Derivative Weighted Active Insulin Control Algorithms and Intensive Care Unit Trials

Suggested Running Title (Active Insulin Control Algorithms)

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ABSTRACT

Critically ill patients often experience stress-induced hyperglycemia. This research demonstrates the effectiveness of a simple automated insulin infusion for controlling the rise and duration of blood glucose excursion in critically ill patients. Heavy derivative controllers derived from a simple, two-compartment model reduced blood glucose excursion 79-89% after a glucose input in proof-of-concept clinical trials. Modelled performance is very similar to clinical results, including a strong correlation between modelled and actual insulin consumed, validating the fundamental models and methods. However, the need for additional dynamics in the model employed is clearly illustrated despite capturing the essential dynamics for this problem.

Keywords: Biomedical Control, Physiological Models, PD Controllers, Non-linear Models.

1. INTRODUCTION

Diabetes is a disorder of the metabolism whereby insufficient insulin is produced by the beta cells, and as such, blood glucose cannot be transported out of the blood. Lack of insulin results in blood glucose levels remaining dangerously high, which untreated over time leads to costly complications, including kidney failure, blindness, nerve damage, heart attack and stroke. Over 120 million people are affected by diabetes worldwide, and this number is expected to rise to 300 million by the year 2025 (Thomsen et al., 2001).

Critically ill patients often experience stress-induced hyperglycaemia and high levels of insulin resistance, even if they have no history of diabetes (Capes et al, 2000; Christensen, 2001; Ousman, 2002; Umpierrez et al, 2002; Bloomgarden, 2003; Finney et al, 2003; Van den Berghe et al, 2001, 2003). Hyperglycaemia can lead to an increased risk of further complications such as severe infections, myocardial infarctions (Capes et al, 2000), polyneuropathy, and multiple-organ failure (Van den Berghe et al, 2001). Tight glucose control has been shown to reduce Intensive Care Unit (ICU) patient mortality by as much as 45% (Van den Berghe et al, 2001). Current protocols lack the consistency to ensure tight control of blood glucose levels, while automated algorithms are still in their infancy.

While ICU patients are often sedated and in a highly monitored state, they are extremely diverse in the causes and dynamics of their hyperglycaemia. As a result, their response to a glucose input can vary significantly due to equally extreme variations in insulin levels, effective insulin utilization, glucose absorption and a variety of other factors. Hence, these trials represent a fairly extreme test of the ability

of the models and control systems developed, and highlight the need for simplicity in a clinical environment.

Automated treatment promises better control of blood glucose with higher consistency and an associated reduction in diabetes related complications. Existing insulin pumps and emerging non-invasive and semi-invasive glucose monitoring systems may be easily interconnected to realise a closed loop system. Ultimately, the control unit should be able to automate 90 – 95% of the day-to-day insulin care. Therefore, the goal is to control the essential dynamics rather than all of the dynamics and exceptional behaviours.

Years of research on modelling and managing diabetes have led to no shortage of theoretical automated solutions (e.g. Ollerton, 1989; Kienetz and Yoneyama, 1993; Fisher, 1991; Furler et al, 1985). However, due to either the complexity of the proposed implementation, models that are not physiologically verified, or lack of required data these solutions have not been trialled. Several researchers have examined the analysis and automation of insulin administration as reviewed by Lehman and Deutsch (1996). In each case, the focus has been on controlling absolute blood glucose excursion rather than the shape of the glucose curve, as is done in heavy derivative control (Chase et al, 2002).

Practical solutions that have reached implementation have been applied primarily to ambulatory diabetic individuals and less often to the more difficult, hyperglycaemic critically ill patient who may not be insulin resistant when healthy. Those implemented in the critical care environment have been based on a sliding scale

format to determine the insulin input as a function of blood glucose level alone (e.g. Chee et al, 2002; Van den Berghe et al, 2001, 2003). These approaches merely add consistency in a semi-automated fashion to the selection of insulin infusion level by medical staff. Since glucose level alone is the determining factor the control implemented is essentially pure proportional. To the best of the author's knowledge, no model based automatic control methods have been clinically trialled for critical care.

Prior work in tightly controlling elevated blood glucose levels using heavy derivative control employed a physiologically verified three compartment model based on the work of Bergman et al (1985). Performance was shown to improve with decreased sensor lag and sampling period and the controlled solution outperformed the simulated normal human response at a sample period of 1 minute (Lam et al, 2002). The primary feature of derivative weighted control is the focus on controlling the shape of the blood glucose curve rather than the absolute magnitude of blood glucose. This approach adds robustness because it can more readily account for varying rates of glucose absorption and other patient specific behaviours. The research presented here develops this heavy derivative control approach to a proof-of-concept clinical trial with Intensive Care Unit (ICU) patients. Results are compared to predicted values to verify the modelling methods and overall approach to controlling blood glucose.

2. CLINICAL TRIAL METHOD

The proof-of-concept clinical trials conducted effectively simulate a true feedback control system with a 15-minute sampling period, which works well and represents a realistic level of system performance (Chase et al, 2002, 2003; Lam et al, 2002). They are designed specifically to test the effectiveness of the heavy derivative control methods under variable glucose inputs and to verify the simulations of the essential dynamics and design that led to them.

Qualifying patients had to be stable, have elevated blood glucose levels over 8 mmol/L (average blood glucose in a healthy individual is 4.5 - 5 mmol/L), have an arterial line and a nasogastric feed, and be expected to remain in the ICU for at least three days. In addition, patients with morbid obesity (BMI > 35 kg/m^2) or neuromuscular blockade were not considered. The clinical trials are a two-day procedure for each participant. The first day of the trial measures the uncontrolled glucose regulatory system response and the second day implements active insulin control. The Canterbury Ethics Committee granted ethics approval for these trials.

2.1 Clinical Trial Day One:

The trial begins at 0700 hours at which time the patient is fasted for four hours. Blood glucose readings are taken every hour to determine a basal blood glucose level. At 1100 hours, blood is taken for C-peptide and blood insulin tests to screen for insulin contamination and determine the basal insulin level, respectively. The patient is then given a 75g oral glucose tolerance test (OGTT) glucose dose over one minute via the nasogastric tube. Plasma glucose is measured at 15-minute intervals until 1500 hours. Paired samples are taken, with one analysed using a bedside G*lucocard*^{TM} *Test Strip 2*

glucose testing kit and the other sent to the laboratory for comparison. The error in the absolute readings are approximately 7% for the G*lucocard*^{TM} *Test Strip 2* tests, and 3% for the laboratory tests at typical elevated blood glucose levels (Phillips et al, 1994; Peters et al, 1996).

2.2 Clinical Trial Day Two:

The procedure is repeated as per day one, however short acting soluble insulin with 0.2U/ml in 0.9% saline is infused via an intravenous cannula using a Graseby 3500 syringe pump. Plasma glucose is measured at 15-minute intervals as previously and the insulin infusion rate is manually adjusted every 15 minutes according to the heavy derivative control algorithm. This approach is designed to specifically test the algorithm. Hence, only glucose measurements were made to simulate a practical implementation and eliminate the impact of any specific equipment.

3. MATHEMATICAL MODELLING

Implementing tight glucose control in critically ill patients via a fully automated insulin infusion system requires a simple model of the glucose regulatory system that accounts for the relationship between intravenous infusion of exogenous insulin and the measured blood glucose level. The initial physiologically verified model employed originated from the work of Bergman et al. (1985), utilizing the concept of a remote compartment for the transport of insulin between the subcutaneous infusion site and its utilization to reduce blood glucose levels.

Intensive care unit (ICU) patients have direct arterial/venous lines that bypass the subcutaneous compartment in the three compartment model, and require only two

compartments. The first compartment models insulin uptake into the blood, and the second models blood glucose level and insulin mediated transport of glucose from the blood. The model is shown schematically in Figure 1 and defined:

$$\dot{G} = -p_G G - S_I I(G + G_B) + P(t) \qquad (1)$$

$$\dot{I} = -n(I + I_B) + u(t)/V_I \qquad (2)$$

where G (mmol/L) is the concentration of the plasma glucose above basal level, G_B (mmol/L). I (mU/L) is the concentration of the plasma insulin above basal level, I_B (mU/L). $u(t)$ (mU/min) is the exogenous insulin infusion rate, $P(t)$ (mmol/L/min) is the exogenous glucose input, V_I (L) is the volume of distribution, and n (min^{-1}) is the rate constant associated with the interstitial transfer of insulin to be utilised. p_G (min^{-1}) and S_I (L/mU/min) are patient specific parameters, where p_G is the fractional clearance of plasma glucose at basal insulin, and S_I is insulin sensitivity as described by Bergman et al (1985). The model is therefore patient specific and is adapted to each person before a controller is developed.

Figure 1 shows the fundamental physiological inputs to Equation (1), specifically insulin and glucose. The insulin inputs on the left side are broken into endogenous, or basal, insulin production, I_B, and exogenous insulin input, $u(t)$, with their compartment dynamics defined by Equation (2) resulting in the insulin input, $I(t)$. The glucose inputs in the bottom of the figure are similarly categorised as endogenous, basal production from the liver, G_B, and exogenous input, $P(t)$, with no additional compartment dynamics. Equation (1) is the pharmaco-dynamic equation for the utilisation of insulin and removal of glucose in the blood plasma and at interstitial

sites in this simplified model, and its output is the net change of blood glucose from basal levels, *G(t)*.

Additional model dynamics linking the two compartments in Equations (1) and (2) may be needed, however any missing dynamics would influence S_I and the insulin utilisation term with little effect on the ability to derive an appropriate controller that acts on blood glucose rise. More specifically, the upward rise of glucose concentration over the first 45-60 minutes does not depend heavily on this term, and it is this rise that the heavy derivative control focuses on limiting.

Hence, a second aspect of this research is to determine from the clinical results whether this simple control model lacks the complexity to sufficiently capture the essential dynamics required for model-based blood glucose control. Given the difficulty of modelling the dynamics of hyperglycaemic critical care patients due to their lack of diabetes history, high glucose intolerance and hyper-insulinemia, the simplest realistic model was used with the goal of adding critical dynamics as they became apparent from clinical results.

Controller parameter determination is therefore accomplished in three steps. First, data is gathered from an uncontrolled oral glucose tolerance test (OGTT). Second, the patient specific parameters, p_G and S_I, are obtained using unconstrained optimisation designed to minimise the difference between modelled and test behaviour. Finally, given a model that fits the error bounds of the uncontrolled patient data, particularly the initial rise, proportional-derivative (PD) control gains, K_p and K_d, are developed using a second unconstrained optimisation to find derivative weighted gains that

minimise the magnitude and duration of blood glucose excursion from the patient's basal level for the same OGTT input.

3.1 Parameter Determination

The total amount of glucose infused simulating an OGTT is 412 mmol, a value obtained by converting 75g of glucose and assuming the patient has the glucose evenly distributed in a V_I = 12L fluid volume with rate constant n = 0.16 (Furler et al, 1985; Bergman et al, 1985). To account for the different rates of uptake, the peak of the simulated exogenous glucose infusion profile, *P(t)*, is set at approximately 80% of the time required for the patient's uncontrolled OGTT peak glucose reading, and modelled as a continuous lognormal function. Hence, the simulated and actual uptake rates for uncontrolled OGTT will be similar and the total glucose input will be identical.

A continuous function is fitted to the patient's uncontrolled, day one, OGTT data using a log-normal function, which captures the fundamental dynamics of such data well (Lam et al, 2002). This function is used to derive a function, $G_{patient}$, which can be discretised for optimisation into a series of time points, $\overline{G}_{patient}$, to enhance the number of points available for data fitting, where $\overline{G}_{patient}$ includes the actual data points taken at the proper times. This approach effectively augments the data taken and smoothes out some of the noise. Similarly, the same data points can be obtained from a simulation of Equations (1) and (2), a set labelled $\overline{G}_m$, to enable a comparison between model and data in the optimisation routine. Unconstrained optimisation using Matlab is then used to determine S_I and p_G so that the square error defined below is minimised.

$$R = (\overline{G}_{patient} - \overline{G}_m)^T (\overline{G}_{patient} - \overline{G}_m) + e^{-p_G C} + e^{-S_I C} \quad (3)$$

where C is a large positive constant (e.g. 1000 for this model), defined to ensure that p_G and S_I remain positive. These exponential terms add the constraints $p_G > 0$ and $S_I > 0$, creating an unconstrained optimisation problem, since meeting these terms are zero when the constraints are satisfied, and lead to a very large penalty otherwise.

By changing the discretisation of $G_{patient}$, certain points in the model solution and the continuous function $G_{patient}$ can be constrained to match more accurately. Typically, several extra time points around the peak of the glucose response curve are added to ensure the rise and inflection of the glucose curve are adequately captured. It is this rise and inflection that are critical for effective control of the blood glucose rise, as it is this portion of the curve that instigates the vast majority of the controlled insulin infusion input.

3.2 Control Design

The controller determines the amount of exogenous insulin, *u(t)*, infused. The model is set to run with a 15 minute sampling interval to match the clinical trial program. A heavy derivative proportional-derivative (PD) controller is employed:

$$u(t) = \max\left[0, U_0 (1 + K_p (G + G_{prime}) + K_d \dot{G})\right] \quad (4)$$

where U_0 (mU/min) is the basal insulin infusion rate typically equivalent to approximately 1U/hr, K_p is the proportional gain and K_d the much larger derivative

gain (Lam et al, 2002). More specifically, the proportional gain is typically 20-50x smaller than the derivative gain so it dominates the control input during the rise and fall of blood glucose. Finally, G_{prime} (mmol/L) is an offset term to the proportional control input, so a high basal glucose level, G_B, can be controlled to a lower target blood glucose level, G_t, by increasing G_{prime}, the difference between the target blood glucose level (G_t) and the actual, elevated basal blood glucose level (G_B).

$$G_{prime} = G_B - G_t \qquad (5)$$

When G_{prime} is more positive, the proportional feedback term is greater. The 'max' function, with argument "0", in Equation (4) ensures that negative insulin demands, encountered as blood glucose falls, are treated as a zero input.

It is important to note that the PD controller defined in Equations (4) and (5) is non-linear. More specifically, it only provides insulin for positive control inputs and does nothing when "negative insulin" is commanded. Per the work in Lam et al (2002), the use of derivative focused PD control in this way helps predict glucose surges, such as after a meal or OGTT input, and therefore provide the proper insulin, which in this case is much like a bolus injection. Similarly, when the glucose is falling the derivative is negative and no insulin is therefore commanded, which would destabilise this system by adding insulin to already falling blood glucose levels and resulting in hypoglycaemia. Therefore, this non-linear PD controller effectively avoids destabilising inputs with a derivative focused PD controller for this process, even though a small lag may occur between intravenous insulin infusion and its utilisation to reduce blood glucose.

The control gains are determined by minimising the objective function (R) defined:

$$R = C_1\left[G(\tilde{t}) - G_t\right]^T\left[G(\tilde{t}) - G_t\right] + C_2\dot{G}(\tilde{t})^T\dot{G}(\tilde{t}) + e^{-K_d C} + e^{-K_p C} \quad (6)$$

where C_1, C_2 and C are positive constants that weight each of their respective terms. The $G(\tilde{t})$ terms are the measured glucose data and in Equation (6) are used to minimise the area between the blood glucose levels from the measured data and the target blood glucose levels, G_t. Similarly, the $\dot{G}(\tilde{t})$ terms in the objective function minimise the slope of the output glucose levels, reducing oscillation in the blood glucose response curve, a problem that can occur if the gains are too large. The exponential terms in the objective function ensure that K_d and K_p remain positive, using the same approach as in Equation (3). The control gains are patient specific, however typical ranges for K_d and K_p found in this study are (0.1-3) and (10-40) respectively with a typical ratio of approximately 25 of K_d to K_p. Overall, optimisation is employed not to find a best solution but to efficiently search a large domain of possible control gains.

Where a proportional controller only infuses significant insulin at elevated blood glucose levels, heavy derivative control predicts the approaching high blood glucose level from the steep gradient and infuses insulin pre-emptively, thus enabling a faster response to increasing blood glucose levels. This approach is similar to a healthy response to increasing blood glucose levels, where gastrointestinal hormones stimulate an anticipatory increase in insulin concentration in preparation for glucose

and amino acids to be absorbed from a meal creating an initial insulin spike (Guyton and Hall, 1996).

Simulation by Lam et al (2002) have shown that the heavy-derivative control method results in an infusion profile similar to a bolus with a background infusion as commonly done by diabetics. This bolus with a background infusion also mimics the post-prandial first and second phase insulin release exhibited by healthy individuals (Del Prato et al, 2002). An infusion that is proportional to blood glucose level alone will infuse insulin when blood glucose is still above the desired level but dropping rapidly, leading to an increased risk of hypoglycaemia (Lam et al, 2002). Pure proportional control will also not mimic the initial sharp, bolus-like, first-phase insulin release that occurs in normal individuals following a glucose input or challenge, as proportional control is strictly a function of the slower rising glucose level that initially starts at the basal level.

4. CLINICAL RESULTS AND DISCUSSION

Table 1 gives the patient age, condition, insulin levels, G_B, peak glucose levels, and patient specific parameters, p_G and S_I, from day one of the trial. The four patients display a diverse range of glucose responses to the OGTT from relatively flat to extremely volatile. The insulin sensitivity values, S_I, are of the same order or higher than existing data for sub-cutaneous delivery (Bergman et al, 1981; Avogaro et al, 1989). However, sub-cutaneous infusions can be subject to up to 20% losses in transportation (Kraegen and Chisholm, 1984). These losses are typically accounted for by a reduced value for S_I, and for intra-venous infusion, the higher values might be expected.

Patient 1 was a 67 year old female subject in the ICU for three days suffering from kidney failure. The kidneys can remove up to 30% of effective insulin, so kidney failure is an “insulin sparing” condition that can lead to a flatter glucose response (Charpentier et al, 2000). The patient was both hyperglycaemic and somewhat hyper-insulinemic as well as indicated by a basal insulin level of 70 pmol/L.

Figure 2 shows the measured and model predicted glucose response for day one (uncontrolled) and day two (controlled). The measured data is presented with the 7% error associated with *GlucoCard*™ 2 (Arkray Inc, 2001) measurements. The magnitude and duration of blood glucose excursion from the basal level are reduced over 50%. The target sub-basal glucose level of 5.5 mmol/L was not fully reached, as the relatively low proportional control is not effective as the tail of the glucose response curve flattens off. This result is an example of the need for gain scheduling or a modified control approach in this flatter response regime. Note also that the uncontrolled response is relatively flat for an OGTT, which is a result of the patient's relative hyper-insulinaemia.

Overall, the automated algorithm provided rapid, effective control of the OGTT input and the simulated controlled response was an extremely good match for the measured data, as seen in Figure 2. The difference in day one and day two basal levels is due to changes in feeding and insulin administration over the night between the OGTTs. Finally, the patient’s blood glucose concentration began to increase steadily back to 10 mmol/L after the controlled day two test when hospital staff returned to their

sliding scale protocol, showing the need for, and effectiveness of, automated methods for tight glucose regulation.

Patient 2 was a 48 year old male tetraplegic with Acute Respiratory Distress Syndrome (ARDS). This patient's history exhibited an extremely variable response to most medications and this experience was reiterated during the trial. As shown in Figure 3, the patient's glucose absorption was much faster on day two, due to delayed gastric emptying on day one. The response on day two also shows the possible effect of an unmodelled insulin accumulation dynamic at 200 minutes. The faster day two gastric emptying and insulin accumulation dynamic were manually modelled with the result shown by the dashed line in Figure 3. The day two simulations also include the sensor error shown in Figure 3. Local hospital protocol generally sets the maximum insulin infusion rate at 6U/hr, however, due to the high glucose levels and large derivative, $\dot{G}$ following the OGTT dose, the control algorithm commanded up to 37U/hr for a given 15 minute period. A constant infusion rate of approximately 6U/hr was required to maintain the final steady state blood glucose level, and along with the relatively low S_I in Table 1, indicates this patient's high insulin resistance. The result is an insulin profile that looks very similar to an insulin injection combined with a steady background infusion, matching current treatment protocols (Lam et al, 2002; Pickup and Keen, 2002).

Patient 3 was a 75 year old male with a head injury. Uncontrolled data from day one, in Figure 4 shows the patient behaves essentially as a Type 1 diabetic, although not previously diagnosed. Insulin level tests confirmed this assumption with a very low insulin level of 3 pmol/L. The controlled glucose response simulation does not

capture the unmodelled dip in the glucose profile at 180 minutes, or the initial stronger glucose rise, further illustrating how the simple insulin utilisation dynamics in Equation (1) are not necessarily fully adequate. These results indicate that some insulin appears to accumulate, or take a slower path, in a remote compartment before utilization, as shown by the dashed line in Figure 4 generated using an approximation of this dynamic in the model. This slower acting insulin accumulation has been recently proposed by other researchers (Hovorka et al, 1998; Cobelli et al, 1998).

Patient 4 was a 59 year old female with sepsis and infection. Day one of the trial gave an almost flat glucose response curve, implying the patient was both hyperglycaemic and (potentially) hyper-insulinaemic. However, the insulin level test was potentially infected as shown by the high insulin laboratory test measurement in Table 1. With the lack of a significant increase in glucose levels from basal and resulting low derivative values, the insulin infusion was effectively constant on day two. The sub-basal target glucose level (G_t = 5.4 mmol/L) was chosen 1 mmol/L below the patient's day two basal level of G_B = 6.4 mmol/L and the control algorithm proved efficient at obtaining this slightly reduced level. Figure 5 also shows an initial dip in the measured data and simulation output on both controlled and uncontrolled data that may be attributed to an unmodelled delay in glucose uptake.

A comparison between the predicted and actual insulin dose for all four patients is shown in Table 2. The total insulin infused over four hours differed from the predicted insulin infusion total by no more than 10.4% with an average error of approximately 3% over the four trials. This strong correlation helps validate the fundamental models and methods employed, despite potential missing dynamics that

must be added. Where the model tends to under predict insulin consumption, it can be attributed to one of at least three factors. First, the discrete 0.2 U/mL insulin infusion levels are not the analogue values available in the model. Second is that for large doses, such as with patient 2, some insulin may be "lost" along the length of the infuser tubing or in physiological saturation dynamics that are not modelled. Third, the patient specific parameters, p_G and S_I, may change over the trial period due to drug interactions or natural fluctuations.

To determine control effectiveness, blood glucose excursion is quantified as the sum of the area under the measured blood glucose curve above the basal glucose level, as illustrated in Figure 6, where A_1 and A_2 denote the blood glucose excursion on day one and two, respectively. The ratio between the controlled, A_2, and uncontrolled areas, A_1, quantifies the effectiveness of the controller. The reduction in basal glucose level from the beginning, G_B, to the end of day two, $G_{B(final)}$, measures the improvement obtained as the controller aims for the lower target basal glucose level. Figure 6 illustrates both performance metrics. For the first four patients the excursion from basal blood glucose level is reduced 79 - 89%, and the basal glucose level is reduced 12 - 41% with specific values given in Table 3.

The unmodelled accumulator dynamic noted in most of the clinical results has four potential causes. The first possible cause is the physiological battle between the body's desire to return to the (elevated) basal level and the controller's attempts to hold it down, as best seen in Figure 2. The second possibility is that the demand for insulin in the blood is secondary to those of the brain and liver, such that meeting these demands first causes a reduction in useful insulin in the blood and a later over

reaction. Third, saturation in transport or utilisation could also lead to a delayed response as seen in these trials. Lastly, it is believed that insulo-penic, or very low insulin level, patients can develop lipo-toxicity, suppressing insulin release from any active beta cells. Therefore, when exogenous insulin is infused these beta cells are free to release endogenous insulin not initially accounted for (Del Prato et al, 2002). Further tests will help clarify the specific causes of this dynamic, and improve the models and clinical trial methods employed.

A second limitation of the proof of concept trials performed that should be noted is the lack of intermittent plasma insulin samples. This data would have aided any model verification, despite using a well-established model. It should be noted that the primary goal was to test the control algorithm, which used only glucose measurements as inputs to the controller, and that plasma insulin levels are not typically able to be determined as rapidly as glucose samples in a clinical environment. The latter aspect points to the potential for estimation of plasma insulin levels as a possible avenue to achieve better control.

Finally, the use of an OGTT to obtain patient specific parameters adds significant time and complexity, especially for a practical implementation. While the OGTT does provide a useful set of data on the patient specific glucose-insulin response a similar result can be seen with an insulin challenge using a fixed insulin bolus in the range of 1.5-2U. The OGTT and the insulin challenge provide similar data about the hyperglycaemic patient specific metabolic system response that can be used to fit the endogenous glucose removal and insulin sensitivity parameters p_G and S_I. Another approach would be to use a default set of parameters based on data from the literature

and then adapt these values as the trial progressed to obtain better accuracy between predicted and actual results from insulin and/or glucose inputs.

5. CONCLUSIONS

The research has succeeded in demonstrating tight feedback controlled blood glucose level regulation in response to a glucose input in critically ill patients using a heavy-derivative controller. The first four trials show a good level of correlation between the simple model and patient data, verifying the basic models and methods employed. In particular, the model's ability to capture the insulin dose to within 10% of actual values validates the fundamental assumptions made. More specifically, heavy derivative control has been demonstrated to be effective in practice and to match the essential dynamics encountered reasonably well, resulting in reductions in glucose excursion of up to 89% and basal glucose reductions of up to 41%. However, the results have also clearly demonstrated the need for additional dynamics in the system model. Hence, the simple glucose-insulin system model employed captures the fundamental dynamics well for these relatively short tests, but is likely too simple for long-term effectiveness over several hours or days. Finally, it has been shown that glucose challenges can be managed effectively and basal values reduced for the difficult hyperglycaemic critical care patient using this very simple feedback control method.

Additionally, two simple measures for capturing the effectiveness of automated glucose regulation are introduced. The comparison of blood glucose excursion area, for a given input, is seen to capture the essential details of the magnitude and duration

of the blood glucose excursion from the patient's basal level. Secondly, many ICU patients have elevated basal blood glucose levels so that comparing the final basal value that the controller achieves is a simple measure of the controller's ability. Future developments include model development, parameter estimate improvements including the use of insulin challenges instead of the OGTT, and enhancement of the control systems employed with an emphasis on adaptive control methods.

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7. REFERENCES

Arkray Inc. (2001). Glucocard™ Test Strip 2 Data Sheet. Supplied by Arkray, Inc. Japan

Avogaro, A., Bristow, J.D., Bier, D.M., Cobelli, C., & Toffolo, G. (1989). Stable-label intravenous glucose tolerance test minimal model *Diabetes 38*, 1048-1055.

Bergman, R.N., Phillips, L.S., & Cobelli, C. (1981). Physiologic evaluation of factors controlling glucose tolerance in man: measurement of insulin sensitivity and beta-

cell glucose sensitivity from the response to intravenous glucose. *J Clin Invest 68*, 1456-1467.

Bergman, R.N., Finegood, D.T., & Ader, M. (1985). Assessment of Insulin Sensitivity in Vivo. *Endocrine Reviews 6*(1), 45-86.

Bloomgarden, Z.T. (2003). Inflammation and insulin resistance *Diabetes Care 26,* 1922-1926.

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

Charpentier, G., Riveline, J.P., & Varroud-Vial, M. (2000). Management of Drugs Affecting Blood Glucose in Diabetic Patients with Renal Failure. *Diabetes Metab 26*(4), 73-85.

Chase, J.G., Lam, Z.H., Lee, J.Y., & Hwang, K.S. (2002). Active Insulin Infusion Control of the Blood Glucose Derivative. *Proc. Intl Conf on Automation, Robotics, Control and Computer Vision (ICARCV 2002)*, Singapore, Dec 3-5.

Chase, J.G., Shaw, G.M., Doran, C.V., Hudson, N.H., & Moorhead, K.T.(2003) Derivative Weighted Active Insulin Control Algorithms and Trials. *5th IFAC Symposium on Modelling and Control in Biomedical Systems,* Melbourne, Australia, Aug 21-23

Chee, F., Fernando, T., & van Heerden, P. V. (2002). Closed-loop control of blood glucose levels in critically ill patients. *Anaesth Intensive Care 30*(3), 295-307.

Cobelli, C., Bettini, F., Caumo, A., & Quon, M.J. (1998). Overestimation of minimal model glucose effectiveness in presence of insulin response is due to undermodeling. *Am J Physiol 275,* E1031-1036.

Christensen, D. (2001). Critical Care: Sugar Limit Saves Lives. *ScienceNews,* 159

Del Prato, S., Marchetti, P., & Bonadonna, R.C. (2002). Phasic Insulin Release and Metabolic Regulation in Type 2 Diabetics. *Diabetes 51*(S1), S109-116.

Finney, S.J., Zekveld, C., Elia, A., & Evans, T.W. (2003). Glucose control and mortality in critically ill patients *Journal of the American Medical Association (JAMA), 290*, 2041-2047.

Fisher, M.E., (1991). A Semiclosed-Loop Algorithm for the Control of Blood Glucose Levels in Diabetics. *IEEE Transactions on Biomedical Engineering 38*(1), 57-61.

Furler, S.M., Kraegen, E.W., Smallwood, R.H., & Chisholm, D.J. (1985). Blood Glucose Control by Intermittent Loop Closure in the Basal Mode: computer Simulation Studies with a Diabetic Model. *Diabetes Care 8*(6), 553-561.

Guyton, A.C., & Hall, J.E., (1996). Insulin, Glucagon, and Diabetes Mellitus, Textbook of Medical Physiology, *WB Saunders Company*, 9th ed. 971-983.

Hovorka, R., Chassin, L., Luzio, S.D., Playle, R., & Owens, D.R. (1998). Pancreatic beta-cell responsiveness during meal tolerance test: model assessment in normal subjects and subjects with newly diagnosed noninsulin-dependent diabetes mellitus. *J Clin Endocrinol Metab 83*, 744-750.

Kienitz, K. & Yoneyama, T. (1993). Robust controller for insulin pumps based on H-infinity theory. *IEEE Transactions On Biomedical Engineering 40*(11) 1133-1137.

Kraegen, E.W., & Chisholm, D.J. (1984). Insulin responses to varying profiles of subcutaneous insulin infusion: kinetic modelling studies. *Diabetologia 26,* 208-213.

Lam, Z.H., Lee, J.Y., Hwang, K.S., Chase, J.G., & Wake, G.C. (2002). Active Insulin Infusion Using Optimal and Derivative-Weighted Control. *J. Medical Engineering and Physics 24*(10), 663-672.

Lehman, E. & Deutsch, T. (1996). Computer assisted diabetes care: a 6-year retrospective. *Computer Methods and Programs in Biomedicine 50*, 209-230.

Ollerton, R. (1989). Application of optimal control theory to diabetes mellitus. *Intl. Journal of Control 50*(6), 2503-2522.

Ousman, Y. (2002). Hyperglycemia in the Hospitalized Patient. *Clinical Diabetes 20,* 147-148.

Peters, A.L., Davidson, M.B., Schriger, D.L., & Hasselblad, V. (1996). A Clinical Approach for the Diagnosis of Diabetes Mellitus. *Journal of the American Medical Association (JAMA), 276*(15), 1246-1252.

Phillips, D.I.W., Clark, P.M., Hales, C.N. & Osmond, C. (1994). Understanding Oral Glucose Tolerance: Comparison of Glucose or Insulin Measurements During the Oral Glucose Tolerance Test with Specific Measurements of Insulin Resistance and Insulin Secretion. *Diabetic Med 11*, 286-292.

Pickup, J., & Keen, H., (2002). Continuous subcutaneous insulin infusion at 25 years: evidence base for the expanding use of insulin pump therapy in type 1 diabetes. *Diabetes Care 25*, 593-598.

Thomson, S., Beaven, D., Jamieson, M., Snively, S., Howl, A., & Christophersen, A. (2001). Type 2 Diabetes: Managing for Better Health Outcomes. *Price-WaterHouse-Coopers Report*, Diabetes New Zealand Inc.

Umpierrez, G.E., Isaacs, S.D., Bazargan, N., You, X., Thaler, L.M., & Kitabchi, A.E. (2002). Hyperglycemia: an independent marker of in-hospital mortality in patients with undiagnosed diabetes. *J Clin Endocrinol Metab 87,* 978-982.

Van den Berghe, G., Wouters, P., Weekers, F., Verwaest, C., Bruyninckx, F., Schietz, M., Vlasselaers, D., Ferdinance, P., Lauwers, P., & Bouillon, R. (2001). Intensive insulin therapy in critically ill patients. *New England J. of Med 345*(19) 1359-1367.

Van den Berghe, G., Wouters, PJ., Bouillon, R., Weekers, F., Verwaest, C., Schetz, M., Vlasselaers, D., Ferdinande, P., & Lauwers, P. (2003). Outcome benefit of

intensive insulin therapy in the critically ill: Insulin dose versus glycemic control. *Crit Care Med 31*, 359-366.

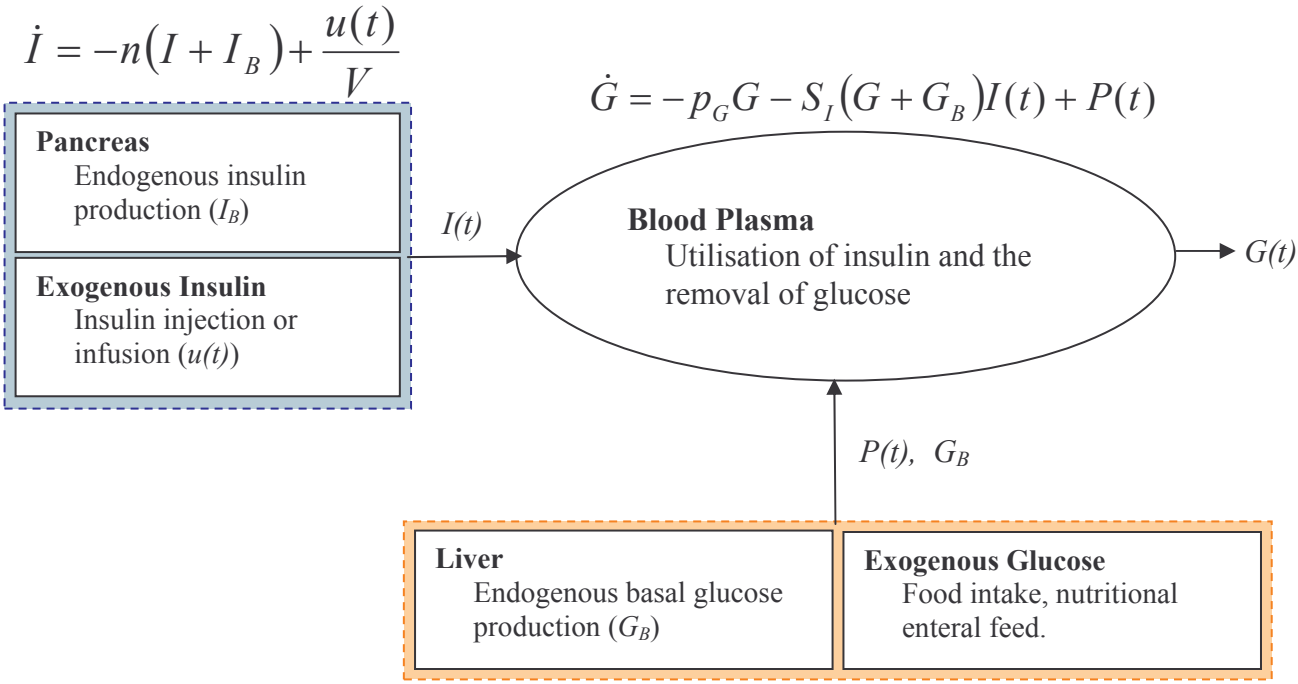

Figure 1: Two compartment glucose-insulin system model with *I(t)* and *P(t)* inputs to blood plasma with measured blood glucose change output, *G(t)*. Each input to the plasma is broken into exogenous and endogenous sources.

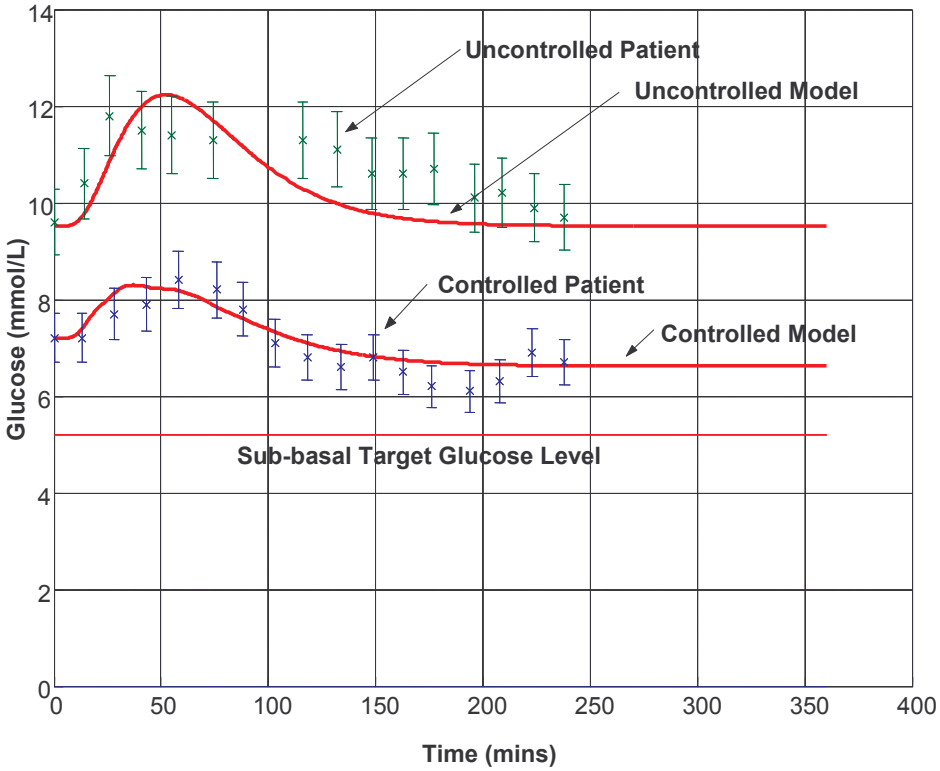

Figure 2: Patient 1 Model vs Measured Glucose – Controlled & Uncontrolled 75g OGTT

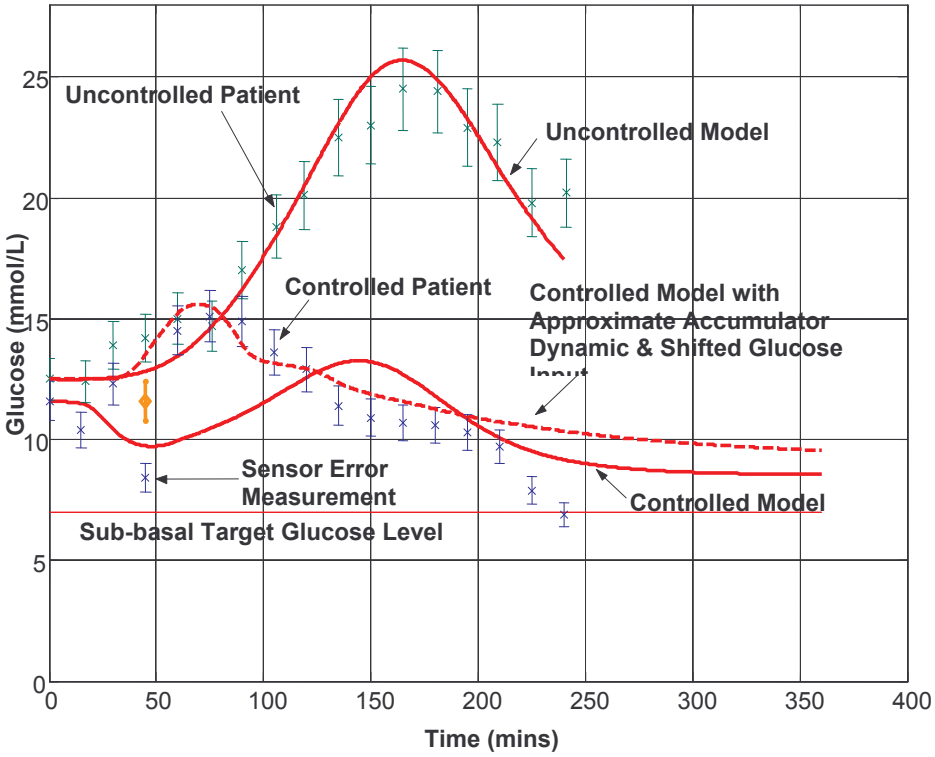

Figure 3: Patient 2 Model vs Measured Glucose – Controlled & Uncontrolled 75g OGTT

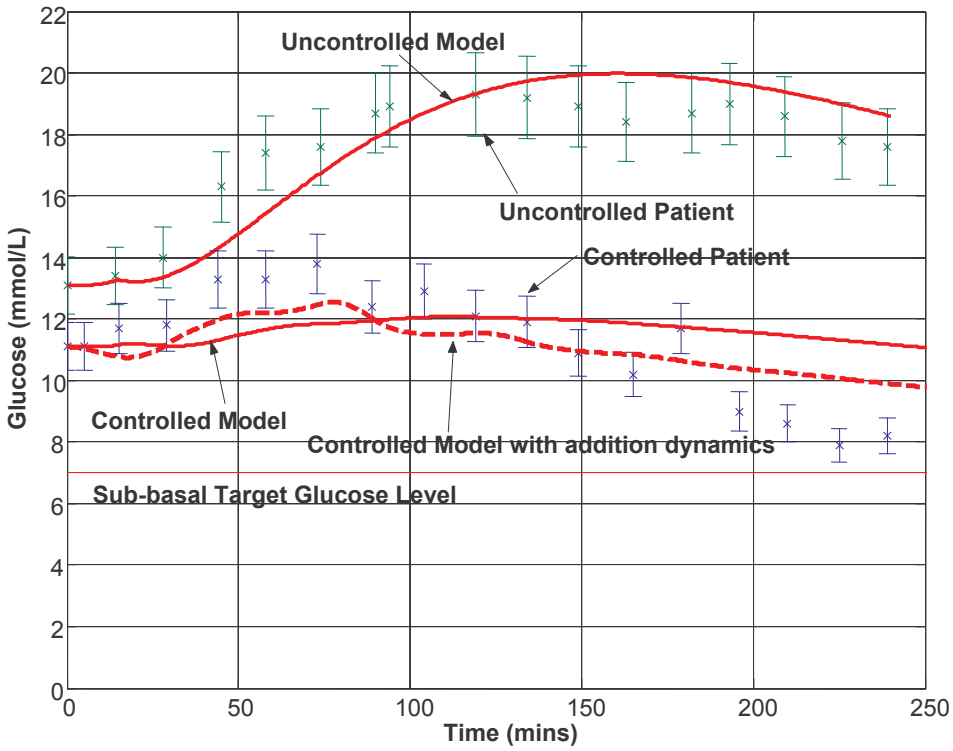

Figure 4: Patient 3 Model vs Measured Glucose – Controlled & Uncontrolled 75g OGTT

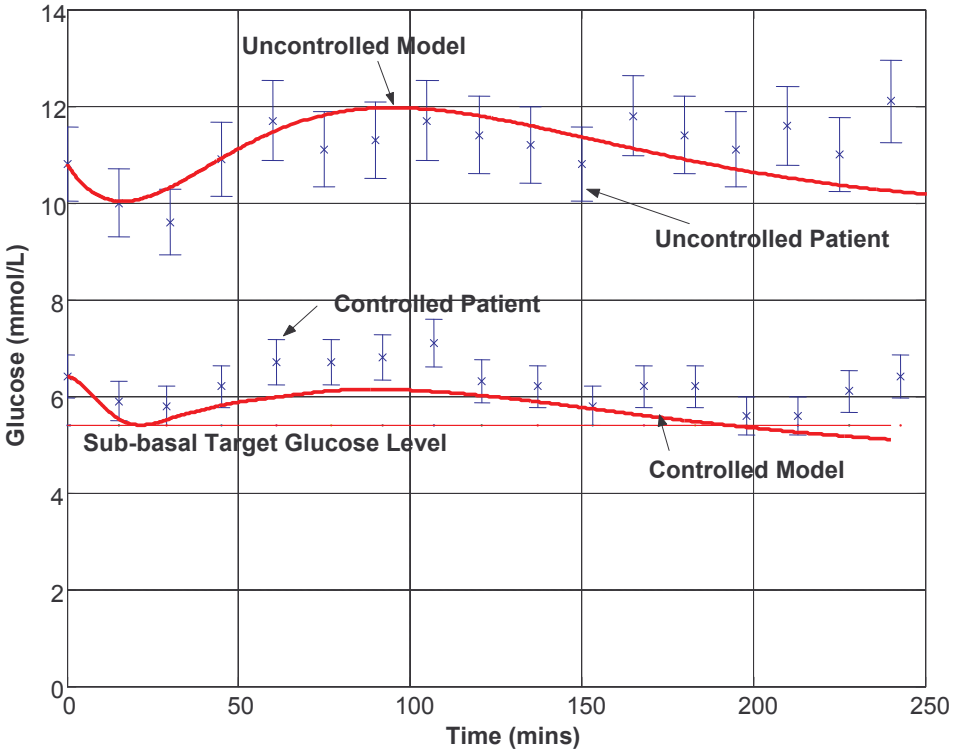

Figure 5: Patient 4 Model vs Measured Glucose – Controlled & Uncontrolled 75g OGTT

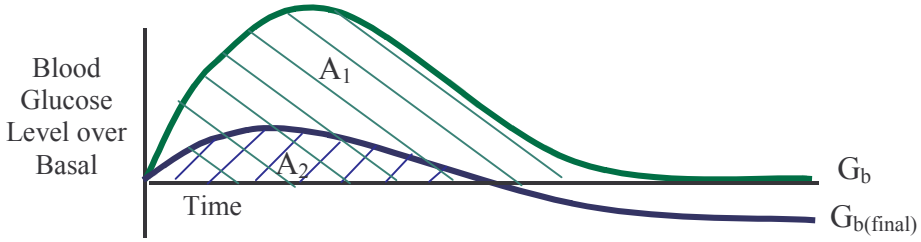

Figure 6: Calculation of Excursion from Basal Glucose Level where A_1 and A_2 represents the areas under the Glucose Curve on Day 1 and Day 2, respectively

Table 1: Patient Summary and Day One Results

Patient	Age	Condition	Basal Glucose, G_B (mmol/L)	Peak Glucose (mmol/L)	Insulin Level (pmol/L)	Patient Specific Parameters		Diabetic Type
						p_G (min^{-1})	S_I (L/mU/min)	
1	67	Kidney Failure	9.5	11.5	70	0.1549	0.0317	Hyperglycaemic, and hyperinsulinemic
2	48	ARDS, Tetraplegic	12.5	24.5	59	0.0187	1.1×10^{-4}	Type 2
3	75	Head Injury	13.8	22.1	3	0.0074	0.0036	~Type 1
4	59	Sepsis	10.8	11.8	295 (infected sample)	0.1	0.0025	Hyperglycaemic, and hyperinsulinemic

Table 2: Comparison between predicted insulin and trial insulin infused

Patient	Model predicted total insulin (U)	Day two clinical trial total insulin (U)	Percentage difference between predicted and infused (%)
1	4.50	4.43	- 1.6
2	38.24	42.65	10.4
3	4.90	4.50	-8.9
4	8.90	8.07	-10.0

Table 3: Comparison of Glucose Excursion for Controlled vs Uncontrolled Data

Patient	Day one – OGTT		Day two – Clinical Trial				A_2/A_1
	G_B (mMol/L)	A_1	G_B (mMol/L)	A_2	$G_{B(final)}$ (mMol/L)	$G_{B(final)}/G_B$	
1	9.6	292	7.2	60	6.1	0.85	0.21
2	12.5	1524	11.6	172	6.9	0.59	0.11
3	13.1	1082	11.1	196	7.9	0.71	0.18
4	10.8	170	6.4	23	5.6	0.88	0.14