COMPARISON OF ADAPTIVE AND SLIDING-SCALE GLYCAEMIC CONTROL IN CRITICAL CARE AND THE IMPACT OF NUTRITIONAL INPUTS

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Abstract: Stress-induced hyperglycaemia is prevalent in critical care. Tight glucose control can reduce mortality up to 43%. An adaptive control algorithm utilising insulin and nutritional feed inputs for targeted glycaemic control in critically ill patients is presented. Validation is performed using retrospective patient data (*n*=19) in simulated glucoregulatory trials. Conventional sliding-scale and insulin-only methods are compared. Results show a reduction in mean glucose levels, and variability. A 312% increase in time spent in the 4-6mmol/L normal glucose band compared to sliding-scale and a 240% increase compared to the insulin-only protocol is reported. Results are obtained using 60% more insulin and 20% more nutrition across a wide cross-section of ICU patients and patient condition, indicating that the timing of control input administration is more crucial than their absolute amounts. The results show potential in reducing ICU mortality and the risk of severe complications.

Introduction

Critically ill patients often experience stress-induced hyperglycaemia, even with no prior diabetes [1, 2]. Hyperglycaemia worsens outcomes, increasing risk of severe infection, myocardial infarction, neuropathy, and multiple organ failure [1]. Tight glucose control can reduce mortality by up to 45% [1, 2].

Insulin-mediated glycaemic control, however, is severely challenged in critical care where effective insulin resistance is usually elevated [3, 4]. In addition, insulin effect saturates at high concentrations [5], limiting the achievable glycaemic reduction. Studies also indicate that high glucose nutritional regimes often result in excess glucose [6], which exacerbates hyperglycaemia. Research with lower glucose nutrition alone in critical care has seen significant reductions in glucose levels [7]. This research incorporates exogenous nutritional input modulation into the insulin-based adaptive control algorithm developed in [8].

Materials and Methods

Chase et al. [8] used an extended system model that captured rate of insulin utilisation, insulin losses and saturation dynamics, and is also used in this study:

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

$$\dot{Q} = -kQ + kI \quad (2)$$

$$\dot{I} = -\frac{nI}{1+\alpha_I I} + \frac{u_{ex}(t)}{V} \quad (3)$$

$$P(t_i < t < t_{i+1}) = \overline{P}_{i+1} + (\overline{P}_i - \overline{P}_{i+1})e^{-k_{pd}(t-t_i)} \text{ where } \overline{P}_{i+1} < \overline{P}_i \quad (4)$$

$$P(t_i < t < t_{i+1}) = \overline{P}_{i+1} + (\overline{P}_i - \overline{P}_{i+1})e^{-k_{pr}(t-t_i)} \text{ where } \overline{P}_{i+1} > \overline{P}_i \quad (5)$$

where $G(t)$ [mmol/L] is the plasma glucose above an equilibrium level, G_E [mmol/L]. $I(t)$ [mmol/L] is plasma insulin concentration resulting from exogenous insulin input, $u_{ex}(t)$ [mU/min]. $Q(t)$ [mU/L] is interstitial insulin concentration and k [1/min] accounts for the effective life of insulin in the system. Patient endogenous glucose clearance and insulin sensitivity are p_G [1/min] and S_I [L/(mU.min)], respectively. V [L] is the insulin distribution volume and n [1/min] is the constant first order decay rate for insulin from plasma. Total plasma glucose input is denoted $P(t)$ [mmol/(L.min)]. k_{pr} is the rise rate of rate of plasma glucose input from enterally administered feed [1/min]. k_{pd} is the decay rate of rate of glucose input into plasma from enterally administered feed [1/min]. $\overline{P}_i$, $\overline{P}_{i+1}$ are stepwise consecutive enteral glucose feed rates [mmol/L.min]. Michaelis-Menten functions are used to model saturation, with α_I [L/mU] used for the saturation of plasma insulin disappearance, and α_G [L/mU] for the saturation of insulin-dependent glucose clearance. In this research, k, n, α_G, α_I and V are a priori identified from generic population values [8].

In this study, non-steady stepwise enteral glucose fluxes are employed for control and modelled using the 2-compartment model in Eqs. (4-5). The exponential rates for total glucose rate of appearance (GRa) rise (k_{pr}) and decay (k_{pd}) can model, simply, the effect of transient net hepatic glucose output and glucose disposal. Impaired splanchnic and peripheral glucose uptake in diabetes and stress-induced hyperglycaemia imply a slow decay rate in total GRa following nutritional feed reduction [9, 10]. Conversely, the rate of peripheral appearance of oral glucose is approximately equal to the intestinal absorption rate, which implies a rapid rise in total GRa following a nutritional feed increase [11].

Thus, k_{pr} and k_{pd} are set to 0.0347min^{-1} and 0.0068min^{-1} corresponding to half-lives of 20 and 100mins to reflect this published data.

The controller targets a 10-15% hourly reduction in glucose level to a limit of 5mmol/L. It is achieved with a combination of insulin bolus, infusion and/or feed rate change. The goal is regulating glucose levels in the 4-6mmol/L band. Prior to resolving the control inputs, S_I must be fitted from the prior hours' data.

The parameter fitting process is described in [12]. p_G is assumed to be 0.01min^{-1}, a value found by [12] to be insensitive across the sampled cohort. The required combination of bolus size, insulin infusion rate and/or nutritional feed rate to achieve the target glucose level in the next hour is determined iteratively using the updated S_I, and Eqs. (1)-(3). Eqs. (4)-(5) are used to determine $P(t)$ based on stepwise fluxes in nutritional input rate.

The patient cohort is from a random selection of 17 patients from a 201 patient data audit at Christchurch Hospital [12] plus 2 patients from a hyperglycaemia control clinical trial cohort [13] (see Table 1).

Table 1: Long-Term Virtual Trial Patient Cohort

Patient number	Medical subgroup	Apache II score	Age	Sex	Mortality	Diabetes
1	Sepsis	17	56	M		Type 2
2	Sepsis	24	64	M		
24	Other medical	25	47	M	Y	Type 1
87	Other medical	26	62	F		
130	Trauma	11	21	M		Type 1
229	Cardiac	15	73	F		
289	Cardiac	18	70	M		
468	General surgical	32	76	M		
484	Other medical	34	30	F		
486	General surgical	22	76	F		Type 2
519	General surgical	29	69	M		Type 2
554	Other medical	26	20	F		Type 1
666	Cardiac	8	44	F		Type 2
847	Other medical	17	67	F		
1016	General surgical	20	37	F		Type 2
1025	Pulmonary	36	48	M		Type 2
1090	General surgical	Unknown	37	F		
1099	Pulmonary	Unknown	24	M	Y	
1125	Other medical	Unknown	72	F	Y	

This cohort represents a general cross-section of ICU population, in medical subgroup, APACHE II score, age, sex and mortality (see Table 1). Ethical consent was granted by the Canterbury Ethics Committee. Each record has glucose measurements every 3h or less, giving adequate data density for accurate model fitting. The average data length is 3.9 days with a range of 1.4-18.8 days.

The simulation trials performed use the retrospective fitted patient profiles of S_I and p_G, which simulate the physiological patient response with the assumption that the parameters are independent of the control inputs administered. Thus, a virtual patient response can be created for any glucose or insulin inputs. A normally distributed error of ±7% is added to the measured glucose values to simulate the sensor error of the Glucocard™ Test Strip II used clinically. The results are compared to the actual hospital data as well as an insulin-only control protocol [8].

Results and Discussion

Figures 1-2 show Patient 87 under sliding-scale control captured directly from retrospective hospital data, the insulin-only protocol from [8], and the variable feed and insulin protocol developed here. Tight glucose control in the 4-6mmol/L desired band is clear with the variable nutrition protocol compared to the other protocols. The total insulin administered by the variable nutrition protocol is 38.5% less than the insulin-only protocol (410.5U versus 667.0U). From the retrospective data, the total insulin infused was 248.0U, indicating another source of poor control.

Time spent in the desired 4-6mol/L band was 89% versus 21.8% for the insulin-only protocol and 10.7% for hospital control. The result for the protocol developed was achieved with identical total enteral glucose administered to the retrospective patient data (1284g versus 1286g).

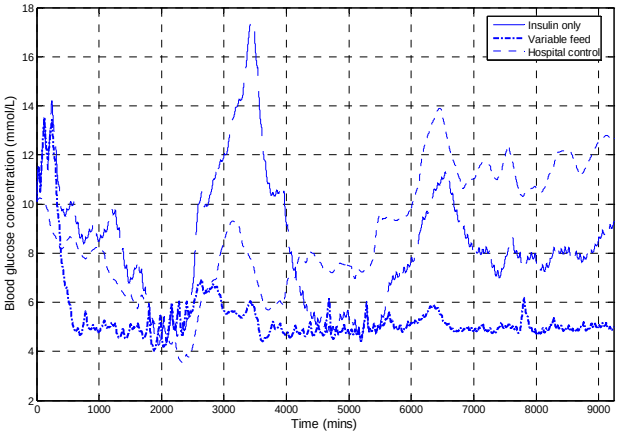

Figure 1: Patient 87 Simulation Trial Results

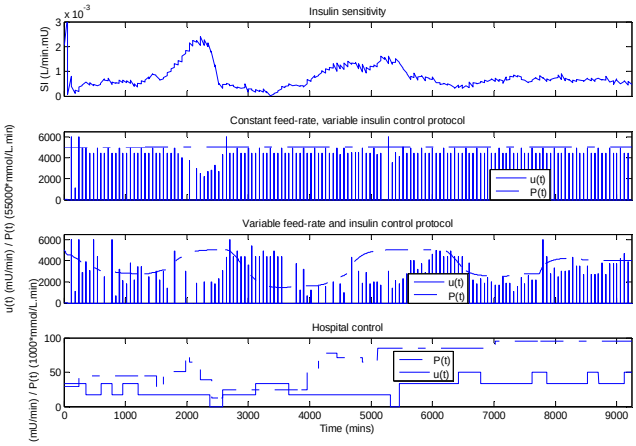

Figure 2: Patient 87 S_I and Control Input Summary

Compared to the insulin-only protocol, which fed the patient at a constant rate, the variable nutrition protocol modulated insulin and nutrition inputs as driven by the estimated effective insulin sensitivity. During periods of high insulin sensitivity, less insulin was required, while the standard feed rate was maintained. When the identified insulin sensitivity decreased, the feed rate was reduced and insulin

increased to maintain blood glucose in the desired band. This result shows that the controller recognizes, and can compensate for, periods where patient condition precludes adequate control with insulin alone.

Thus, the increase in glucose level between 2500 and 4500mins with the insulin-only protocol corresponds to a period of low insulin sensitivity. With no feed rate reduction, increased insulin resistance resulted in the glucose level rising to its maximum value of 17.3mmol/L, even though the insulin administered was identical to other periods in the simulation and at saturation limits.

Glucose levels were normal in the 4-6mmol/L band under hospital control only during periods of minimum retrospective feed rate between 1600 and 2800mins. This case shows that feed rate reduction is the only alternative to maintain euglycaemia under these typical high insulin resistance levels.

A summary of the results is shown in Tables 2 and 3. The variable nutrition and insulin controller increased the time spent in the 4-6mmol/L band by 240% compared to the insulin-only protocol and 312% versus the retrospective data. Time above 6mmol/L is reduced by 231% and 237% respectively. No hypoglycaemic events occurred in all protocols.

Table 2: Mean Blood Glucose Levels and Percentage Time in the 4-6mmol/L Band

		Mean Blood Glucose			Percentage of time in 4-6mmol/L band (%)		
Controller Type		Variable feed and insulin	Constant feed-rate, variable insulin	Hospital sliding-scale	Variable feed and insulin	Constant feed-rate, variable insulin	Hospital sliding-scale
Patient No.	1	6.0	12.1	9.3	66.8	1.6	10.2
	2	5.9	9.8	7.8	78.4	0.9	3.6
	24	6.6	12.4	12.2	80.1	0.0	0.0
	87	5.4	8.4	8.8	89.1	21.8	10.7
	130	7.0	13.2	11.2	60.1	0.0	10.3
	229	5.4	7.7	7.5	84.6	30.2	15.5
	289	5.3	5.5	6.8	80.8	79.8	13.2
	468	8.5	10.4	7.4	43.4	0.0	18.5
	484	7.5	12.3	11.5	70.0	0.0	0.0
	486	6.5	9.4	8.9	60.7	10.6	12.0
	519	5.6	7.8	6.3	78.6	51.4	33.9
	554	6.0	7.6	6.9	66.5	36.1	20.9
	666	7.2	12.4	5.3	35.7	0.0	74.9
	847	6.2	6.2	7.3	75.5	75.7	21.7
	1016	7.5	9.4	7.2	24.7	0.0	10.7
	1025	6.4	7.9	8.0	59.5	41.3	21.0
	1090	5.2	5.3	3.9	84.4	82.6	46.8
	1099	5.3	5.5	6.5	88.6	82.4	35.8
	1125	5.9	7.3	5.4	61.0	21.8	51.8
Mean		6.3	9.0	7.8	67.8	28.2	21.7
S. D.		0.9	2.6	2.2	17.9	31.8	19.3
Range		3.3	7.9	8.3	64.4	82.6	74.9

Table 4 shows the glucose and insulin prescribed by the 3 protocols. The total insulin prescribed by the variable insulin and nutrition protocol averages 33% less than the insulin-only protocol and 60% more than retrospective patient data. The efficiency of the protocol developed is further revealed in the total glucose administered, which exceeded the retrospective patient data by 19.5% on average. The developed protocol feeds an average of 718kcal/day of glucose compared to the 634kcal/day by the hospital protocol, which also had greater variability. Hence, better control was obtained with 60% more insulin and 20% more feed. This last result also indicates that it is the strategic timing of insulin and nutrition delivery, rather than their absolute level, which determines tightness of control.

Table 3: Percentage Time Outside the 4-6mmol/L Band

		Percentage of time below 4-6mmol/L band (%)			Percentage of time above 4-6mmol/L band (%)		
Controller Type		Variable feed and insulin	Constant feed-rate, variable insulin	Hospital sliding-scale	Variable feed and insulin	Constant feed-rate, variable insulin	Hospital sliding-scale
Patient No.	1	0.9	0.0	0.7	32.3	98.4	89.1
	2	0.0	0.0	0.0	21.6	99.1	96.4
	24	0.0	0.0	0.0	19.9	100.0	100.0
	87	0.0	0.0	2.6	10.9	78.2	86.8
	130	0.0	0.0	0.0	40.0	100.0	89.7
	229	1.7	0.0	0.0	13.8	69.8	84.5
	289	0.8	0.0	0.0	18.4	20.3	86.8
	468	0.0	0.0	0.0	56.6	100.0	81.6
	484	0.0	0.0	0.0	30.0	100.0	100.0
	486	3.6	0.0	0.0	35.7	89.4	88.0
	519	2.3	0.0	3.4	19.1	48.7	62.7
	554	3.9	0.0	16.9	29.6	63.9	62.3
	666	0.0	0.0	8.9	64.3	100.0	16.3
	847	2.3	0.0	0.0	22.3	24.3	78.3
	1016	0.0	0.0	0.0	75.3	100.0	89.3
	1025	4.2	0.0	0.7	36.3	58.8	78.3
	1090	0.0	0.0	53.3	15.6	17.4	0.0
	1099	0.0	1.2	0.0	11.4	16.4	64.2
	1125	2.8	0.0	8.6	36.1	78.2	39.5
Mean		1.2	0.1	5.0	31.0	71.7	73.4
S. D.		1.5	0.3	12.5	17.9	31.9	27.5
Range		4.2	1.2	53.3	64.4	83.6	100.0

Table 4: Total Insulin and Glucose Administered

		Total insulin administered (U)			Total glucose administered (g)			Percentage of maximum glucose (1000kcal/day) administered (%)	
Controller Type		Variable feed and insulin	Constant feed-rate, variable insulin	Hospital sliding-scale	Variable feed and insulin	Constant feed-rate, variable insulin	Hospital sliding-scale	Constant feed-rate, variable insulin	Hospital sliding-scale
Patient No.	1	1488	2042	1125	2720	5355	2606	51	49
	2	370	486	213	931	1285	672	72	52
	24	127	215	183	305	583	577	52	99
	87	411	667	248	1284	1833	1286	70	70
	130	97	143	111	188	393	143	48	36
	229	567	1032	232	2564	2868	1940	89	68
	289	88	108	42	440	476	312	92	65
	468	58	77	41	176	238	264	74	111
	484	125	172	200	312	476	492	66	103
	486	123	162	82	307	464	296	66	64
	519	706	1234	221	2836	3499	1856	81	53
	554	134	198	90	508	643	348	79	54
	666	150	169	61	203	464	62	44	13
	847	60	109	41	426	441	407	97	92
	1016	159	166	62	239	464	166	51	36
	1025	101	163	59	412	476	370	86	78
	1090	99	135	39	415	464	125	89	27
	1099	64	77	51	440	464	480	95	103
	1125	104	156	41	287	476	141	60	30
Mean		264.7	395.1	165.3	789.2	1124.4	660.2	71.8	63.4
S. D.		347.9	515.9	244.6	894.5	1359.7	722.5	17.3	28.7
Range		1430.1	1964.6	1085.5	2659.2	5117.0	2543.5	53.0	97.4

Figure 3 summarises these results by plotting percentage time in the 4-6mmol/L band versus the log mean fitted S_I on the x-axis. The general trend, as illustrated by Patient 87, is percentage time-in-band and mean blood glucose level decrease with all protocols with decreasing mean insulin sensitivity. With insulin alone, performance is highly dependent on the patients' effective insulin resistance due to the limitations from saturation [8]. The variable feed rate and insulin protocol provided tighter blood glucose control across the range of observed insulin sensitivities with significantly higher time-in-band. The insulin-only protocol only reached similar levels at high insulin sensitivities, and even then, with significantly more administered insulin. For hospital control, greater variation in blood glucose control was recorded, as expected (R=0.4877, p<0.04), and showed tighter control than the insulin-only protocol only at low insulin sensitivities, where clinically selected feed reductions affected the comparison.

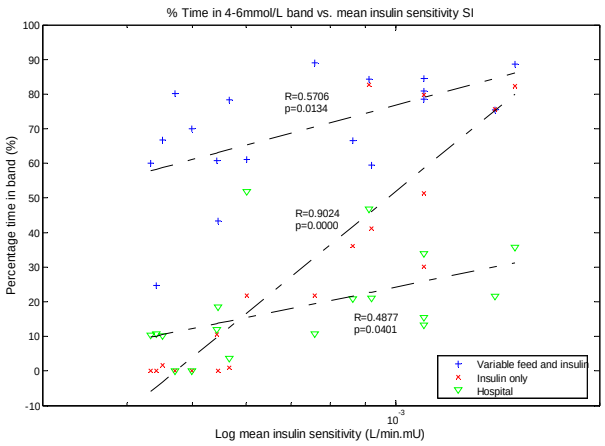

Figure 3: Insulin Sensitivity, S_I, versus Time in the 4-6mmol/L Band

It is important to note that most, or all, of the clinical, hospital reductions in feed rate were not performed for hyperglycaemia. Similarly, the insulin-only protocol had a conservative 1000kcal/day constant feed rate to manage, showing more efficient insulin delivery than hospital control despite this handicap. Hence, some improvement could be expected in the insulin-only protocol results.

Conclusions

The long-term simulated trials conducted across a wide ICU population showed that glucose management with intensive insulin therapy and feed rate modulation results not only in a reduction in absolute glucose levels, but in the severity of fluctuation in glucose levels. A 312% increase in time spent in the desired 4-6mmol/L band is achieved compared to using a constant feed rate and the same insulin control. Furthermore, the results are achieved with just 60% more insulin and, surprisingly, 20% more glucose nutrition compared to retrospective data. Note that the cohort selected exhibited wide ranging, time-varying patient condition with regard to insulin resistance. The variable insulin and feed control protocol developed exhibited far higher robustness to inter-patient variability and time-varying physiological condition than the insulin-only protocol, enabling more stable regulatory performance. Clinically, these results indicate the potential in both simulation and shorter, pilot clinical trials to reduce ICU mortality.

References

[1] G. Van den Berghe, P. J. Wouters, R. Bouillon, F. Weekers, C. Verwaest, M. Schetz, D. Vlasselaers, P. Ferdinande, and P. Lauwers, "Outcome benefit of intensive insulin therapy in the critically ill: Insulin dose versus glycemic control," *Crit Care Med*, vol. 31, pp. 359-366, 2003.

[2] J. S. Krinsley, "Association between hyperglycemia and increased hospital mortality in a heterogeneous population of critically ill patients," *Mayo Clin Proc*, vol. 78, pp. 1471-1478, 2003.

[3] K. C. McCowen, A. Malhotra, and B. R. Bistrian, "Stress-induced hyperglycemia," *Crit Care Clin*, vol. 17, pp. 107-24, 2001.

[4] B. A. Mizock, "Alterations in fuel metabolism in critical illness: hyperglycaemia," *Best Pract Res Clin Endocrinol Metab*, vol. 15, pp. 533-51, 2001.

[5] R. L. Prigeon, M. E. Roder, D. Porte, Jr., and S. E. Kahn, "The effect of insulin dose on the measurement of insulin sensitivity by the minimal model technique. Evidence for saturable insulin transport in humans," *J Clin Invest*, vol. 97, pp. 501-507, 1996.

[6] C. Weissman, "Nutrition in the intensive care unit," *Crit Care*, vol. 3, pp. R67-75, 1999.

[7] J. F. Patino, S. E. de Pimiento, A. Vergara, P. Savino, M. Rodriguez, and J. Escallon, "Hypocaloric support in the critically ill," *World J Surg*, vol. 23, pp. 553-9, 1999.

[8] J. G. Chase, G. M. Shaw, J. Lin, C. V. Doran, C. Hann, M. B. Robertson, P. M. Browne, T. Lotz, G. C. Wake, and B. Broughton, "Adaptive bolus-based targeted glucose regulation of hyperglycaemia in critical care," *Med Eng Phys*, vol. 27, pp. 1-11, 2005.

[9] E. Kiwanuka, R. Barazzoni, and P. Tessari, "Glucose kinetics and splanchnic uptake following mixed meal ingestion in cirrhotic-diabetic subjects," *Diabetes Nutrition & Metabolism*, vol. 14, pp. 315-324, 2001.

[10] B. Ludvik, J. J. Nolan, A. Roberts, J. Baloga, M. Joyce, J. M. Bell, and J. M. Olefsky, "Evidence for decreased splanchnic glucose uptake after oral glucose administration in non-insulin-dependent diabetes mellitus," *Journal of Clinical Investigation*, vol. 100, pp. 2354-2361, 1997.

[11] J. Radziuk, T. J. McDonald, D. Rubenstein, and J. Dupre, "Initial Splanchnic Extraction of Ingested Glucose in Normal Man," *Metabolism-Clinical and Experimental*, vol. 27, pp. 657-669, 1978.

[12] C. E. Hann, J. G. Chase, J. Lin, T. Lotz, C. V. Doran, and G. M. Shaw, "Integral-based parameter identification for long-term dynamic verification of a glucose-insulin system model," *Comput Methods Programs Biomed*, vol. 77, pp. 259-70, 2005.

[13] J. G. Chase, X. W. Wong, G. M. Shaw, C. E. Hann, J. Lin, and T. Lotz, "Clinical Trials of Active Insulin and Nutrition Control in Critically Ill Patients," presented at The 12th International Conference on Biomedical Engineering (ICBME), Singapore, 2005.