered questions that help define the overall problem, and illustrate the potential for applying dynamic systems modeling and control methods to achieve significant clinical improvements. More specifically, while other studies are being undertaken to further validate many of the results already available across broader populations and cohorts, the clinical evidence for tight control is greater than for some current practice of tolerating a level of hyperglycaemia [39].

1.1 Similarities to the General Diabetes Control Problem

It should be noted that the management of hyperglycaemia in critical care has many parallels to managing glycaemic levels in Type 1 and insulin dependent Type 2 diabetic individuals. Given the growing and predicted epidemic incidence level of both types of diabetes in western populations [40, 41], modeling and control of diabetes mellitus has been a periodically popular research area over the last 25 years. In particular, predictions [42] that the cost of diabetes and its complications will reach up to 10% of healthcare costs by 2020 are driving research at a variety of levels. However, while this review is directed primarily towards controlling glycaemic levels in critical care, it might be expected that the commonalities of these problems will see

successful clinical results from critical care work their way towards clinical management of diabetes.

Both problems share the metabolic system models for the pharmacokinetics of insulin and the pharmaco-dynamic interaction of glucose and insulin. Equally importantly, the critical care environment offers a more controlled environment for developing control methods and models, as well as added modeling simplicity given the typical use of intravenous insulin, and intravenous or enteral nutrition delivery. Thus, one approach would see solutions developed in critical care “trickling down” to solutions for ambulatory diabetic individuals, as shown in Figure 1, where the number of variables, non-linearities and uncertainties increases down the pyramid. Hence, this work focuses on the top of the pyramid, model-based control of hyperglycaemia in critical care where the patient’s environmental variables and inputs are better known and/or more readily controlled.

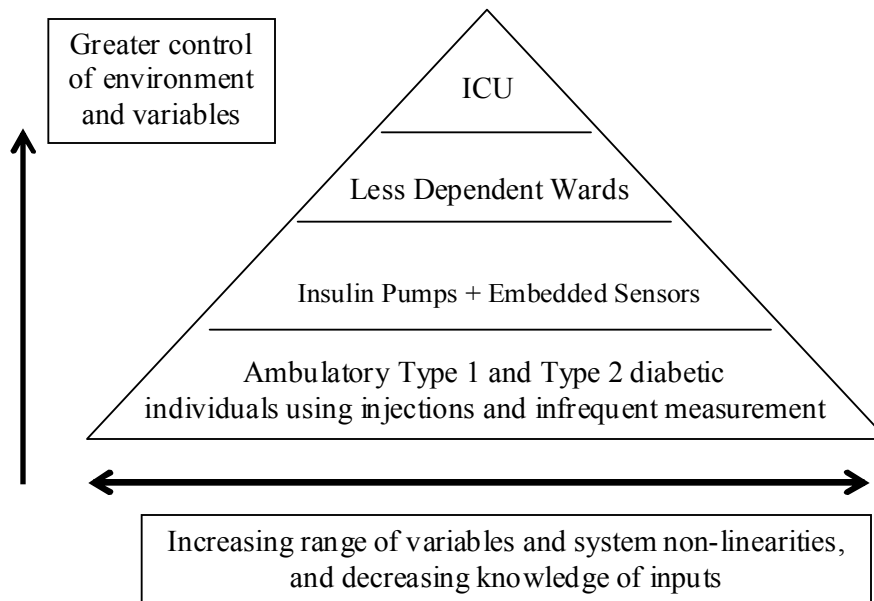


Figure 1: Pyramid description of glycaemic control problems in terms of ability to control variables based on knowledge of their value or input (vertical axis), and the range of variables to be considered and resulting level of uncertainty (horizontal axis).

1.2 Main Elements and Preface

There are typically three main elements in any similar control problem:

- Sensors and signal processing
- Dynamic modeling and parameter identification
- Control method or protocol

Sensors and signal processing determine the quality and frequency of data for the controller. The dynamic model and parameter identification methods relate to the (predictive) accuracy of any controller, and thus its ability to safely and accurately lower glucose levels in this case. Finally, the control algorithm employs both these elements to determine the appropriate intervention to achieve a set performance goal. Generically, these three elements are all inter-related and lower complexity or quality from one is typically offset by requiring greater quality or complexity from the others. Figure 2 shows a schematic of the basic control schemes employed and to outline the general control problem and its major elements.

This review covers all three elements for the hyperglycaemia control problem in critical care. Significant commonalities to the more general diabetes management problem are also discussed as they arise. The discussions in each case focus on what is currently available and those emerging technologies or methods that may offer significant potential to improve capability. Hence, it is a review of the existing state of the art in each of these areas listed above, as well as discussing the potential new approaches and technologies that will affect the problem in future.

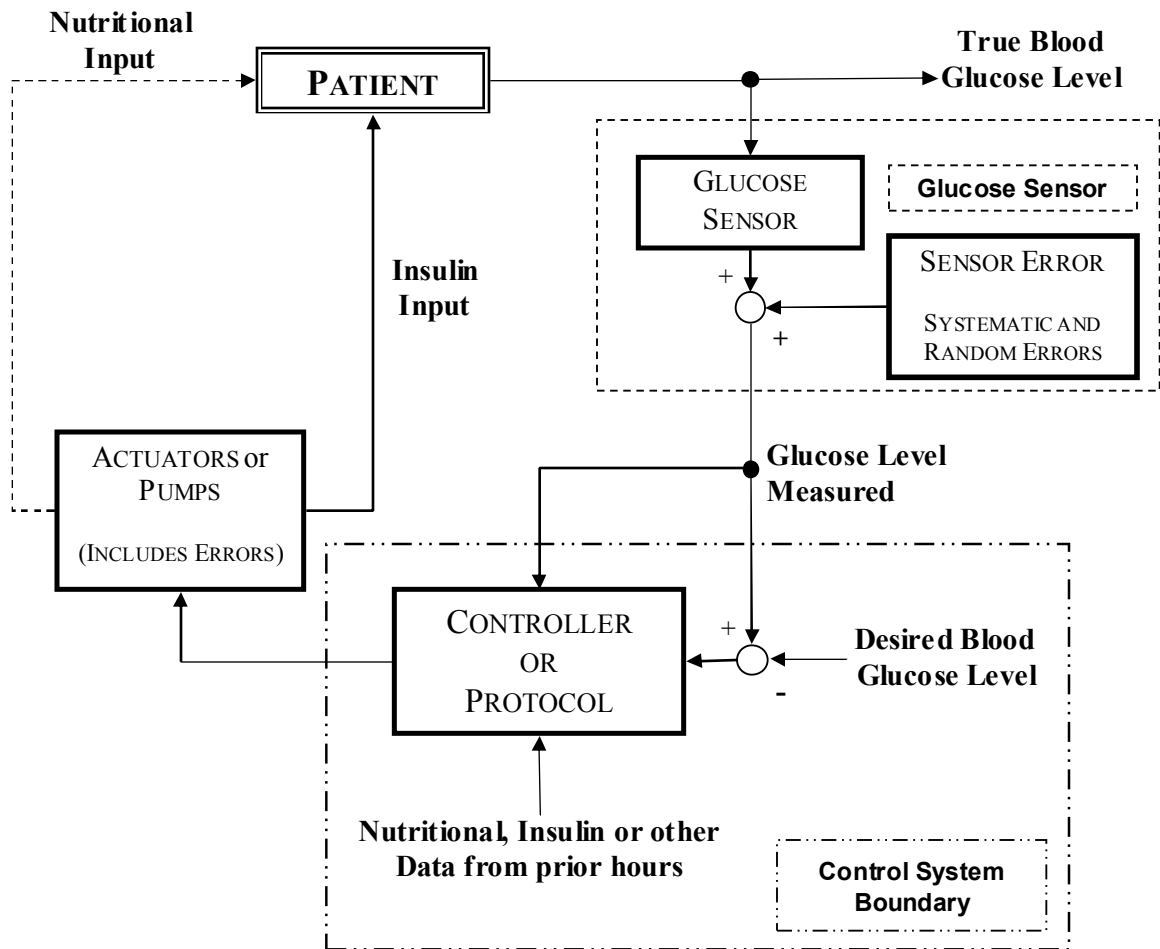


Figure 2: Basic model-based glycaemic control loop schematic showing the primary blocks encompassing sensing, actuation and control implementation. The control system boundary is shown by dash-dot lines, and the nutritional input line is dashed to indicate that this quantity may be controlled as part of glycaemic control or set based on other clinical requirements. Sensor errors are shown as a separate block due to their potential size and impact on control.

2.0 Sensors and Signal Processing

In glycaemic control, the primary measurement available is plasma glucose level. Current glucose sensing methods can be broken into four broad areas for control

applications. These areas represent distinctions in quality, time, software storage and links, and data density, all of which impact the resulting control problem.

- **Lab or Gold Standard Measures:** These tests consist of laboratory reference measurements using standard techniques. They offer the lowest error ($< 3\%$) and best repeatability [43]. Turnaround time for results can be quite long due to the logistics of sending samples to a lab. However, modern blood gas analysers can now be installed in specific units offering similar results to clinical staff within 1-3 minutes [43-45].
- **Point of Care Tests (POCT):** These tests can be linked directly to patient databases and records and are becoming standard in many ICUs. They range from blood gas analysers to specialised POCT pin-prick test strip devices. Accuracy ranges from blood gas analysers ($< 3\%$) [43, 44, 46, 47] to pin-stick results (typically 7-12%) [48, 49]. Data density is typically no greater than hourly due to discomfort and the effort required around other clinical duties.
- **Pin-Stick Bedside Test Kits:** The current standard in many ICUs and most ambulatory diabetic individuals. They offer rapid results in less than 30 seconds and require only 1-2 minutes of total clinical effort, but have errors of 7-12% over common glycaemic ranges [50-56]. They are rarely used more than hourly. In critical care, pin-stick measures can be used to extract subcutaneous blood or sampled from an arterial line. The latter approach eliminates the 5-20 minute lag in plasma glucose levels that can exist between plasma and interstitial fluid [57-59].
- **Semi-Invasive “Continuous” Sensors:** Emerging sensors offering automated or semi-automated measurement of blood glucose concentration. The most

commonly reported types, at this writing, are the Minimed/Medtronic CGMS and the GlucoWatch Biographer [60-62]. They offer very frequent measurements every 5-15 minutes, but with errors up to 40% reported over a wide variety of studies [60-72].

Portable blood gas analysers offer the best quality results for fitting models to determine control inputs due to their lower error. At the other end of the spectrum, emerging sensors, such as the CGMS, offer very high data density, but with greater error. The standard pin-stick bedside testing kit is still the most commonly used measure. It offers greater ease of use than a portable or local blood gas analyser with slightly greater error, but much lower data density than emerging continuous sensors. Finally, note that plasma insulin measurement would offer added information for modeling and control, however the lab turnaround time for this measurement is generally too long to be of direct use in real-time clinical control.

Hence, there is a significant tradeoff involved in selecting the type of measurement or accounting for the type available in a specific clinical setting. Less frequent measurement requires greater prediction capability from the model. More frequent measurement allows potentially much simpler models. In contrast, greater errors will require more intensive signal processing, as well as models more robust to those errors in patient specific parameter fitting and prediction.

Perhaps the most common clinical measurement issue in glycaemic control is frequency. More frequent measurement than most typical clinical practice has been a hallmark of both initial landmark glycaemic control studies [2, 24-26], varying

between 1 and 4 hours. However, specialised additional staff were required to manage the extra workload reported. Other pilot studies and surveys have reported the extra clinical burden of intensive insulin therapy for glycaemic control as “burdensome” or “taxing” [73-77]. Hence, the ability to limit or automate measurement via implanted continuous sensor could be seen as critical. Thus, emerging sensors offer significant promise for automating glycaemic control in this regard.

Frequent measurement and its impact on glycaemic control have been studied both in simulation [78-80] and clinically [79, 81-83], including the analysis of long-term retrospective data [84]. Results show that fewer, less frequent measurements often result in greater glycaemic variation in critical care and poorer outcome [80, 85, 86]. Similar results have been seen in treating ambulatory diabetic individuals [87, 88].

Overall, the different types of measurement offer a series of fundamental tradeoffs. Typically, a given unit will have a standard set of measures and practices, which the control engineer will have to work with, removing choice in the type of sensor. It might be expected that if current semi-invasive sensors continue to improve they will come to replace many of the other types. However, significant hurdles related to error, ease of use, and reliability remain [89, 90]. Hence, while there may currently be little choice in many practical cases, this area is rapidly developing.

3.0 Models and Patient Specific Parameter Fitting

Metabolic modeling has been used to study physiological behaviour and/or to control glycaemia for a long time, with a very deep history in the published literature. The

vast majority of these models have their roots in basic compartment modeling with differential equations [91]. The primary use of metabolic models has been the development of model-based measures to assess metabolic parameters, with a particular focus on measuring insulin sensitivity [92-99]. Hence, the main feature in the development of many metabolic models has been increasing levels of physiological accuracy and/or resolution with a concomitant increase in the number of patient specific parameters to be identified. The fundamental physiology typically modelled for this control problem is shown schematically in Figure 3.

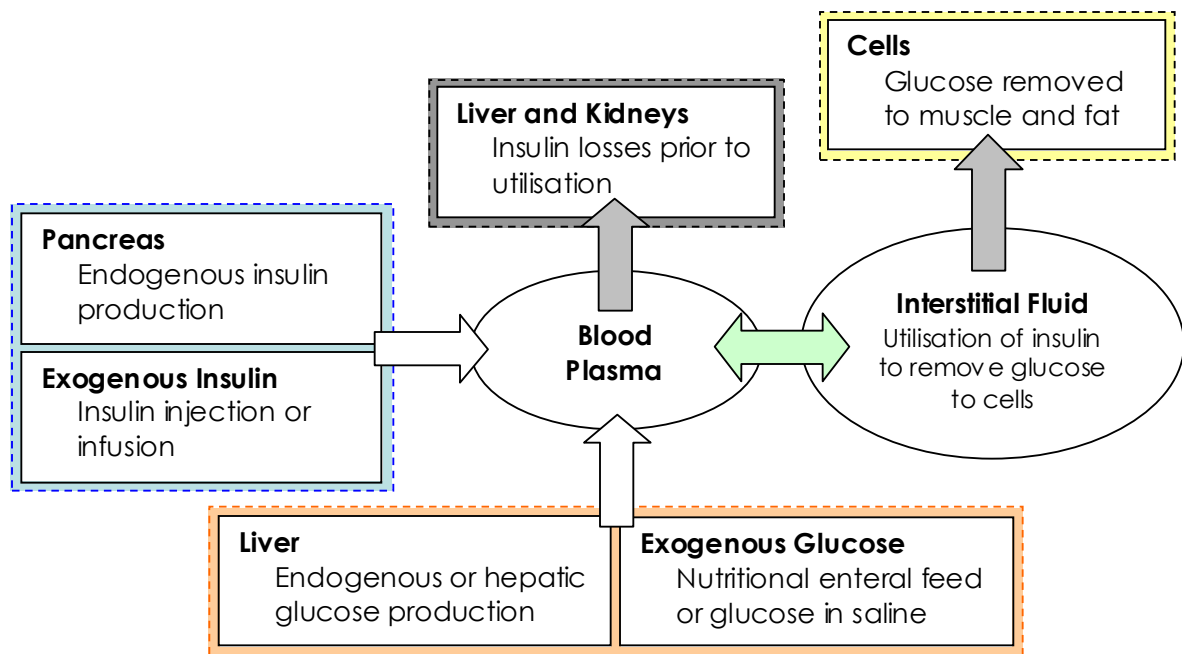


Figure 3: Basic outline of the fundamental physiology of glucose sources, insulin sources and their utilisation to remove glucose. Bi-directional arrows indicate potential for flow in both directions of glucose and/or insulin. Exogenous insulin is assumed intravenously administered in this case, and exogenous glucose appears via absorption from the gut or intravenous nutrition.

Clinical glycaemic control modeling is similar in its need for physiological accuracy to ensure accurate prediction of the outcome of a clinical intervention and thus, good control. However, it may require less physiological resolution given the lesser amount

of data typically available to fit patient specific parameters in critical care, as compared to the frequent sampling typical of clinical physiology studies. Hence, most clinical model-based control applications look for the simplest model to be effective.

3.1 Metabolic Models

Given the extensive history of metabolic modeling of the glucose-insulin system this paper will not go into great length in this regard. In particular, a number of very good reviews exist [91, 100, 101] that offer a broader overview. Instead, a briefer overview of the basic model types used for clinical glycaemic control is presented to illustrate the basic approaches employed thus far.

Metabolic control systems and models start with titration models and controllers, such as the bio-stator [102]. However, perhaps the best known model is the Minimal Model of Bergman et al [94, 103]. This simple model had two compartments for insulin pharmacokinetics and a third equation for insulin-glucose pharmacodynamics.

$$\dot{X}(t) = -p_2 X(t) + p_3 (I(t) - I_b) \quad (1)$$

$$\dot{G}(t) = -X(t)G(t) + p_1 (G_b - G(t)) + P(t) \quad (2)$$

where t is time, $G(t)$ is the plasma glucose concentration at time t , $I(t)$ is the plasma insulin concentration at time t , and $X(t)$ is the interstitial insulin at time t . G_b is the basal plasma glucose concentration, $P(t)$ is the appearance rate of glucose from exogenous input and I_b is the basal plasma insulin concentration. Patient specific parameters p_1 , p_2 and p_3 are transport rates between the various compartments with

the ratio p_3/p_2 representing insulin sensitivity. Note that several forms of this model have evolved and are reported across a wide range of the literature.

Typing “minimal model bergman” into the PubMed database returns over 130 results, including at least 6 review articles, indicating the interest and use of this model. Similar searches deliver even more results. Most of the compartment models used for physiological studies or control have some origin in the Minimal Model. More importantly, this model clearly illustrates the three basic dynamic terms that must be captured for any glycaemic control problem:

- Insulin pharmacokinetics and distribution
- Glucose pharmacokinetics and/or appearance, where meal models for $P(t)$ in Equation (2) would add compartments
- Glucose-insulin pharmacodynamics accounting for the removal of glucose

For each point, more or less compartments or terms may be used, as compared to Equations (1)-(2). Additionally, non-linearities for specific observed, or hypothesized, physiological dynamics may be added as necessary.

However, the Minimal Model has some significant limitations, particularly with regard to use in clinical glycaemic control [104, 105]. More specifically, it does not account for saturation of glucose removal by insulin [106-108], saturation of insulin transport [106, 109-111], measurable and unmeasurable glucose compartments [112-115], or the dynamics of insulin receptors and their mass [116], to name a few. All of

these issues have been raised in the extensive physiological modeling literature, and several modified versions of this model developed as a result.

All of these models are of import and worthy of consideration in the clinical glycaemic control problem in critical care, particularly given the diversity of dynamics and non-linearities considered. However, there is not the scope in this article to do justice to metabolic modeling as a whole. Perhaps the best overall review of metabolic modeling in its entirety is by Carson and Cobelli [91].

3.2 Metabolic Models Used in Critical Care Glycaemic Control

There have been three metabolic models used in clinical examination of critical care patients and glycaemic control [82, 83, 117-121]. Each model is substantially different, based in part on the different control approaches used. The first model is that of Chee et al [119, 120] who used an optimised PID form of control.

$$\text{Insulin increment} = \begin{cases} 4 \text{ U/hr, if } \|\overline{W}_{Zone}\| > 4.5 \\ 2 \text{ U/hr, if } 3.6 \leq \|\overline{W}_{Zone}\| \leq 4.5 \\ 1 \text{ U/hr, if } 2.7 \leq \|\overline{W}_{Zone}\| \leq 3.6 \\ 0 \text{ U/hr, if } \|\overline{W}_{Zone}\| < 2.7 \end{cases} \quad (3)$$

where

$$\|\overline{W}_{Zone}\| = \frac{1}{\sum_{i=1}^{24} i} \left(\sum_{n=1}^{24} n \cdot W_{Zone}[n] \right) \quad (4)$$

$$\text{Bolus} = \begin{cases} 6\text{U/hr, if } \Delta y_{proj} \geq 2\text{mmol/l} \\ 4\text{U/hr, if } 1 \leq \Delta y_{proj} < 2\text{mmol/l} \\ 0\text{U/hr, if } \Delta y_{proj} < 1\text{mmol/l} \end{cases} \quad (5)$$

where

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

$$X_i = x_i - \tilde{x} \text{ and } Y_i = y_i - \tilde{y} \quad (7)$$

$$\tilde{x} = \frac{x_{\max} + x_{\min}}{2} \text{ and } \tilde{y} = \frac{y_{\max} + y_{\min}}{2} \quad (8)$$

x_{\max} = maximum time value in the 30 - min window

x_{\min} = minimum time value in the 30 - min window

y_{\max} = maximum BGL value in the 30 - min window

y_{\min} = minimum BGL value in the 30 - min window

The integral control (Equation (3)) is implemented when sliding tables do not provide adequate glycaemic reduction and the amount of additional insulin is calculated using Equation (4), a normalized weighted average of the BGL (blood glucose level) zones using a 2-hour triangular window. Derivative control is implemented using Equation (5)-(8). Expert control is implemented by keeping an active sliding table and ‘offsetting’ the recommended sliding table input according to several conditions, based on Equations (3)-(5), in order to determine a the control input.

The second model is that of Hovorka et al, which was used for controlling Type 1 diabetes [117] and, in similar form, for critical care glycaemic control trials [121].

$$\dot{Q}_1(t) = - \left[\frac{F_{01}^c}{V_G G(t)} + x_1(t) \right] Q_1(t) + k_{12} Q_2(t) - F_R + U_G(t) + EGP_0 [1 - x_3(t)] \quad (9)$$

$$\dot{Q}_2(t) = x_1(t) Q_1(t) - [k_{12} + x_2(t)] Q_2(t) y(t) G(t) = Q_1(t) / V_G \quad (10)$$

$$F_{01}^c = \begin{cases} F_{01} & \text{if } G \geq 4.5 \text{ mmol/l} \\ F_{01}G/4.5 & \text{otherwise} \end{cases} \quad (11)$$

$$F_R = \begin{cases} 0.003(G-9)V_G & \text{if } G \geq 9 \text{ mmol/l} \\ 0 & \text{otherwise} \end{cases} \quad (12)$$

$$U_G(t) = \frac{D_G A_G t e^{-t/t_{\max,G}}}{t_{\max,G}^2} \quad (13)$$

$$\dot{S}_1(t) = u(t) - \frac{S_1(t)}{t_{\max,I}} \quad (14)$$

$$\dot{S}_2(t) = \frac{S_1(t)}{t_{\max,I}} - \frac{S_2(t)}{t_{\max,I}} \quad (15)$$

$$\dot{I}(t) = \frac{U_I(t)}{V_I} - k_e I(t) \quad (16)$$

where

$$U_I(t) = S_2(t)/t_{\max,I} \quad (17)$$

$$\dot{x}_1(t) = -k_{a1}x_1(t) + k_{b1}I(t) \quad (18)$$

$$\dot{x}_2(t) = -k_{a2}x_2(t) + k_{b2}I(t) \quad (19)$$

$$\dot{x}_3(t) = -k_{a3}x_3(t) + k_{b3}I(t) \quad (20)$$

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

bioavailability, A_G , and the time-of-maximum appearance rate of glucose in the accessible compartment, $t_{max,G}$. The insulin subsystem is described by Equations (14)-(19). S_1 and S_2 are a two-compartment chain for absorption of subcutaneously administered rapid-acting insulin, $u(t)$ the insulin input (bolus/infusion), and $t_{max,I}$ the time-to-maximum insulin absorption. $I(t)$ is the plasma insulin concentration, k_e is the fractional elimination rate and V_I the distribution volume. The insulin action subsystem consists of three components, endogenous glucose production, transport/distribution and disposal (x_1 , x_2 and x_3). Finally, k_{ai} and k_{bi} ($i=1,\dots,3$) represent the activation and deactivation rate constants of insulin action respectively.

Finally, Chase et al used a model loosely based on Bergman's minimal model with additional non-linear terms and a grouped term for insulin sensitivity [78, 81-84, 118]. This model has been employed in several critical care glycaemic control trials using different control approaches, as well as in retrospective analyses.

$$\dot{G} = -p_G G - S_I(G + G_E) \frac{Q}{1 + \alpha_G Q} + P(t) \quad (21)$$

$$\dot{Q} = -kQ + kI \quad (22)$$

$$\dot{I} = -\frac{nI}{1 + \alpha_I I} + \frac{u_{ex}(t)}{V} \quad (23)$$

$$P(t_i < t < t_{i+1}) = \bar{P}_{i+1} + (P(t_i) - \bar{P}_{i+1})e^{-k_{pd}(t-t_i)} \text{ where } \bar{P}_{i+1} < P(t_i) \quad (24)$$

$$P(t_i < t < t_{i+1}) = \bar{P}_{i+1} + (P(t_i) - \bar{P}_{i+1})e^{-k_{pr}(t-t_i)} \text{ where } \bar{P}_{i+1} > P(t_i) \quad (25)$$

where $G(t)$ is the plasma glucose above an equilibrium level, G_E , and $I(t)$ is the plasma insulin resulting from exogenous insulin input, $u_{ex}(t)$. The effect of previously

infused insulin being utilised over time is represented by $Q(t)$, with k accounting for the effective life of insulin in the system. Patient endogenous glucose clearance and insulin sensitivity are p_G and S_I , respectively. V is the insulin distribution volume and n is the constant first order decay rate for insulin from plasma. Total plasma glucose input is denoted $P(t)$. Michaelis-Menten functions are used to model saturation, with α_I used for the saturation of plasma insulin disappearance, and α_G for the saturation of insulin-dependent glucose clearance [84, 122]. k_{pr} and k_{pd} are the effective half lives of glucose transport from gut to plasma for both increasing (k_{pr}) and decreasing (k_{pd}) feed rates respectively, and \bar{P}_i and \bar{P}_{i+1} are the steps in enteral glucose feed rates.

The final two equations account for glucose appearance from enteral nutrition via feeding tube as the glycaemic control studies using this model [81-83] modulate both insulin and nutrition inputs to reduce plasma glucose levels. This approach thus looks at both sides of the glucose balance, exogenous insulin removal of glucose and glucose appearance from exogenous nutrition, to reduce glycaemic levels in the face of insulin resistance and insulin saturation.

This approach of modulating nutrition in addition to exogenous insulin is a significant departure from other approaches in this field, which use insulin alone to reduce glycaemic levels [2, 24-26, 118-122]. Despite concerns, recent studies show that low-calorie nutritional inputs reduce hyperglycaemia [6, 9, 10, 123, 124], and above ~30% of standard goal feed rate do not increase infectious complications [125-127]. More specifically, Krishnan et al [128] showed that feeding over 66% of the ACCP recommended rates increased the likelihood of ICU mortality, and suggested that the ACCP caloric targets may thus be set too high. In addition, hyperglycaemia has also

been shown to exacerbate muscle protein catabolism in burn patients [129] indicating that excessive nutrition and hyperglycaemia should be avoided in this instance, as well. Similarly, parenteral administration of glucose up to 25kcal/kg, typically up to 50% dextrose, did not increase hyperglycaemia or infections complications [124]. Finally, reduced caloric nutritional support has been effective in paediatric cases and for the obese [123, 126, 130]. Thus, there is reasonable evidence that moderate reductions in nutrition may increase survival and will not reduce other clinical outcomes. However, extreme or long-term underfeeding should be avoided [131].

Modulating nutritional dextrose inputs also provides a physiologically non-saturable path to reduce plasma glucose, at least to the point of eliminating nutritional input entirely. It is important to note that this approach is focused on controlling the dextrose carbohydrate content exacerbating hyperglycaemia, rather than the overall nutritional profile. This last issue could be practically addressed, for example, by separating the dextrose and protein-fat nutritional inputs infused.

3.3 Fitting Methods and Patient Specific Parameter Identification

Most model-based glycaemic control requires a patient specific model due to variation between patients in insulin sensitivity and other critical dynamic parameters. In particular, Hann et al [84] used the model of Equations (21)-(23) to show significant variation in insulin sensitivity over time for a critically ill cohort. These variations in glycaemic level and effective insulin resistance are due to the evolution of patient condition in the critically ill, where differences in cohort and level of critical illness will affect the behaviours observed.

In particular, as patient condition evolves the levels of stress and counter-regulatory hormones change dynamically, leading to significant variation in effective insulin resistance. An extreme case is the significant drop in insulin sensitivity (increase in insulin resistance) observed with the adrenergic surge prior to atrial fibrillation [81-83]. Interactions from steroid and other drug therapies that affect insulin resistance also play a role [18, 132-134], although the effect of steroids has recently been preliminarily reported to be limited in some cases [135]. More specifically, steroid administration is strongly associated with higher glycaemic levels [132, 133] in many, but not all, cases [22]. However, the effect on glycaemic levels will also depend significantly on the level of dosing by the individual intensivist, as seen for example in the call for moderate steroid dosing in treating sepsis [18, 134].

Note that the amount of variation seen will also depend heavily on the patient cohort. For example, cardiac surgery critical care patients may be less variable and experience less hyperglycaemia during recovery than those suffering from sepsis, ARDS or multi-organ failure [24, 28, 35-38]. More specifically, less critically ill cohorts may experience a more straightforward, predictable evolution of patient condition than more critically ill cohorts.

Thus, the fitting procedure and/or model used for glycaemic control must be able to account for significant patient variation over time. It must also be computationally simple enough to be performed in “clinical real time” of 1-5 minutes, or faster. Finally, fitting the patient specific parameters in any of the models presented typically presents a non-convex optimisation problem, due primarily to the series of non-linear differential equations involved [91].

The most commonly used method for fitting parameters in compartment models is non-linear recursive least squares (NRLS) [91, 136]. Given the non-convex nature of the problem this method will produce results that are starting point dependent. Hence, to guarantee optimal results a range of initial values can be used [91, 109]. The minimum or average result is often used, or the full resulting distribution can be employed in further analysis [109].

NRLS is also computationally intense [91], particularly where longer periods of data are being fit. The main reason is that it depends on re-simulating the data every optimisation step, leading to a large amount of computation for more complex models and/or longer periods of data [84]. However, modern computing power generally manages this issue, except for extreme circumstances, given the 1-5 minute period in which parameters must be identified for most real-time clinical control applications.

Iterative, Bayesian and gradient descent based methods have also been used in a variety of forms [137-141]. Given the non-convex and non-linear models involved, these methods are all specific to the exact model and methods employed. Thus, they are essentially problem specific and not necessarily generalisable to broader situations.

An emerging method that simplifies many of these problems is the integral method in Hann et al [84]. Integrating the differential model equations converts the problem to one of matching areas under curves. Parameterising unknown, time-varying patient specific parameters as piecewise constant or higher order functions recreates the

problem in terms of unknown constants that are more readily identified. Using measured data and numerical integration, the problem can thus be converted into a convex linear least squares problem to obtain these constants. More importantly, it does not require repeated re-simulation of the system model and optimises the parameters in what is effectively a single step. The result is thus convex and not starting point dependent. It has been used in a variety of clinical glycaemic control studies [81-84, 118] and in other similar biomedical models [142-144].

Overall, a variety of fitting methods are available. Traditional methods, such as NLS, offer results with some potential limitations depending on the specific problems. Integral methods are a newer, emerging method that may offer some advantages in simplicity and convexity, again dependent on the specific problem defined. Both approaches are capable of delivering the patient specific parameters required for most, if not all, models currently employed for clinical glycaemic control. Fitting method efficacy is also dependent on the data density available, creating an interaction with the measurement methods employed [84, 137]. Thus, the choice of fitting method is primarily dependent on the specific problem. The main requirement is to ensure that the method chosen works well with the models employed and the specific clinical situation [91, 145].

4.0 Glycaemic Control Methods and Results

Given a model, a glucose sensor and patient specific parameter identification method, the fundamental glycaemic control problem is simply defined. The fundamental goal is to maintain glycaemic levels in an acceptable range, typically somewhere in the 4-8

mmol/L range. Tighter regulation toward 4.5-5.0 mmol/L is considered better, based on the limited large-scale clinical trials and validation to date. More specifically, the reductions in mortality seen by van den Berghe et al [2, 24] were greater with an average glycaemic target of 6.1 mmol/L than those of Krinsley [25, 26] with a higher target of 7.75 mmol/L, implying a potentially continuous scale of improved outcome mortality with lower glycaemic limit.

The primary control input is the administration of exogenous insulin, typically intravenously in critical care. Other studies have examined the impact of reduced dextrose nutritional inputs on glycaemia with positive results [6-9], and this approach has been brought to clinical glycaemic control in critical care [80-83] offering a second control input. More importantly, since insulin effect saturates around 5-10 U/hr in continuous infusion [106, 107], modulating the nutritional input offers a means of reducing glucose levels in the face of significant insulin resistance, as seen in the very critically ill. It is particularly relevant where insulin alone may not be able to fully achieve the desired glycaemic reductions.

Finally, there have now been several reports on intensive insulin therapy with differing performance metrics. Recent surveys have shown that while tight control is recognised as important, there is little agreement on what levels are desirable or achievable [4, 33, 73, 74, 77]. This difficulty is likely due to the impact of trying to rationalise results from different protocols and patient cohorts to determine what methods might work best for a given clinical situation.

4.1 Performance Metrics

A variety of performance metrics have been used in different critical care glycaemic studies. These metrics can be summarised as four basic goals:

- **Average Blood Glucose Level:** calculated over all measurements [25, 26] or over limited measurements, such as first morning measurement [2, 24]. The average is the simplest performance measure and the one used in both landmark clinical studies. However, it provides no further information on glucose excursions or tightness of control. An important consideration is the use of a trapezoidal mean to obtain the proper mean value if the sampling period is irregular [85, 86].
- **Time in a Glycaemic Band:** calculated as the time or percentage of measurements in a specific band, such as 4-6.1 mmol/L [79-83] or 4.5-6.1 mmol/L [121]. Maximising this metric is essentially equivalent to minimising the Hyperglycaemic Index (HGI) or area under the glucose curve level [29, 146]. This metric provides a surrogate measure of the average value, as well as an indication of the tightness of the glycaemic control result.
- **Glucose Variability:** measured as the standard deviation or 90% interval over the data. This metric has only been employed recently [79, 88] and measures the tightness of blood glucose control around the average or target value. It is also increasingly important in managing Type 1 diabetes [87]. However, it provides no indication of the absolute glycaemic levels obtained and some methods assume normal or other distributions that may not match the data. Hence, confidence intervals determined from the data may prove more useful.

- **Hypoglycaemic Episodes:** measured as the number or percentage of measurements that are below a defined hypoglycaemic threshold. The typical definition is 2.2 mmol/L, although some studies use higher thresholds [80, 121]. Variability also captures some of this information when associated with the average or median glucose values. More importantly, this measure is a critical indicator of the safety of the control methods used.

Hence, the performance metric chosen can be quite different depending on the specific clinical goals desired. In general, accounting for, or at least examining, all four metrics provides the most useful information in evaluating the impact of control.

Note that only the first metric, the average glucose value, has been correlated with the clinical outcome mortality for cohorts of patients. More specifically, it is currently assumed, based on limited results to date, that tight control and mortality are linked by average glucose value obtained, and that the relation in between may be linear or a continuous range, as shown schematically in Figure 4. However, recent results also link range and/or peak glucose values to critical care mortality [23, 28, 36, 85, 86], providing impetus to using other, more easily measured or tracked metrics, as well.

Note that further, large clinical studies, which are currently lacking, might help clarify the assumed relationship between hyperglycaemia and mortality, by adding more data points to Figure 4. In particular, the shaded area indicates the potential for different results due to patient cohort and/or protocol employed. More specifically, it is not yet proven that using the same protocol with a different cohort will have substantially the same results, and similarly for a different protocol on substantially the same cohort as

a prior study. Therefore, such studies would help clarify the performance requirements for clinical outcome.

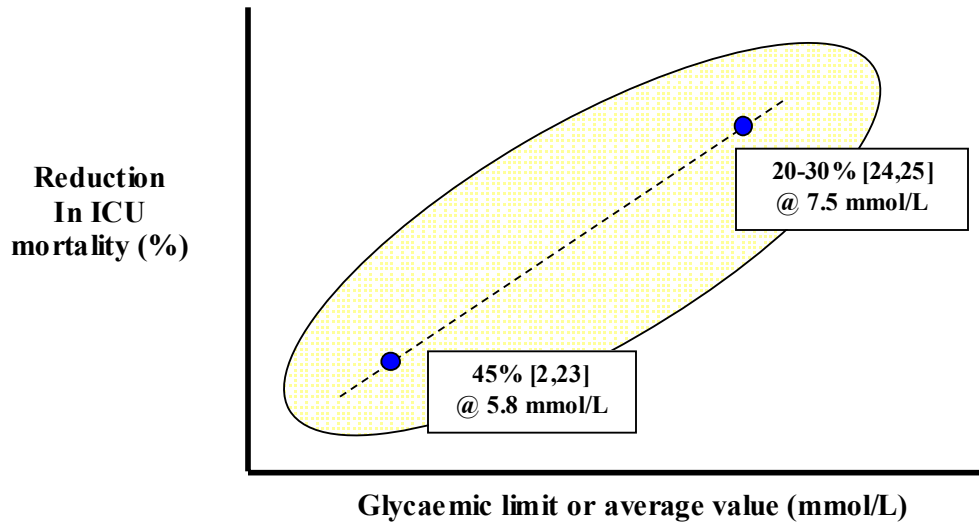


Figure 4: Average glucose value obtained and clinical outcome in reduced mortality with assumed linear relationship (dashed). The shaded area indicates the potential variability in results that could occur due to different patient cohorts or protocols.

Thus, it is possible that control methods that are similar in one metric, but different in others, may have different clinical outcomes. Such a result would cloud the issue of what is required from a clinical control protocol to obtain the desired clinical outcome. This difficulty would be particularly apparent when balancing the clinical effort and time required implementing a protocol, and the clinical outcome achieved. However, it would also provide input as to what type of performance is necessary. Such further clinical studies and analyses are yet to be done, leaving the question of exactly what type of performance metrics and requirements are ideal unanswered at this time, particularly with respect to the added impact of patient cohort on the results.

4.2 Impact of Patient Cohort

Figure 4 also illustrates how the composition of the patient cohort may have a significant impact on the performance achieved. The more critically ill the cohort, as measured by APACHE II, TISS or other relevant score, the more insulin resistant and variable [84] are their glucose dynamics. One reason is that the more critically ill cohorts have greater incidence of sepsis and multi-organ failure in particular, both of which are associated with increased insulin resistance and hyperglycaemia. In comparison, post-surgical ICU cohorts, such as after cardiac surgery in [2, 24, 121] tend to have fewer complications and a more straightforward, predictable evolution of their condition, resulting in lower APACHE II and other scores.

Thus, the less critically ill cohort may be easier to control, or to achieve a lower target, than another more critically ill cohort. This result will also interact with the efficacy of the sensing and control schemes employed to deliver that control. More specifically, a poor control protocol may achieve lesser results on a similar cohort. Similarly, a control protocol may work well for a specific, defined patient cohort or type, but be less well matched to a different type or types of patient. Hence, the impact of patient cohort composition exists, but may be very difficult to separate from the control methods except for broad comparisons.

One such comparison can be made between the two landmark studies [2, 24-26], where the cohort of van den Berghe et al had a median APACHE II score of 9 and the average score for Krinsley was 16.9. Similarly, Krinsley was unable to titrate glucose levels to a target lower than 7.75 mmol/L, achieving an average value of approximately 7.5 mmol/L, without excessive input and effort. In comparison, van

den Berghe et al achieved 5.8 mmol/L with a target of 6.1 mmol/L for their less critically ill cohort. More specifically, van den Berghe et al studied a post cardiac surgical population whereas Krinsley had a broader general ICU cohort with relatively much higher APACHE II scores. Note that not all published studies report APACHE II or other comparable scores, which makes comparison difficult.

4.3 Clinical Model-based Glycaemic Control Results

As noted previously, there are only three primary sets of model-based glycaemic control trials reported [81-83, 118-122, 147-149] based on the research group and modeling approach employed. A fourth is not model-based [79, 80], but was developed from the model-based trials of [81-83, 118, 122] to have similar behaviour and results to the computerised method, as shown in both simulation and clinical pilot trials. Each study takes a very different control approach, thus providing a brief overview of what is possible.

Chee et al [119, 120] used PID control with CGMS sensors in an automated closed loop feedback system, while their earlier work used a sliding scale control method [147]. Their results were reported for trials over 4-9 patients in limited pilot studies. The average glucose values obtained under control were 11.5 +/- 2.99 mmol/L using 6.5 +/- 5.5 U/hr of insulin for the PID controllers [119, 120]. These results were shown to be tighter than achieved for these patients under standard hospital protocols before or after the trial period for each patient, indicating the potential of improved tightness of control with automation. Although the glucose levels are not very low the standard deviations were reduced by 50% from the hospital protocol results. The

similar trial by Chee et al [147] used a sliding scale method, which is not model-based, but achieved similar results.

However, these trials also required several interventions by medical staff where the controller failed to provide proper input. Some of these were due to difficulties with the larger sensor errors and sensor failure. Importantly, it should also be noted that a main goal of this trial was to employ emerging CGMS technology and link it to feedback control. In this aspect, it was successful and delineated some of the important issues related to using these sensors.

Plank et al [121] use a model predictive controller (MPC) to provide tight control over a series of 48-hour trials for post-cardiac surgery patients. Results were compared to data for patients on standard unit protocol in a randomised trial. The controller and model are similar to those in a prior work for diabetic individuals [117]. Hourly adjustments of insulin infusions were used as the control input with a glycaemic target band of 4.5-6.1 mmol/L. The cohort was post-surgical with an APACHE II score averaging 10-12 across the three centres. Time in the target band ranged from 42-56% across the three centres with no time spent below the target minimum of 4.4 mmol/L. Average glycaemic levels ranged from 6.1-6.8 mmol/L and the MPC group used more insulin, as might be expected. Overall, the results show the efficacy of automated, model-based control in maintaining euglycaemia versus standard methods and the greater information arising from reporting time in a glycaemic band, as well as average glucose level.

Chase et al [81] and Wong et al [82, 83], undertook a series of 8 clinical case study patient trials where both exogenous insulin and nutrition feed rates were varied for control. The cohort was significantly more critically ill relative to other reported studies in intensive insulin therapy, with an average APACHE II score of 23 (range: 17-31) and APACHE III scores of 40-91. The approach measures glucose every 30-60 minutes and intervenes hourly to achieve a target blood glucose value set for the subsequent hour. The mean error between the achieved blood glucose and the targets over all trials was 8%, with 42% of all target glucose values achieved within 5%. More importantly, 94% of all target glucose measurements were within the reported sensor error. The remaining, large outlying errors are attributed to significant changes in patient condition, such as atrial fibrillation, observed over the hour between intervention and target measurement. Figure 5 shows the glucose targets, glucose measurements, model parameters for insulin and glucose, and insulin and glucose inputs as controlled for a typical patient [82]. However, these trials were only 10-24 hours and thus primarily focused on blood glucose target accuracy, blood glucose reductions into a glycaemic band, and maintaining blood glucose levels, rather than long-term time in a band. Hence, longer trials are required to validate this control approach for long-term care.

Finally, a paper-based protocol [79, 80] designed to mimic the computerised model-based system from [81-83, 118, 122], was implemented to offer the efficacy of the computerised protocol with easy implementation. Implemented as a clinical practice change in the Christchurch Hospital ICU, it relies on 1-2 hourly measurements. Control is provided via hourly interventions modulating both insulin and nutrition.

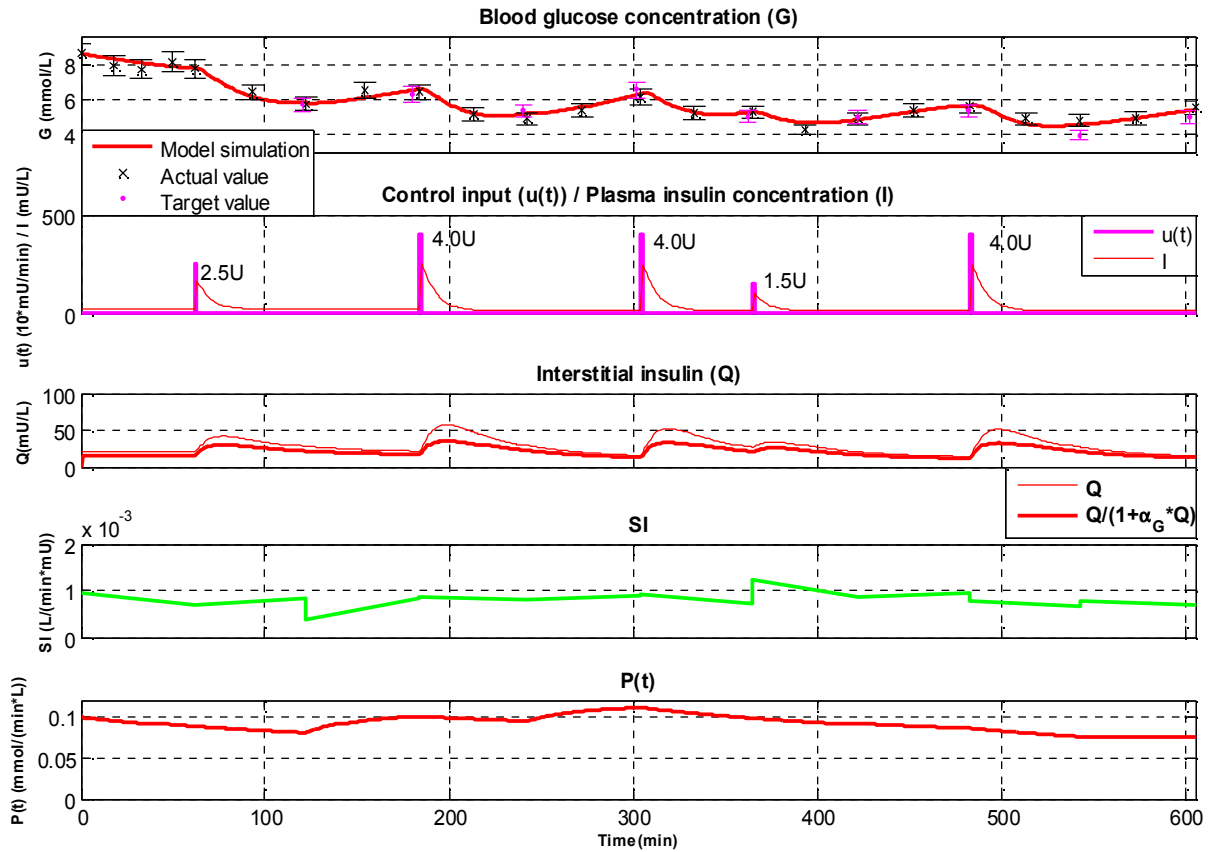


Figure 5: Patient trial progression using Equations (21)-(25) in an adaptive, model predictive control scheme [82]. Glucose measurements every 30 minutes and hourly target values show measurement error bars.

An initial 11 patient pilot study comprising over 1500 hours of control resulted in an average glucose level of 5.8 ± 0.9 mmol/L over all patients. The average feed rate was 63% of the clinically determined goal feed, which is 7% higher (absolute) than retrospective hospital data [84]. The average insulin consumption was 2.6U/hour, indicating that reducing dextrose feed also enables insulin consumption at rates below reported saturation limits, while providing effective tight control. The minimum blood glucose reported across the 11 patients was 3.2 mmol/L with only 21 measurements less than 4.0 mmol/L. Finally, the time in the desired 4-6.1 mmol/L band was 63% with 89% of measurements in the 4-7.0 mmol/L band and 95% in the 4-7.75 mmol/L

band. Figure 6 shows the glucose response over 164 hours for an initial pilot study patient with APACHE II score of 21 that achieves a mean glucose value of 5.4 mmol/L from an average use of 2.3 U/hour. Approximately 50% of all control used 2-hourly measurements, addressing issues of patient comfort and clinical effort. More importantly, additional clinical intervention was never required for safety or other reasons. Overall, the results indicate the potential to achieve very tight control within clinically reported desirable glycaemic bands for a very critically ill cohort, with no extra medical intervention or hypoglycaemic episodes.

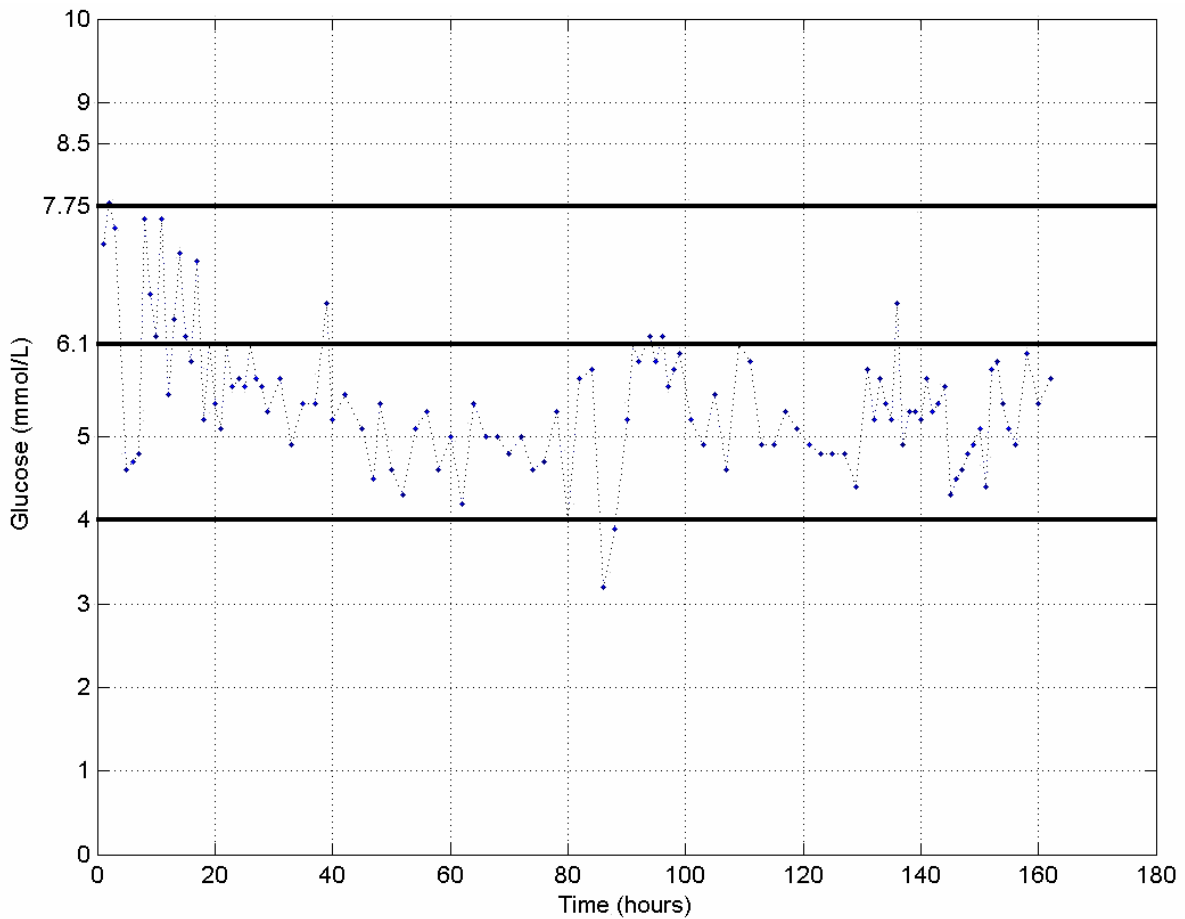


Figure 6: Long-term glycaemic control response for a single patient covering 164 hours with 85% of the time spent in the 4.0-6.1 mmol/L range and 98% in the 4-7.75 mmol/L band. Note that 50 of 112 measurements made were for 2-hourly sampling under this protocol [79, 80]. For clarity only the glucose measurement value is shown.

4.4 Comparison to Other Clinical Intensive Insulin Therapy Results

Other clinical intensive insulin therapy trials for controlling hyperglycaemia in critical care have recently been reported [150, 151]. These protocols are not model-based and follow on from the initial major clinical studies [2, 24-26]. As they are primarily pilot studies, they have had more limited patient numbers and primarily focus on achieving tight control, rather than the clinical or mortality outcome. They also had different cohorts and, not unexpectedly, different results.

Chase et al [79, 80] compares several of these protocols [2, 24-26, 79, 81, 82, 150, 151] in a simulated trial using the virtual cohort of [84]. This virtual cohort consists of 18 patients with an average stay of 3.6 days and consists of relatively more critically ill patients with a mean APACHE II score of 21.9. It was used to safely develop and analyse glycaemic control protocols [80-83, 118, 122] prior to clinical validation in pilot trials, and further details can be found in these references. Specifically, the virtual cohort used a model to fit the patient specific, time-varying profiles of insulin sensitivity and endogenous clearance [84]. These profiles are then used with the same, or different, nutritional and insulin interventions. Hence, these virtual patients provide a safe platform for testing new protocols before working directly with patients, as they are “driven” by clinically measured model-based variations in metabolic parameters. More importantly, the initial clinical results obtained are very similar to those found in the simulated trials, verifying the overall virtual cohort design approach [80].

The results in Table 1 show that the computerised protocol of [81-83] and its table-based version [79, 80] offer far tighter control for this critically ill cohort. The primary reasons for this outcome are twofold. First, these protocols modulate both

insulin and nutrition, and for this level of critically ill cohort insulin alone may not be enough to reduce and maintain glycaemic levels [118, 122, 148]. Secondly, these protocols measure more frequently than most other protocols, providing more opportunity to intervene and correct highly dynamic patients before extreme excursions in glycaemic level occur. In particular, less frequent measurement leads to less frequent change in the intervention. For a highly dynamic patient, these less frequent changes result in larger excursions into hyper- and hypo- glycaemic ranges [78, 80].

Table 1: Simulated glycaemic control protocol comparisons

	SPRINT	AIC4	Mayo clinic	Leuven	Bath	Yale
Log Median	5.79	5.93	8.59	5.60	6.21	6.70
Multiplicative STD	1.29	1.35	1.29	1.65	1.45	1.4
68.3% range	(4.50-7.45)	(4.39-8.01)	(6.68-11.05)	(3.40-9.24)	(4.27-9.03)	(4.78-9.40)
95.5% range	(3.50-9.58)	(3.25-10.82)	(5.20-14.20)	(2.06-15.24)	(2.94-13.13)	(3.41-13.18)
Time in 4-6.1 band	61.7%	62.2%	11.2%	35.8%	45.5%	22.3%
Time in 4-7.75 band	83.5%	82.9%	27.4%	51.0%	70.0%	64.8%
Time less than 4	4.4%	1.1%	0.6%	23.6%	7.1%	5.9%
Time higher than 7.75	12.1%	16.1%	72.0%	25.3%	22.9%	29.3%
Average insulin (U/hr)	2.4	2.6	1.6	3.0	5.8	4.6

These virtual cohort simulation results are further validated by the fact that the reported percentages of hypoglycaemic measurements and average glucose levels achieved are very similar to those reported in the original studies. This latter result indicates that for more critically ill and highly variable patients, it is possible to achieve a similar average glucose value for less critically ill cohorts using the same protocol. However, glycaemic variability is significantly increased due to the more

dynamic and unpredictable patient dynamics. As a result, hypoglycaemic episodes can increase and the time in band can decrease as well.

This last result is clearly evident in the recent study by Van den Berghe et al. [152], applying the Leuven protocol [2] on a more critically ill medical ICU cohort than the original study (mean APACHE II score 24 ± 10), where hypoglycaemia was experienced by 25.1% of all patients with a stay longer than 3 days. While patients with length of stay greater than three days achieved a mean morning glucose level of 6.0 mmol/L, the standard deviation was ± 1.44 mmol/L, indicating significant potential variability and thus the potential for the hypoglycaemic events reported. Interestingly, the mean caloric intake from carbohydrate/dextrose in this study was 700-900 kcal/day, which is significantly lower than in the original study and close to the second tertile of the ACCP guideline reported by Krishnan et al [128] to be a more optimal level of intake with respect to mortality.

Overall, these results further reinforce several major aspects in controlling hyperglycaemia. First, is the need to measure frequently, perhaps with emerging continuous sensors. Second, is the use of more than average glucose values for reporting performance, such as considering the need to control blood glucose variability. Finally, safety is an important consideration for the highly dynamic, very critically ill patient, and all of these results indicate that frequent measurement with different forms of intervention is important to early detection, and correction, of emerging or actual hypoglycaemia and thus patient safety.

4.5 Impact of Measurement Frequency on Model-Based Control

Section 4.4 notes that measurement frequency has a significant impact on the tightness of control that can be obtained as noted from the results of several studies. However, tighter control requires more frequent measurement for the highly dynamic critical care patient if safety is to be maintained. Hence, there is a tradeoff with regard to clinical applicability and capability, and the burden on clinical staff.

The model-based and model-derived methods reported here require measurement intervals of 30-120 minutes for the insulin and nutrition protocols [78-80, 82, 83], with little difference reported between measurements of 30 and 60 minute intervals. Longer intervals of 120 minutes were established once a patient was defined as stable by the protocol and was used for approximately 50% of all patient treatment time. The model predictive methods of Plank et al [121] measured every 60 minutes to achieve their results. However, their trials followed patients for only 48 hours and longer trials might have encountered more stable patients and the opportunity to measure at longer intervals. Notably, both approaches and protocols reported no hypoglycaemic events after significant periods of tight control, where some ad-hoc protocols are reporting at least one hypoglycaemic event for 5-25% of patients [2, 152].

However, until more reliable continuous sensors emerge, this issue will hinder greater or more rapid uptake in clinical practice. Currently, hourly measurements with these protocols have not led to a reported increase in clinical burden, particularly where two hourly measurements are available in some cases. Thus, the tradeoff remains, regardless of measurement type, of measurement frequency versus safety for the highly dynamic critically ill patient. The primary question is then one of how to

identify these more critically ill and potentially more dynamic patients during those periods. This avenue has yet to have any reported results.

4.6 Other Recent Clinical Intensive Insulin Therapy Results and Approaches

It is important to note that those protocols discussed in Section 4.4, as well as other model-based approaches, are not the only protocols tested clinically. The area of glycaemic control in critical care is rapidly expanding in interest and publication numbers. In this instance, there are two other approaches that should be considered for completeness: 1) nomogram or sliding scale/titration approaches and 2) estimator-based approaches. The former is one means of standardising care across patients, while allowing the flexibility to provide patient specific care, and the latter uses very simple equations based on clinical or empirical data, or very simple models.

Nomograms do not use models per se, however they are not necessarily entirely ad-hoc methods either. Instead, they use empirically based charts and tables, typically taken from clinical experience and trial, to adjust the therapy given and provide a patient specific approach. Chant et al [153] used a nomogram for an 86 patient study that showed that lowered average morning glucose levels 27% to an average level of 7.1 mmol/L. However, hypoglycaemia occurred more often in the controlled group with 3.8% of patients having at least 1 episode. The measurement frequency averaged 7 measurements per day for the nomogram group indicating a lighter clinical load for these results. Similarly, Thomas et al [154] used a web-based insulin dose calculator to determine the required intervention and reduced mean glucose concentrations to 6.3 mmol/L from 7.3 mmol/L in a retrospective control group. However, patient mortality was unchanged over the 790 (total, with 502 intervention, 288 control) patient study.

Finally, Kanji et al [155] achieved a glucose target range of 4.5-6.1 mmol/L for 11.5 \pm 3.7 hours/day using a standardised sliding scale and nursing-based titration of insulin infusions. However, while good average glucose levels were achieved for approximately 50% of the time, severe hypoglycaemia still occurred in 4% of patients, down from 16% under the regular care it compared with. Similarly, dextrose intervention therapy was required 0.91 times per patient per day. These latter results indicate the overall difficulty that can be encountered in controlling highly dynamic patients. Finally, all of these cases used only insulin as an intervention to reduce glycaemic levels. Overall, such standardised methods can be seen to work well for some cohorts or situations, but not necessarily over all possible units.

There are two recent and significant results using very simple models or estimators to determine the necessary insulin intervention. These estimators are typically based on simple gradient estimations to estimate the impact of an intervention. This approach is taken by the GRIP system [156], which used insulin and a computer system to help control glycaemic levels in a surgical intensive care unit. GRIP treated 179 patients for 957 patient days with no system induced hypoglycaemia. Glucose levels were in the target range of 4.0-7.5 mmol/L 78% of the time where the system had a preset target level of 6.5 mmol/L. Nurses reported the system easy to use and an improvement over paper protocols due in part to the mean 4.9 glucose measurements required per day for the system. Finally, the Glucommander [157] is an impressive study with over 5000 patients and 120,000 hours of treatment. This system has been implemented for several years calculates insulin infusion level as a simple equation of current glucose level and then modifies that value for patient specificity using an array of insulin vs glucose multiplier slopes. Results show that a mean glucose level

of 8.33 mmol/L was achieved in an average of 3 hours and held that average level around 8.0 mmol/L over several days as required with variation of $\pm 1.0-1.5$ mmol/L. Hypoglycaemia less than 2.2 mmol/L was still recorded in 2.6% of patients, indicating that some patients are still quite variable. Overall, these systems and approaches offer less variability and more standardised control than sliding scales, nomograms or other current methods, however they do not appear to match some of the reported model-based methods for the potential to tightly regulate glycaemic levels at this time.

4.7 Type 1 Diabetes Applications and Analyses of Model-based Control

Although not the focus of this article, there have been clinical applications of model-based control to ambulatory diabetic individuals and animal models. Given the similarity of the system to be controlled, they are worthy of mention as alternative approaches that might be applied to this problem. In addition, some of the works reported here have emerged from this research area and further crossover in both directions seems almost certain.

The ADICOL project trialled closed loop, smart insulin pump technology by Hovorka et al [158]. Hovorka et al also utilised MPC methods for Type 1 diabetes [117] with some good success. Andreassen et al undertook a probabilistic approach to predicting blood glucose levels [159]. They also examined diabetes advisory capabilities with the DIAS system in Arleth et al [160], which also employed a specially developed mixed-meal model to account for the appearance of carbohydrate as plasma glucose [161]. The DIAS system was unique in using a discrete, empirical model of glucose-insulin dynamics, based on a collection of euglycaemic and hyperglycaemic clamp

test results, rather than a dynamic model based on differential equations. Hence, this model predicted glucose levels as a series of finite states over time, based on the interventions and other dynamic inputs. Additional clinical results include the application of model-based PD control and relatively frequent measurement to investigate the regulation of post-prandial glucose excursions [162, 163]. Finally, PID control was implemented in an artificial pancreas using implanted sensors and insulin pumps as summarised in Steil et al [164], showing the potential and technologies involved in achieving automated control with implanted sensors and systems.

Finally, it bears mentioning that there have been several model-based control analyses performed in simulation. In fact, hundreds of papers exist on developing control systems for diabetes management using only simulation or limited clinical data. A brief, and definitely not exhaustive, overview of the types of control that have been examined would include the review by Lehman et al [100]. Many of the systems presented use control as a means of providing clinical advice or testing the efficacy of a new protocol [165-173] and are thus primarily diabetes management advisory systems rather than automated controllers. A more complex, higher performance example uses model predictive control on a 19th order, non-physiological model of the glucose-regulatory system, resulting in a 40% peak reduction and 23% reduction in settling time to basal level [174]. Optimal control using grid search theory, robust H-infinity control, simple PD controllers, and variable structure controllers have also been studied, to name a few, each using different models and/or approaches [173-182]. In each case, the focus has been on controlling absolute blood glucose excursion, focusing on the post-prandial regulation of glucose levels in Type 1 diabetes. The models used often required either patient specific parameters that are

not generically available, and/or knowledge of glucose or exercise inputs that would not be known a priori. Additionally, most were not clinically validated. However, these approaches do illustrate the very wide range of model-based control schemes that might be applied to clinical applications in critical care or broader populations.

5.0 Future Developments and Requirements

A significant question that arises is what future developments will arise in this field. Although primarily speculative, there are some developments that will have to occur to see widespread implementation. These developments focus primarily not on providing tight control, but on making that provision clinically less burdensome.

First, emerging continuous sensors will have to keep emerging as they offer the ability to automate the measurement process, which is reported as the most burdensome aspect of providing intensive insulin therapy and tight control. Currently, these sensors are not accurate or reliable enough to provide the quality required for model-based protocols. Thus, improved sensors, which are undoubtedly under development, and/or improved signal processing is required to make the best use of these sensors in a real-time control system.

The second area for significant development is in the signal processing and data analysis employed. Currently, signals are not significantly conditioned, which may well be ignoring significant added data of interest to the problem, such as variability. In addition, the measured and fitted results are not yet significantly analysed, and the development of stochastic models to better manage patient and signal variability is

already starting to occur [183]. Stochastic models based on observed clinical dynamics therefore represents a largely untapped area for further optimising management of these highly variable patients where significant impact can be made.

Finally, current research focuses on controlling hyperglycaemia, as it is obviously not a fully solved problem. However, as more trials and methods are developed and improvements made, further applications are likely to be identified. In particular, the ability to monitor other conditions in the critical care patient using real-time identified, patient specific model parameters offers some significant potential [82]. This type of capability is not available with an ad-hoc protocol that does not use model-based control. However, such applications are likely to arise as methods and models develop, and any further correlations between patient metabolism and outcome become more apparent.

6.0 Summary, Conclusions and Recommendations

Hyperglycaemia is prevalent in critical care and has a significant impact on patient mortality, outcome and healthcare cost. Tight regulation can significantly reduce these negative outcomes, but achieving it remains clinically elusive, particularly with regard to what constitutes tight control and what protocols are optimal in terms of results and clinical effort. This overview has examined the current state of the art and, perhaps more importantly, the state of the possible in the clinical, model-based control of hyperglycaemia in critical care. The goal of such control would be the eventual automation or semi-automation of this treatment to achieve good outcomes with

minimal extra clinical effort. Hence, with limited published studies it is very much an emerging field rather than a mature area of research.

The review outlines the main components of these type of control systems and outlines the current state of the art in each. In particular, the impact of choices on other control elements is noted where it has been reported in the literature. More importantly, this review attempts to set down the current state of the art, while outlining how emerging technologies and methods may impact these approaches. A simple conclusion is that there is a great deal of research still to be done, and this review perhaps indicates that there are still more unasked questions than those that have been answered in addressing this clinical biomedical control problem.

Hence, a simple set of recommendations for future research areas for this problem, as well as broader metabolic control problems, might readily include:

- Enhanced models of insulin kinetics, particularly with regard to subcutaneous injection delivery and/or different types of insulin, would add robustness to the overall control problem, particularly where large insulin doses are utilised and extend capability to less acute wards and ambulatory individuals.
- Enhanced models of glucose-insulin kinetics in the interstitium would enhance an area where current models may not suffice.
- Better methods of managing measurement error, either via improved sensor design or improved signal processing methods, would allow emerging continuous sensors to be used more confidently.

- Greater understanding of the dynamic physiological variability encountered in critical care and its root causes would enable more robust modeling and control, and some results would extend to broader metabolic control scenarios. In particular, how does insulin sensitivity, a major driving factor in this problem, vary with patient condition and how can this information be used to deliver better control?
- More trials are required to better define the relationships between measurable performance metrics, patient cohort, and clinical outcome, to enable better comparison of results and determine a more optimal, clinically recognised set of guidelines and goals.
- More futuristically, new methods of measuring other variables, such as insulin concentration or their surrogates, which are useful in clinical real-time applications, would enable more robust model identification and tighter control in clinical settings.

All of these broader topics would result in improved understanding, and thus control, of metabolic function in critical care by reducing uncertainty. They would also enable the more comprehensive clinical trials required. However, they would also be critical steps towards moving, per Figure 1, towards less acute wards and managing the ambulatory diabetic individual, where a significant part of the long term future of this research area lies.

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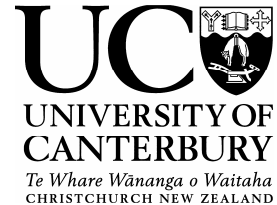
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Re: Submission for Biomedical Signal Processing & Control.

Prof Allen,

15th March 2006

Thank you for your email concerning our manuscript "*Model-based Glycaemic Control in Critical Care – A review of the state of the possible*" by Chase, Shaw, Wong et al et al. Attached is a revised paper based upon your further comments and requests.

We have made the two changes you requested, as follows:

1. We added the page numbers to the conference references, or where it's CDRom only (as is becoming more standard) the number of pages. We also tidied up all others that we found missing a portion and eliminated a handful of weaker unnecessary references that the reviewers overlooked.
2. We added 4 figures. The original figure 2 is still there as figure 4 in the same location. These are:
 - the control loop showing all major effects or areas (fig2, p.8)
 - a physiology diagram showing the fundamental physiology, which we thought would add clarity to the modeling (fig3, p.12)
 - a set of clinical data showing all variables for the model-based control (fig5, p.32) to show the model variables etc over a short 10-hour targeted trial
 - clinical results in glucose only for a long term control result over 164 hours (fig6, p.33) to illustrate the idea of tight control over the long term.

Hopefully, that clarifies the modeling and control aspects, as well as showing what the data might typically look like for the newer reader. The final file is uploaded.

Thanks again for your time and effort in this matter, as well as providing the opportunity to put this article forward. We look forward to your response.

Best Regards,

A handwritten signature in black ink, appearing to read 'J. Geoffrey Chase'. The signature is written in a cursive, flowing style.

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