Journal of Diabetes Science and Technology
Volume 3, Issue 5, September 2009

SYMPOSIUM

Blood Glucose Controller for Neonatal Intensive Care: Virtual Trials Development and First Clinical Trials

Aaron Le Compte, BE(Hons), Ph.D.,[1] J. Geoffrey Chase, Ph.D.,[1] Adrienne Lynn, M.B.Ch.B., FRACP,[2] Chris Hann, Ph.D.,[1] Geoffrey Shaw, M.B.Ch.B., FJFICM,[3,4] Xing-Wei Wong, Ph.D.,[1] and Jessica Lin, Ph.D.[1]

Abstract

Background:

Premature neonates often experience hyperglycemia, which has been linked to worsened outcomes. Insulin therapy can assist in controlling blood glucose (BG) levels. However, a reliable, robust control protocol is required to avoid hypoglycemia and to ensure that clinically important nutrition goals are met.

Methods:

This study presents an adaptive, model-based predictive controller designed to incorporate the unique metabolic state of the neonate. Controller performance was tested and refined in virtual trials on a 25-patient retrospective cohort. The effects of measurement frequency and BG sensor error were evaluated. A stochastic model of insulin sensitivity was used in control to provide a guaranteed maximum 4% risk of BG < 72 mg/dl to protect against hypoglycemia as well as account for patient variability over 1–3 h intervals when determining the intervention. The resulting controller is demonstrated in two 24 h clinical neonatal pilot trials at Christchurch Women's Hospital.

Results:

Time in the 72–126 mg/dl BG band was increased by 103–161% compared to retrospective clinical control for virtual trials of the controller, with fewer hypoglycemic measurements. Controllers were robust to BG sensor errors. The model-based controller maintained glycemia to a tight target control range and accounted for interpatient variability in patient glycemic response despite using more insulin than the retrospective case, illustrating a further measure of controller robustness. Pilot clinical trials demonstrated initial safety and efficacy of the control method.

continued →

Author Affiliations: [1]Department of Mechanical Engineering, University of Canterbury, Christchurch, New Zealand; [2]Neonatal Department, Christchurch Women's Hospital, Christchurch, New Zealand; [3]Department of Intensive Care, Christchurch Hospital, Christchurch, New Zealand; and [4]Christchurch School of Medicine and Health Science, University of Otago, Christchurch, New Zealand

Abbreviations: (BG) blood glucose, (CDF) cumulative distribution function, (IQR) interquartile range, (LBG-P) low blood glucose to performance, (NICU) neonatal intensive care unit

Keywords: blood glucose, hyperglycemia, insulin, neonatal intensive care unit, premature birth

Corresponding Author: J. Geoffrey Chase, Ph.D., Department of Mechanical Engineering, University of Canterbury, Private Bag 4800, Christchurch, New Zealand; email address geoff.chase@canterbury.ac.nz

Abstract cont.

Conclusions:

A controller was developed that made optimum use of the very limited available BG measurements in the neonatal intensive care unit and provided robustness against BG sensor error and longer BG measurement intervals. It used more insulin than typical sliding scale approaches or retrospective hospital control. The potential advantages of a model-based approach demonstrated in simulation were applied to initial clinical trials.

J Diabetes Sci Technol 2009;3(5):1066-1081

Introduction

Premature infants commonly demonstrate poor glycemic control, and 40–80% of low birth weight infants experience hyperglycemia during the neonatal period.[1,2] Metabolic homeostasis in the preterm infant is often compromised by immaturity of control systems. Additionally, the metabolic response to stress is characterized by major changes in glucose metabolism.[3] Increased secretion of counter-regulatory hormones leads to a prominent rise in endogenously produced glucose and the rate of hepatic gluconeogenesis as well as a reduction in insulin sensitivity. Inhibiting the physiological response to increased glycemic levels are factors such as increased insulin resistance, absolute or relative insulin deficiency, and drug therapy.[4–7]

Hyperglycemia is not only a marker for severity of illness, it has also been linked to worsened outcomes, leading to an increased risk of further complications such as sepsis, retinopathy of prematurity, and mortality.[8–12] Hyperglycemia may also cause an osmotic diuresis and intraventricular hemorrhaging.[3,5] High rates of proteolysis are also common in low birth weight infants, reducing muscle mass and inhibiting growth.[13,14]

Tight glucose control has been shown to reduce adult intensive care unit patient mortality by up to 45%.[8,10,15,16] Hyperglycemia in preterm neonates is often treated by glucose restriction and/or the use of insulin infusions. A small number of prospective trials have used insulin infusions to treat hyperglycemia and/or promote growth.[4,13,17–24] Positive outcomes of insulin infusion have been reduced proteolysis, improved glucose tolerance, and improved weight gain. Hypoglycemia presents a problem in some studies. The Neonatal Insulin Replacement Therapy in Europe Study trial, which used a fixed dose of insulin and modulated glucose infusions, was stopped early due in part to excess hypoglycemia.[17] Alternatively, Vlasselaers and colleagues[25] found improved short-term outcomes for pediatric intensive care patients. Thus the use of insulin in this population remains controversial.[26,27]

Blood glucose (BG) control for the neonate poses several challenges that differ from the adult critical care case. Blood volumes in preterm infants are relatively small, thus the number of BG measurements must be optimized to a minimum useful number to conserve volume. Endogenous energy supply stores are limited in preterm infants at birth.[28–30] Thus preterm infants must be constantly fed to provide enough energy for basal requirements in addition to growth.[31] In contrast, the adult can tolerate periods of reduced caloric intake. Finally, also unlike the adult case, growth is a major goal of neonatal care. Thus the anabolic effects of insulin are of relatively high importance.[14,24]

Great interpatient heterogeneity in response to glucose and insulin infusions is a well-reported hallmark of neonatal glucose metabolism, making safe, adequate control difficult.[1,19] Thus knowledge of the metabolic state of the infant is vital for optimal, safe BG control using insulin administration. Model-based methods can provide information about the patient's response to insulin based on serial BG measurements and insulin and nutrition data.[32] This metabolic information can be combined with a controller utilizing model predictions to achieve targeted BG control. This approach has been validated in adult critical care studies.[33,34] However, sudden changes in patient condition independent of metabolic state indicate that limits on model-based controller actions are required to maximize safety and control performance.

Therefore, there are several design parameters that must be considered in developing a safe, effective, and optimal neonatal glycemic control algorithm. Virtual trials offer the opportunity to explore control strategies in simulation before pilot clinical trials.[35] In particular, the proposed control algorithm needs to reduce elevated BG level in a controlled, predictable manner, accounting for external nutrition. The controller must also account for interpatient variability and varying physiological condition. Hence it must be adaptive and/or able to identify changes in patient dynamics, particularly with respect to insulin sensitivity. The protocol should require only infrequent sensor measurements to minimize labor and comply with existing medical protocols on the treatment of neonatal hyperglycemia to ensure the method developed could be readily implemented in a clinical environment. Finally, the controller must be robust to sensor errors.

Methods

System Model

The model is based on an adult critical care glycemic model[35,36] that has been adapted and validated[36,37] to account for the main physiological differences in neonates.[38] The overall model is defined as

$$\dot{G} = -p_G.G - S_I.G.\frac{Q}{1+\alpha_G Q} + \frac{P(t) + (P_{END} * m_{body}) - (CNS * m_{brain})}{(V_{G,frac}(t) * m_{body})} \quad (1)$$

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

$$\dot{I} = -\frac{nI}{1+\alpha_I I} + \frac{u_{ex}(t)}{(V_{I,frac} * m_{body})} + e^{-(k_I u_{ex}(t))} I_B \quad (3)$$

where $G(t)$ (mmol/liter) is the total plasma glucose, $I(t)$ (mU/liter) is the plasma insulin, $u_{ex}(t)$ (mU/min) is exogenous insulin input, and I_B (mU/liter/min) is basal endogenous insulin secretion, with k_I representing the suppression of basal insulin secretion in the presence of exogenous insulin. The effect of previously infused insulin being utilized over time is represented by $Q(t)$ (mU/liter), with k (1/min) accounting for the effective life of insulin in the system. Body weight and brain weight are denoted by m_{body} (kg) and m_{brain} (kg), respectively. Patient endogenous glucose clearance and insulin sensitivity are p_G (1/min) and S_I (liter/[mU/min]), respectively. The parameter $V_{I,frac}$ (liter/kg) is the insulin distribution volume per kilogram body weight, and n (1/min) is the constant first-order decay rate for insulin from plasma. Total plasma glucose input is denoted by $P(t)$ (mmol/min), endogenous glucose production is denoted by P_{END} (mmol/kg/min), and $V_{G,frac}$ (liter/kg) represents the glucose distribution volume per kilogram of body weight. CNS (mmol/kg/min) represents noninsulin-mediated glucose uptake by the central nervous system as well as the liver, kidneys, and red blood cells.[39] Michaelis–Menten functions are used to model saturation, with α_I (liter/mU) used for the saturation of plasma insulin disappearance and α_G (liter/mU) for the saturation of insulin-dependent glucose clearance.

Table 1 summarizes the parameters used in this model based on available kinetic studies in neonates. For the simulations in this study, k, n, α_I, α_G, CNS, I_B, $V_{I,frac}$, p_G, and P_{END} are set to generic population values based on reported clinical neonate data. Prior clinical and model sensitivity studies[36,38,40] have shown this choice to be robust. The model presented in **Equations (1)–(3)** adapt several parameters from similar adult models to appropriate values for the neonate. Specifically, volume of glucose distribution in **Equation (1)** is modeled as a time-varying parameter based on gestational age,[29] and endogenous glucose production (P_{END}) and central nervous system uptake (CNS) terms are expressed on a weight basis. Insulin-mediated glucose uptake saturation and plasma insulin clearance terms were updated to reflect neonatal physiology.[13,14,41,42] Grid search was used to identify population-constant values for P_{END} and p_G, and parameter sensitivity studies with the neonatal model found fit and prediction performance to be robust to variations in population constants within reported physiological values. Model fit and prediction performance of the neonatal model was found to be similar to adult models utilized for simulation studies.[36] Further details of model development and performance analysis are available in Reference 38.

Table 1.
Constant Model Parameter Values

Parameter	Value	Reference(s)
k	0.0086 min^{-1}	36
n	0.90 min^{-1}	13, 14, 41, 42
α_I	1.70 x 10^{-3} liter/mU	36
α_G	0 liter/mU	41
CNS	0.088 mmol/kg/min	43
m_{brain}	0.14 * m_{body} kg	44
I_B	12 mU/liter/min	41, 42
$V_{I,frac}$	0.045 liter/kg	45, 46
$V_{G,frac}$	Extracellular fluid proportion liter/kg	47–50
P_{END}	0.02838 mmol/kg/min	38, 42, 51–56
p_G	0.003 min^{-1}	38

Controller Development

The insulin sensitivity parameter, S_I, (liter/mU/min) drives the dynamics of the BG model and is assumed independent of exogenous insulin and nutrition administration over the period between interventions. The insulin sensitivity parameter is fitted using an integral-based fitting method[36] and represents the body's overall glycemic response to exogenous insulin. Once a patient-specific profile of time-varying insulin sensitivity is generated, it can be used to predict BG concentration based on different insulin and nutrition control schemes. Such analyses are effectively *in silico* or in virtual trials, and have been successfully used to develop glycemic control protocols for adult intensive care[35,57] and type 1 diabetes patients.[58]

The clinical implementation procedure for the targeted model-based controller is shown in **Figure 1**. The BG history, along with insulin and nutrition history, is used to fit the patient's insulin sensitivity profile in real time. This profile is then used by the controller to solve Equations (1)–(3) to predict BG concentration based on insulin and nutrition rates. Thus the controller adapts to the current metabolic state of the neonate in real time. The controller uses a bisection algorithm to determine the insulin infusion rate that will bring the BG closest to a target BG, if the target is physiologically possible with safety. Thus every BG measurement is followed by a controller intervention to alter the insulin infusion rate. The virtual trial procedure replaces the "patient" in **Figure 1** with a forward solution of the model using an insulin sensitivity profile generated from retrospective data and adds sensor noise and other variations as required.

Crucially, blood volumes in neonates are very small,[45,46] which significantly restricts the frequency of BG sampling, providing an additional challenge for model-based control in the neonatal setting. Thus it is important to optimize the number of BG measurements required for control. Clinically, volume restrictions mean most neonates will not be sampled more frequently than every 2 h (12/day) overall as a maximum rate.

Controllers using 1–4 h BG measurement and intervention intervals were examined and compared to retrospective hospital control and simulations using a typical insulin sliding scale shown in **Table 2**. Additionally, a BG measurement timing scheme based on current BG concentration was tested. In particular, a high BG concentration carries little risk of hypoglycemia and may thus require less frequent BG sampling compared to periods at lower concentrations to reduce potentially unnecessary

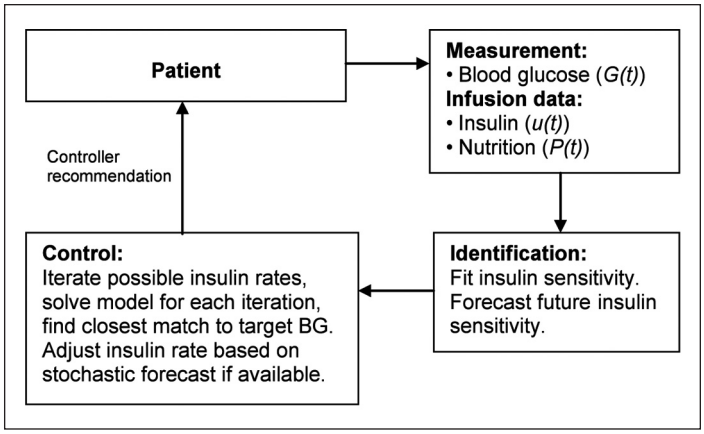

Figure 1. Controller implementation schematic.

Table 2.
Typical Insulin Sliding Scale Used in Simulation

Blood glucose	Insulin rate [U/kg/h]
>360 mg/dl	0.100
270–360 mg/dl	0.075
180–270 mg/dl	0.050
90–180 mg/dl	0.025
<90 mg/dl	Stop

volume loss or save such measurements for when they might potentially be used more valuably. Hence a BG-concentration-derived measurement scheme was simulated where measurements were taken every 3 h if BG > 144 mg/dl and any decrease in BG since the previous measurement was less than 36 mg/dl/h. Measurements were taken every 2 h if BG was within the 72–144 mg/dl range and hourly otherwise up to a limit of 12 measurements per day. All initial simulations were performed with uniformly distributed 7% measurement error.[59,60]

The metabolic status of a critically ill neonatal patient can change rapidly. This change is reflected by sudden rises and drops in insulin sensitivity. Additionally, sudden changes in apparent insulin sensitivity may be caused by sensor noise and/or measurement error.[10] Thus, for example, a balance is required between the speed at which a controller reacts to correct BG rises due to sudden changes in metabolic state and the risk of running higher insulin infusion rates when a sudden apparent rise in BG resolves quickly or was due to measurement error.

To explore the balance between speed of control response and robustness against sudden metabolic changes, two sets of controller schemes were evaluated:

- Scheme A controllers set a relatively high upper limit of 0.5 U/kg/h for the maximum controller insulin infusion rate and limited the maximum increase in insulin infusion rate permitted from one intervention to the next.
- Scheme B controllers used a lower maximum insulin infusion rate of 0.1–0.5 U/kg/h but had no limit on the ability to increase the insulin infusion rate (up to the maximum allowable).

Performance was measured as more BG measurements within a clinically recommended target 72–126 mg/dl band while minimizing or eliminating measurements lower than 47 mg/dl. The low-BG-to-performance (LBG-P) ratio provides a measure of the increased risk of low BG measurements under tight glycemic control compared to the increase in measurements within the target BG band. The LBG-P ratio is defined as

$$\frac{\%\ \text{measurements} < 47\ \text{mg/dl}}{\%\ \text{measurements withing 72–126 mg/dl band}} * 100 \quad (4)$$

Both insulin rate control schemes were tested with 1, 2, 3, and 4 h BG measurement intervals to assess the robustness of each scheme to increasing measurement interval length. Selection criteria for choosing the best control strategy assessed time in the target band, robustness to increased measurement interval length, and LBG-P ratio. Finally, the effect of BG sensor error was explored in simulated trials by adjusting the amount of uniformly distributed noise added to simulated BG measurements to 2%, 5%, 10%, 15%, and 20%, representing the range (and beyond) seen in clinical practice depending on the BG measurement device/analyzer used.[59,60]

Stochastic modeling of the insulin sensitivity parameter can provide bands of forecasted BG probability for a given intervention. These bands can delimit the 5–95% confidence interval for future BG concentration based on current insulin sensitivity for a particular patient and observed changes in insulin sensitivity within the retrospective patient cohort used to generate the stochastic model. The forecast bands can be used to provide further protection against hypoglycemia by providing a statistical measure of confidence against low BG concentrations. Control implementing the stochastic model was investigated in simulation by decreasing the controller-selected insulin rate when required to ensure the 5–95% future BG confidence interval was always greater than 4 mmol/liter. Further details of the stochastic modeling process are available from Lin and associates.[61,62]

Clinical Trials

Initial pilot clinical trials were performed in the Christchurch Women's Hospital Neonatal Department to test the basic safety and efficacy of the model-based controller developed. Two trial patients are presented in this article to demonstrate model capability leading to future trials of the system in a clinical environment to assess improvement over standard neonatal intensive care unit (NICU) control protocols. Inclusion criteria were birth weight < 1500 g, BG ≥ 180 mg/dl, a clinical decision to commence insulin infusions, and an *in situ* arterial line. The trials were performed for 24 h to allow close supervision by members of the controller development team. Outside the trial period, infants continued on insulin infusion according to the standard care protocol for Christchurch Women's Hospital.

Blood glucose measurements were taken every 1 to 3 h for up to 24 h, and the insulin infusion rate was adjusted as determined by the model-based controller after each BG measurement. Insulin was given via intravenous cannula using Alaris CC pumps (Alaris, San Diego, CA) as a continuous infusion. The concentration of insulin was (5*weight [kg]) U made up to 20 ml with 0.9% saline solution to achieve a concentration of 0.25 U/kg/ml. New insulin infusion rates were determined after every measurement using the optimal controller selected from the simulation study results highlighted in **Table 3**, and a neonatal clinician approved every change in insulin infusion rate before adjusting the pump. The pilot study was approved by the Upper South A Ethics Committee.

Patient Cohorts

Retrospective data for 25 episodes of insulin usage over 21 patients from the Christchurch Women's NICU was used in the study. Ethics approval for the collection and publication of data was obtained from the Upper South A Ethics Committee. The clinical details of the cohort are shown in **Table 4**. Inclusion criteria were a period of treatment with insulin and at least six BG measurements per day. Data were collected only while patients received exogenous insulin infusions. Two study patients (20 and 22) had multiple episodes of insulin usage during their NICU stay. The patients were continuously fed with dextrose provided from triphosphopyridine nucleotide, expressed breast milk, or a combination of both. Hourly varying insulin sensitivity was fitted to each of the 25 patient profiles to generate a cohort of 25 "virtual patients" used for simulation.

Two 24 h pilot clinical trials of the model-based controller are presented in this report. The two subjects were born

at 27.3 and 25.4 weeks gestational age and birth weight 770 and 720 g, respectively. The trials were conducted at age 9 and 2 days, respectively.

Results

In Silico Virtual Trials

Table 3 compares BG control metrics for the effect of controller rules on insulin infusion rates for several combinations of maximum insulin infusion rate and maximum increase in insulin infusion rate per intervention. Scheme A, with a 0.01 U/kg/h limit on insulin infusion rate increases, had a median BG greater than 108 mg/dl for all measurement interval cases, as well as a relatively low proportion of measurements within the 72–126 mg/dl range. Thus scheme A does not react to changes in metabolic state fast enough for optimal control. The results for scheme A simulations with higher allowable insulin infusion rate increases of

Table 3.
Effect of Controller Rules for Insulin Infusion Rate Increases on Blood Glucose Control and Hypoglycemia[a]

Controller scheme	Max insulin rate	Max increase in insulin per intervention	Measurement interval (h)	% of measurements			BG median (mg/dl)	LBG-P ratio
				Within 72–126 mg/dl	<72 mg/dl	<47 mg/dl		
A	0.5 U/kg/h	0.01 U/kg/h	1	65.9	1.6	0.14	115	0.2
			2	63.5	2.5	0.28	115	0.4
			3	56.9	3.1	0.34	117	0.6
			4	54.9	3.3	0.46	119	0.8
		0.03 U/kg/h	1	81.7	1.7	0.23	110	0.3
			2	76.1	3.4	0.45	108	0.6
			3	69.3	5.8	0.60	110	0.9
			4	64.6	7.1	0.91	110	1.4
		0.05 U/kg/h	1	85.7	1.8	0.23	108	0.3
			2	80.0	3.7	0.68	106	0.9
			3	71.9	6.7	0.94	108	1.3
			4	68.8	7.3	1.37	106	2.0
B	0.1 U/kg/h		1	77.1	1.7	0.14	110	0.2
			2	71.4	3.4	0.28	110	0.4
			3	65.6	5.9	0.94	112	1.4
			4	62.9	6.1	0.91	110	1.5
	0.15 U/kg/h		1	83.9	1.8	0.23	108	0.3
			2	77.9	4.1	0.40	106	0.5
			3	70.6	6.9	1.11	108	1.6
			4	67.0	7.8	1.48	106	2.2
	0.3 U/kg/h		1	89.0	2.5	0.23	106	0.3
			2	79.2	5.8	0.96	106	1.2
			3	72.3	9.1	1.45	106	2.0
			4	68.9	9.4	1.82	104	2.6
	0.5 U/kg/h		1	88.5	3.0	0.39	106	0.5
			2	80.4	6.0	1.13	106	1.4
			3	72.3	8.9	1.96	106	2.7
			4	68.5	10.0	2.73	104	4.0

[a] Low-blood-glucose-to-performance ratio compared low BG to performance, which is defined as the ratio of the percentage of measurements <47 mg/dl and the percentage of measurements within the 72–126 mg/dl range.

0.03 and 0.05 U/kg/h per intervention show a similar level of performance. The (largest) 0.05 U/kg/h increase limit achieved higher percentage of measurements within the target BG band. However, the 0.03 U/kg/h increase limit achieved a lower LBG-P ratio and 2–4 h measurement intervals.

Scheme B, with an upper insulin rate of 0.1 U/kg/h, yielded a lower percentage of measurements within the 72–126 mg/dl range across all measurement frequencies compared to the higher-performing scheme A results, suggesting that 0.1U/kg/h is low for a maximum insulin infusion rate. The results for scheme B simulations with 0.3 and 0.5 U/kg/h upper insulin rate limits showed little difference in measurements within the 72–126 mg/dl band despite the availability of higher insulin infusion rates. However, these two control schemes recorded the highest percentage of measurements less than 47 mg/dl, and the high LBG-P ratio reflects that the increased risk of low BG measurements was greater than the possible increase in measurements in the target BG band compared to other insulin schemes.

Table 4.
Patients and/or Episodes Selected for Long-Term Data Collection[a]

Patient	Length of fitting (days)	Average BG measurements per day	Gestation age at birth (weeks)	Age at start of data (days)	Weight at birth (g)
1	12.7	8.1	23.0	<1	600
2	13.9	5.3	24.4	4	650
3	8.8	5.9	23.7	<1	625
4	12	5.4	25.4	<1	800
5	5.9	6.1	26.6	7	840
6	3.9	11.2	25.0	<1	900
7	4.6	5.4	26.3	7	810
8	4.3	4.9	26.6	6	825
9	3.8	6.1	26.6	3	915
10	2.7	5.1	27.9	3	1280
11	4.9	7.4	28.1	<1	1275
12	1.4	10.7	28.6	<1	845
13	2.4	8.8	27.7	<1	860
14	7.6	7.0	24.9	3	735
15	8.6	6.6	26.9	2	880
16	1.8	9.4	29.9	<1	865
17	1.9	5.9	26.4	7	990
18	3.8	5.5	26.6	3	920
19	1.8	11.5	28.6	4	930
20	4.7	6.0	26.6	4	860
21[b]	5.8	8.1		20	
22	11.8	10.0	25.4	2	800
23[c]	12.7	9.3		22	
24[c]	5.9	8.1		41	
25[c]	1.3	7.1		56	
Cohort	4.7 (2.6–8.7)	7.0 (5.9–9.3)	26.6 (25.4–27.7)	3.0 (1.0–7.0)	860 (800–915)

[a] Cohort summaries are presented as median (IQR), and patients with repeated episodes of insulin usage are only included once for gestation age at birth and weight at birth summaries.
[b] Second episode of insulin usage for patient 20.
[c] Subsequent episodes of insulin usage for patient 22.

Thus scheme A, with a 0.03 U/kg/h allowable insulin infusion increase rate, and scheme B, with an upper limit of 0.15 U/kg/h of insulin, represent the best performing versions of each control scheme. The scheme B simulation achieved a higher proportion of measurements within the target band across all measurement frequencies. However, the scheme B simulation showed a higher proportion of measurements below 47 mg/dl for longer measurements intervals than the scheme A counterpart, a result emphasized by the higher LBG-P ratio. Thus scheme A, with a maximum increase in insulin rate of 0.03 U/kg/h, highlighted in **Table 3**, provides an effective compromise between controller performance and robustness to increased times between measurements and was chosen as the controller for the remaining simulations in this study.

Table 5 compares BG performance metrics, along with insulin intake, between the actual retrospective NICU control and simulated sliding scale and model-based targeted control. The BG target is 108 mg/dl or a 15% reduction per hour from the current BG concentration, whichever is the greater value. The median BG for all model-based control cases presented in **Table 5** is at, or close to, the target BG. The percentage of measurements within the 72–126 mg/dl and 72–144 mg/dl ranges are 65–82% and 76–90%, which is 103–161% and 61–91% higher (relatively) than retrospective hospital control, respectively. The sliding scale results showed higher median BG than either model-based control or retrospective results.

The length of time between BG measurements reduces the quality of model-based control, dropping from 82% to 65% of BG measurements within the 72–126 mg/dl band for 1 to 4 h measurement intervals. The proportion of simulated measurements below 47 mg/dl is less than the retrospective control data for 1–3 h measurement intervals but slightly greater for 4 h measurement intervals. The width of the interquartile range (IQR) for retrospective control was 65 mg/dl and for sliding scale control was 65–70 mg/dl, in contrast to 18–36 mg/dl for 1 and 4 h model-based control. Sliding scale control results were largely similar over the range of measurement frequencies.

Figure 2 shows the empirical cumulative distribution functions (CDFs) for BG measurement between simulated trials and retrospective control. The results for 1–4 h measurement frequencies all intersect the 50th percentile area at approximately the target value of 108 mg/dl. The major difference in control quality between the simulation lies within the slope of the lines, where more frequent BG measurement and controller intervention results in a steeper slope and thus a tighter BG distribution.

All model-based controller results are significantly different from the retrospective BG measurement distribution ($p < .01$, Kruskal–Wallis test). *Post hoc* testing revealed significant differences in BG distribution for 1 h versus 2 h simulation model-based control and retrospective control versus all model-based simulated distributions ($p < .05$, Mann–Whitney test). It is important to note that the curves presented in **Figure 2** are not symmetrical; the slope at lower BG ranges is steeper, thus BG results when not within the target range are skewed toward the upper BG range, as mild hyperglycemia is considered safer than an increased risk of hypoglycemia. **Figure 3** shows the median CDF and 5–95% range of CDFs of the per-patient control results for the model-

Table 5.
Comparison of Glycemic Control Performance between Retrospective Control, Typical Sliding Scale Control, and Targeted Model-Based Control with Increasing Blood Glucose Measurement Interval

Control scheme	Measurement frequency (h)	Total measurements	Median BG (mg/dl)	BG IQR (mg/dl)	% of measurements within range			Average insulin (U/kg/h) x 10^{-2}
					72–126 mg/dl	72–144 mg/dl	<47 mg/dl	
Model-based controller	1	3555	110	101–119	81.7%	90.1%	0.23%	5.4
	2	1771	108	97–122	76.1%	86.4%	0.45%	5.6
	3	1175	108	95–126	69.3%	81.3%	0.60%	5.7
	4	879	110	94–130	64.6%	76.3%	0.91%	5.5
Retrospective		1091	144	113–178	30.9%	45.6%	0.73%	3.4
Sliding scale	1	3555	155	122–187	26.0%	40.1%	0.20%	2.9
	2	1771	155	124–189	24.8%	39.5%	0.34%	2.9
	3	1175	153	122–191	24.9%	40.9%	0.34%	3.0
	4	879	153	124–194	25.0%	41.4%	0.57%	3.0

based controller with 2 h measurement frequency and retrospective data. The interpatient variation in BG control with the model-based controller is much tighter compared to retrospective control. Thus the model-based controller better modulates insulin to account for each individual patient's glycemic response.

Insulin use between the measurement frequencies was similar for model-based control and 65–74% higher (relatively) than hospital control. It is interesting to note in **Table 5** that higher average insulin rates did not necessarily correspond with greater proportion of measurements within target BG ranges. The highest proportion of measurements within the target band was for the 1 h control, and interestingly, higher time in the target band did not correspond with differences in average insulin usage.

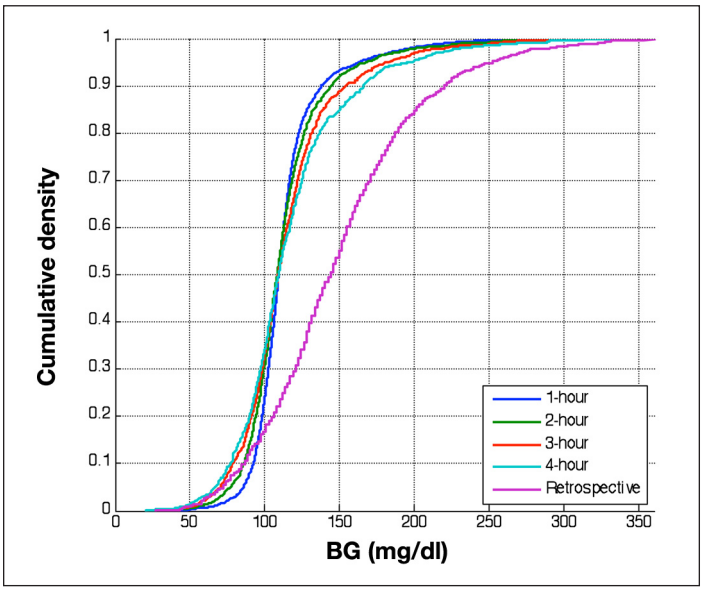

Figure 2. Empirical CDFs of BG measurements for retrospective hospital control versus simulated trials of 1, 2, 3, and 4 h measurement and intervention frequency.

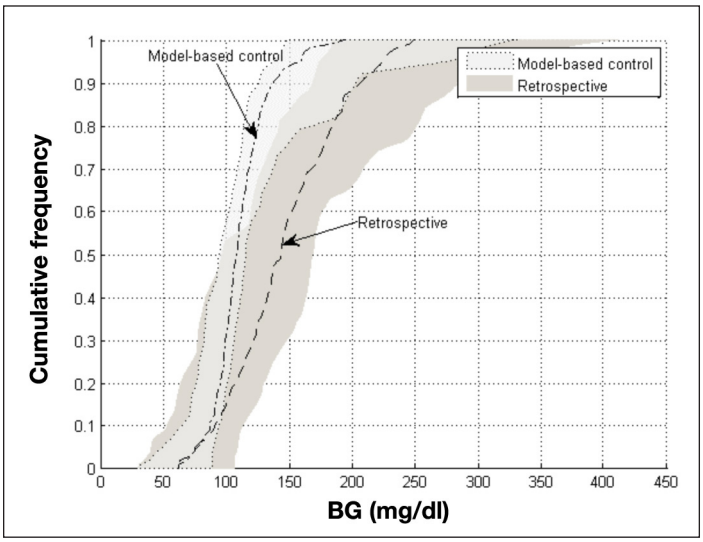

Figure 3. Median and 5–95% interval of per-patient BG CDFs.

Figure 4 compares the proportion of BG measurements within the target 72–126 mg/dl band for retrospective and simulated control. Only one patient retrospectively had greater than 50% of BG measurements within the target band under hospital control. All patients had greater than 50% of BG measurements within the target band in simulation. The 45° line in **Figure 4** represents the line of no change in performance. All results are above this line, indicating that the model-based controller achieved a higher proportion of BG measurements within the target band. The distance from the line is a measure of the increase in BG measurements within the target band per patient. Analysis of the model-fitted BG curves also indicated that a higher proportion of simulated patient time was spent within the target BG concentration. Of the 3770 h of simulated data, 2407–2983 simulated patient hours were spent in the target range for 1–4 h interval control interventions, compared to 1041 h from retrospective control.

Figure 5 compares retrospective control and simulated model-based control for a typical patient. The bottom panel of **Figures 5** shows the model's ability to track the insulin sensitivity profile in real time based on data available at the bedside. This tracking is achieved through the integral-based fitting method[36] and through

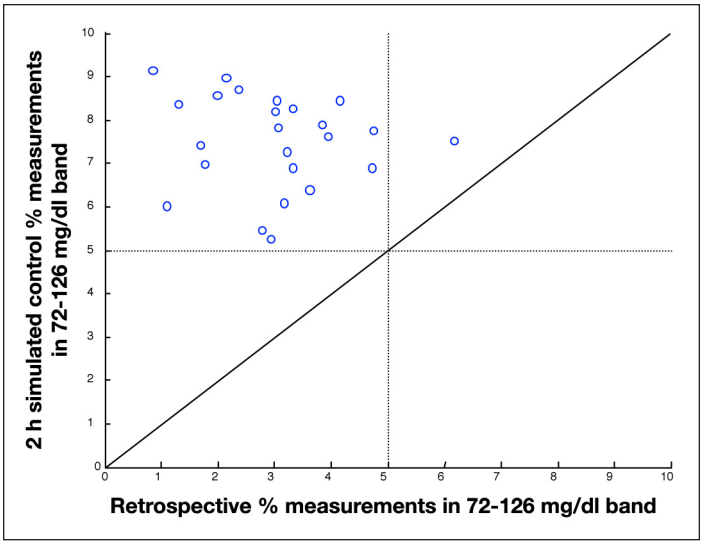

Figure 4. Comparison of percentage of BG measurements within the 72–126 mg/dl BG range for retrospective and 2 h simulated control. Each circle represents one of the 25 patient profiles.

the independence of insulin sensitivity as a model parameter.

Table 6 compares glycemic control performance with simulated uniformly distributed BG measurement errors of 2%, 5%, 7%, 10%, 15%, and 20% added for a controller using a 2 h measurement interval. As expected, more accurate control is achieved with lower measurement noise, with 78% versus 65% time in the 72–126 mg/dl band for ±2% versus ±20% measurement error. Similar patterns appear for other measurement frequencies.

Figure 6 shows the percentage of measurements within the 72–126 mg/dl band and less than 47 mg/dl for 1–4 h measurement frequencies. Absolute time in band decreased 7–17% for an 18% absolute increase in simulated sensor error and a corresponding absolute increase of 1.0–2.6% for measurements less than 72 mg/dl. The effect of sensor error on overall BG control is shown in **Figure 7**. Increased measurement error results in a less steep CDF. However, even with 20% simulated sensor error, **Figure 7** shows significantly increased tightness of BG control compared to retrospective clinical control results.

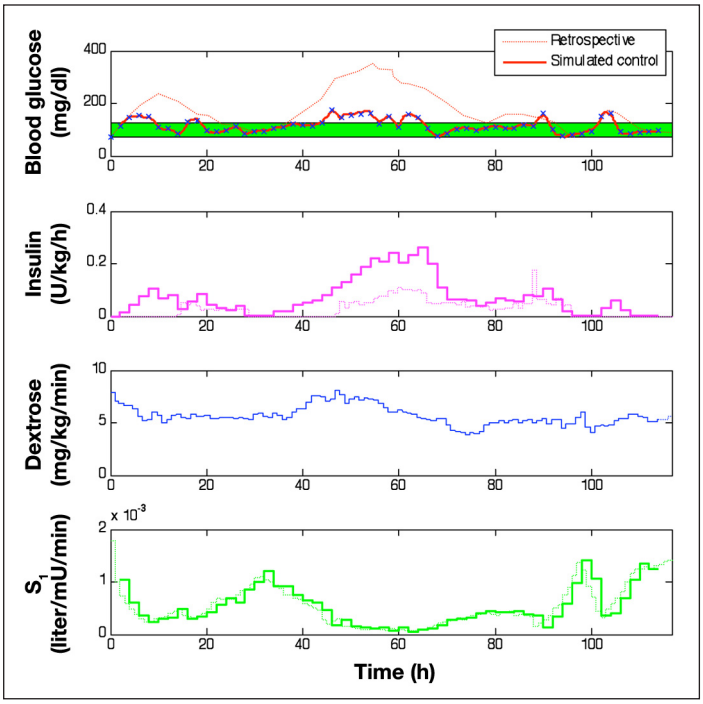

Figure 5. Comparison of BG, insulin, nutrition, and SI profiles for patient 11 under retrospective control (dashed line) and simulated model-based control (solid line).

Table 6.
Comparison of Glycemic Control Performance with Increasing Simulated Blood Glucose Sensor Error for 2 h Measurement Interval

Sensor error	Median BG (mg/dl)	BG IQR (mg/dl)	% measurements within range:		
			72–126 mg/dl	<72 mg/dl	<47 mg/dl
±2%	108	97–131	78.3%	3.2%	0.40%
±5%	108	97–131	77.4%	3.3%	0.34%
±7%	108	97–122	76.1%	3.4%	0.45%
±10%	110	95–122	74.6%	3.1%	0.40%
±15%	110	95–126	69.5%	4.8%	0.51%
±20%	110	94–126	65.2%	5.3%	0.40%

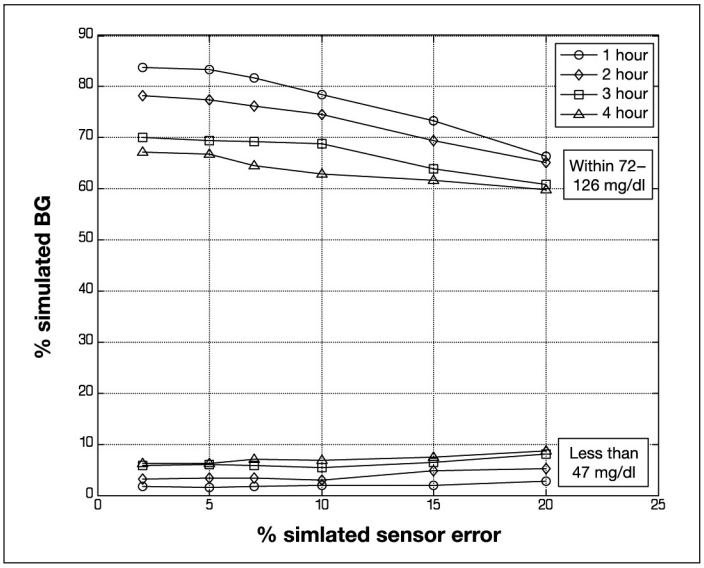

Figure 6. Effect of simulated BG sensor error on BG control.

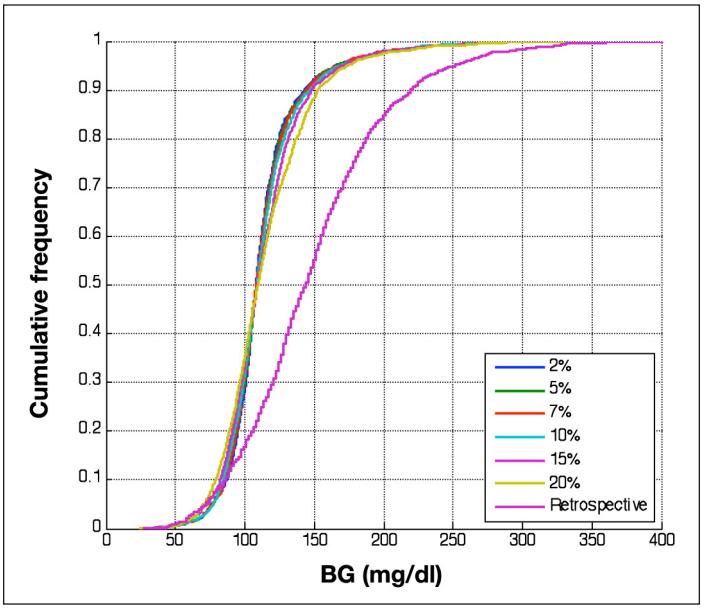

Figure 7. Empirical CDFs of model-based controller results incorporating sensor error compared to retrospective hospital control. The main group of CDFs represent 2–20% sensor error for the model-based controller as summarized in **Table 6**.

Table 7 shows BG control performance metrics for the BG-concentration-based variable measurement frequency scheme. This measurement scheme resulted in lower time in target BG band, higher median BG, and wider BG IQR. This result is emphasized in **Figure 8**, which compares results from constant measurement frequencies to the BG-concentration-based measurement scheme and retrospective data. The retrospective and BG-concentration-based measurement frequency results fall below a linear line through the constant measurement frequency results. Thus these measurement frequency schemes do not make a more optimal use of the measurements available compared to the clinically easier regular measurement frequency.

Table 8 shows the effect of using the stochastic model to further optimize interventions. These virtual trials include 7% simulated BG sensor error and 2 h measurement intervals. The lower 5% limit of the forecast bound was set to 72 mg/dl. If the lower 5% of predicted BG was below 72 mg/dl, a guaranteed maximum risk, the controller would reduce the insulin infusion rate until the lower bound was above the threshold. The stochastic model reduced BG measurements less than 72 and 47 mg/dl and reduced the LBG-P ratio, thus lessening the risk and extent of hypoglycemia.

Table 7.
Blood Glucose Controller Performance for Blood-Glucose-Based Measurement Interval Scheme

Number of measurements	1407
% measurements within 72–126 mg/dl	55%
% measurements <72 mg/dl	4.1%
% measurements <47 mg/dl	0.40%
BG median	119 mg/dl
BG IQR	101–144 mg/dl

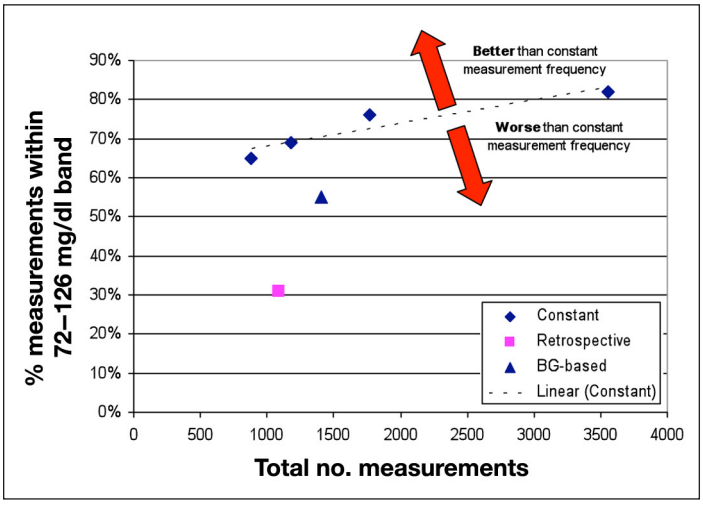

Figure 8. Blood glucose within target band compared to measurement frequency for constant and BG-concentration-based measurement frequency schemes and retrospective data.

Clinical Pilot Trials

Trial patient 1, shown in **Figure 9**, was on insulin overnight before the study commenced. The controller maintained BG within the target band throughout the majority of the trial. This patient had several extra blood gases taken due to changes being made in the mechanical ventilation, and these measurements were also used to adjust the insulin infusion rate. This patient had comparatively high insulin sensitivity, and thus most BG measurements were toward the lower end of the BG forecast range. Median BG prediction accuracy was 9.8% for an average BG measurement interval of 1.8 h.

Trial patient 2, shown in **Figure 10**, received 34–60% of total dextrose from glucose administered with morphine and dobutamine solutions due to critical illness. The controller achieved a steady decrease in BG from 259 mg/dl over 10 h to the target band. At approximately 27 h, the patient self-extubated and was in a stressed condition, resulting in a sharp rise in BG at the end of the trial. Arterial access was lost, and the study was stopped after 20 h of control. Median BG prediction accuracy was 8.8% for an average BG measurement interval of 2.0 h.

Discussion

Hyperglycemia has been linked to worsening outcomes for premature infants. However, there is currently no set protocol or best-practice method available. The success

Table 8.
Blood Glucose Controller Performance Incorporating Stochastic Model Generated from Fitted Insulin Sensitivity Profiles for Patients in Table 4

	No stochastic forecasts	Stochastic model
% measurements within 72–126 mg/dl	76%	76%
% measurements <72 mg/dl	3.4%	3.2%
% measurements <47 mg/dl	0.45%	0.34%
Num. patients with a measurement <47 mg/dl	4	4
BG median	108	108
BG IQR	97–122	97–122
LBG-P ratio	0.59	0.44

of model-based control in limited trials in adult intensive care patients[33,34] and a model-derived protocol developed from model-based simulations in large-scale clinical implementation[10] suggest that an adaptive, patient-specific, model-based approach could provide a useful tool for metabolic management in neonates.

Insulin sensitivity is well established as a time-varying, patient-specific aspect of metabolism that may be influenced by level of critical illness[63–66] and interventional procedures,[67,68] and any protocol to dose insulin must be continuously adjusted to account for and track changes in insulin response. The model-based control scheme presented in this study identifies insulin sensitivity during each intervention cycle presented in **Figure 1**. Thus the controller can account for changes in insulin sensitivity that may result from clinical interventions or changes in patient condition.

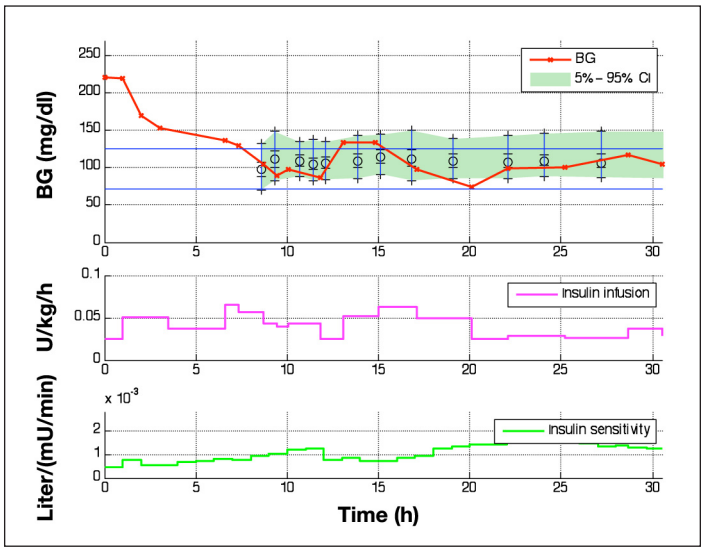

Figure 9. Neonatal intensive care unit clinical control trial 1. The top panel shows BG response with stochastic model forecasts (shaded area), the second panel shows insulin infusion rate as determined by the controller, and the bottom panel shows model-fitted insulin sensitivity. CI, confidence interval.

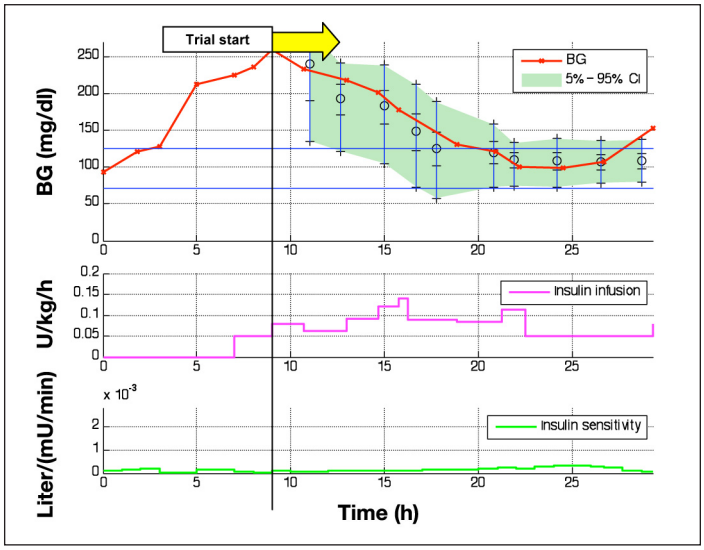

Figure 10. Neonatal intensive care unit clinical control trial 2. The top panel shows BG response with stochastic model forecasts (shaded area), the second panel shows insulin infusion rate as determined by the controller, and the bottom panel shows model-fitted insulin sensitivity. CI, confidence interval.

The overall design goal for the model-based control was to manage patient variability to achieve a consistent glycemic level despite changes in patient condition and response to insulin. An example of this goal is shown in **Figure 5**, where retrospective glycemic level closely follows the inverse of the insulin sensitivity curve. The model-based control glycemic level in **Figure 5** is less influenced by the level of insulin sensitivity and demonstrates the goal of removing the tight correlation of insulin sensitivity and glucose level. Improved glycemic control can improve insulin sensitivity over the course of several days in intensive care in adults.[10,69] This longer-term effect cannot be predicted in simulation and represents a limitation of these simulations. The potential for a controller to improve glycemic outcome depends on the ability to handle patient changes between interventions, typically over the course of several hours. Improvements in insulin sensitivity resulting from tighter glucose control can be considered another source of patient variability over periods of several days.[69]

Interestingly, despite the targeted BG controller using model-based BG forecasts to implement insulin dosage, the implementation of limits on maximum insulin rate and rate of change of insulin infusions produced noticeable variations in controller quality, as evidenced by the spread of times in relevant glycemic bands and the LBG-P ratio shown in **Table 3**. This result highlights the dynamic, evolving nature of the neonatal patient and emphasizes the importance of frequent BG measurement and control cycles. Future work may look at patient-specific stochastic models of insulin sensitivity to capture periods of high glycemic variability and further refine controller performance.

The results for the sliding scale protocol showed very little variation over the 1 to 4 h measurement intervals simulated. This may be due to the very discrete nature of the sliding scale used and perhaps highlights that more frequent measurement must be combined with a more refined protocol in order to safely achieve glycemic reductions and control.

The results of this study show that time in a relevant glycemic band is a clearer indication of control performance than a median value when comparing control protocols. The median BG did not change significantly for most, if not all, cases. However, time in band decreased dramatically in the presence of long measurement intervals out to 4 h, indicating increased glycemic variability and thus potentially worse outcomes.[16,70] The BG IQR width also showed these changes in BG variability. However, time in band provides an easy-to-visualize method of comparison. Finally, CDFs provide the means to both compare protocols and obtain proportion of measurements in any preferred glycemic band. Total time within a target band may be obtained from simulated BG curves and provide a measure of glycemic control independent of measurement and intervention frequency.

As much as possible, accurate, safe glycemic control requires a complete and accurate knowledge of the model inputs. The integral-based fitting method provides robustness by effectively acting as a low-pass filter to reduce the effect of noise in BG concentration sensing, as shown by the relatively robust results of **Table 6**. As well as BG concentration, the history of insulin and nutrition administration needs to be accurate to effectively determine patient-specific and/or time-varying parameters. Thus efficient data flow is an important design concern to minimize time-consuming and error-prone bedside data entry.

Clinical implementation requires efficient use of clinical staff time and hospital resources. Measurement frequency is often a balance between nursing burden and accuracy of control.[71,72] An additional aspect to more frequent BG measurement specific to the neonatal case is that the doors to the incubator are open more often, which may negatively affect the infant's hydration status.[73] The frequency of measurement and intervention and the effects of noise in BG measurement equipment are readily incorporated into simulation to determine the effects of these parameters.

Optimization of control with respect to frequency of BG measurement is an important design factor for the low-blood-volume neonate. Simulation results for constant measurement frequency schemes are presented in **Tables 4** and **5** and show the level of trade-off between frequent BG measurement and quality of glycemic control. Variable frequency BG measurement schemes are explored in Reference 38, and control may be customized to practices in specific neonatal units, with the results of **Tables 4** and **5** providing an expected overall level of glycemic control.

Pump flow rates in neonatal intensive care are typically very low, given the very small doses. Pump accuracy can affect the quality of control as well as insulin adsorption to pump tubing.[74,75] This effect can be minimized by either adding albumin to the insulin mixture or flushing the infusion pump tubing with insulin solution prior to use. Christchurch Women's Hospital flushes all insulin tubing to minimize the adsorption effect.[74,75] Thus this effect is not evident or embedded in the retrospective data used in this study. Insulin delivery factors such as pump accuracy and insulin adsorption can serve as potentially larger sources of apparent insulin sensitivity variability in the neonate compared to the adult, and insulin-handling protocols such as tubing flushing and priming should be standardized to improve repeatability between NICU wards and patients.

The ideal range for BG concentration in neonatal intensive care is under debate.[1,76] Unlike adults, a major proportion of energy for brain metabolism is provided by fuels other than glucose (e.g., ketones).[29] Thus the neonatal brain may be more resistant to hypoglycemia compared to the adult. However, persistent low BG concentration (<47 mg/dl) can reduce cerebral development and lead to long-term neurological deficiencies.[77] Likewise, the upper limit for clinically desirable BG concentration is also subject to debate.[1] For this study, the range of 72–126 mg/dl as used in several adult studies was targeted. However, to date, no outcome-based study has provided a specific insight or result in this regard.

A paper-based protocol [Specialised Relative Insulin Nutrition Tables (SPRINT)] developed from a similar model has been used on 394 adult intensive care patients.[10] The SPRINT protocol uses 1–2 h measurement intervals and modulates both insulin and nutrition to achieve tight glycemic control. The protocol targets a 72–110 mg/dl BG band and achieved 79% of measurements within the 72–126 mg/dl band, which is similar to the 82% and 76% of simulated measurements in this study within the same band using 1 and 2 h measurement frequencies. The addition of nutrition modulation provides another pathway for BG reduction that can be effective during periods of very low insulin sensitivity, particularly as adults appear to exhibit greater insulin effect saturation than preterm neonates.[78] In contrast, extremely preterm infants lack substantial endogenous stores of energy and thus must be fed constantly to maintain basal energy expenditure and provide excess for growth.[28] Therefore, any similar system for neonates would likely be an "insulin-only" controller or one that sought to maximize nutritional inputs.

Interestingly, incorporating the stochastic model resulted in a relatively small control improvement as shown in **Table 8**. While it appears the stochastic model was not able to prevent a period of hypoglycemia, it did limit the length of time spent at hypoglycemic BG concentrations. Analysis of the model-fitted BG curve indicated a total of 8.8 h over all patients was spent at a BG concentration of <2.6 mmol/liter when the stochastic model was used, an 18% reduction from 10.7 h without the stochastic model. The stochastic modeling approach employed here was originally developed for adult critical care, which used a lower target BG concentration of 90 mg/dl,[61,62] compared to 108 mg/dl used in this study. Thus the higher target for this initial neonatal controller avoids some hypoglycemia, and it is expected the incorporation of the stochastic model would have a greater effect at lower target BG concentrations.

The two clinical pilot trials presented in **Figures 9** and **10** provide an initial demonstration of clinical implementation of the results of the virtual simulation controller development method. The attending clinical was permitted to override the model-based insulin rates during the trials; however, the attending doctors approved every insulin rate change. The level of insulin sensitivity for the second trial patient was much lower compared to the first trial patient. The model-based controller reacted to the identified differences in insulin sensitivity in real time to adjust insulin dosing to maintain control. Thus the controller is able to adapt to interpatient variations in glycemic response in a clinical setting, as indicated by the simulation results presented in **Figure 3**. The virtual trial environment allowed a range of clinical scenarios to be tested in simulation, allowing the successful implementation of the controller into the busy neonatal clinical environment. Future trials to comprehensively validate the control methodology would include model-based insulin control for the entire length of time on insulin and quantitative evaluation model prediction performance of efficacy of control over a larger range of patients to assess model applicability and any potential refinements.

Further improvements to the model could incorporate daily nutritional and volume goals that can be set by clinicians with model-based targeted control taking care of glycemia, thus relieving clinical staff from estimation and *ad hoc* decision making. The ideal content and composition of nutritional regimes for preterm infants is still under debate.[31] The appropriate proportions of dextrose, protein, and lipids given in the NICU may be different to what an infant receives *in utero*. While the relevant major organs express many of the biological mechanisms responsible for glucose regulation from a relatively early age, the fetus depends on the mother to control energy supply. Thus the controller is essentially attempting to replicate some of the mother's functions, as well as account for the synchronized processes that regulate fetal growth that are perturbed by premature birth and life outside the womb.

Conclusions

This study presents an adaptive, model-based predictive controller designed to incorporate the unique metabolic state of the neonate. The controller was developed in virtual trial simulations on a 25-patient cohort, and results were compared to retrospective hospital control data. Time in the target 72–126 mg/dl band was increased by up to 161% over hospital control using more insulin. Despite increased insulin use, the level of low or hypoglycemic BG levels was reduced, clearly highlighting both the profile or path-dependent nature of insulin dosing as well as the patient specificity and/or robustness of the model-based approach presented. The effects of measurement frequency and BG sensor error were evaluated, and a stochastic model was seen to provide further protection against hypoglycemia by providing a guaranteed maximum risk (5%) of BG less than 72 mg/dl. Clinical pilot trials confirmed the safety and efficacy of the model-based system to control glycemia to a target glucose range prior to a larger pilot study.

Funding:

This study was supported by the New Zealand Tertiary Education Commission.

References:

1. Cowett RM, Farrag HM. Selected principles of perinatal-neonatal glucose metabolism. Semin Neonatol. 2004;9(1):37–47.
2. Dweck HS, Cassady G. Glucose intolerance in infants of very low birth weight. I. Incidence of hyperglycemia in infants of birth weights 1,100 grams or less. Pediatrics. 1974;53(2):189–95.
3. Ditzenberger GR, Collins SD, Binder N. Continuous insulin intravenous infusion therapy for VLBW infants. J Perinat Neonatal Nurs. 1999;13(3):70–82.
4. Thabet F, Bourgeois J, Guy B, Putet G. Continuous insulin infusion in hyperglycaemic very-low-birth-weight infants receiving parenteral nutrition. Clin Nutr. 2003;22(6):545–7.
5. Hemachandra AH, Cowett RM. Neonatal hyperglycemia. Pediatrics Rev. 1999;20:16–24.

6. Goldman SL, Hirata T. Attenuated response to insulin in very low birthweight infants. Pediatric Res. 1980;14(1):50–3.
7. Farrag HM, Cowett RM. Glucose homeostasis in the micropremie. Clin Perinatol. 2000;27(1):1–22.
8. Van den Berghe G, Wouters P, Weekers F, Verwaest C, Bruyninckx F, Schetz M, Vlasselaers D, Ferdinande P, Lauwers P, Bouillon R. Intensive insulin therapy in the critically ill patients. N Engl J Med. 2001;345(19):1359–67.
9. Krinsley J. Decreased mortality of critically ill patients with the use of an intensive glycemic management protocol. Crit Care Med. 2003;31:A19.
10. Chase JG, Shaw G, Le Compte A, Lonergan T, Willacy M, Wong XW, Lin J, Lotz T, Lee D, Hann C. Implementation and evaluation of the SPRINT protocol for tight glycaemic control in critically ill patients: a clinical practice change. Crit Care. 2008;12(2):R49.
11. Ertl T, Gyarmati J, Gaál V, Szabó I. Relationship between hyperglycemia and retinopathy of prematurity in very low birth weight infants. Biol Neonate. 2006;89(1):56–9.
12. Garg R, Agthe AG, Donohue PK, Lehmann CU. Hyperglycemia and retinopathy of prematurity in very low birth weight infants. J Perinatol. 2003;23(3):186–94.
13. Agus MS, Javid PJ, Ryan DP, Jaksic T. Intravenous insulin decreases protein breakdown in infants on extracorporeal membrane oxygenation. J Pediatr Surg. 2004;39(6):839–44.
14. Agus MS, Javid PJ, Piper HG, Wypij D, Duggan CP, Ryan DP, Jaksic T. The effect of insulin infusion upon protein metabolism in neonates on extracorporeal life support. Ann Surg. 2006;244(4):536–44.
15. Van den Berghe G, Wilmer A, Milants I, Wouters PJ, Bouckaert B, Bruyninckx F, Bouillon R, Schetz M. Intensive insulin therapy in mixed medical/surgical intensive care units: benefit versus harm. Diabetes. 2006;55(11):3151–9.
16. Krinsley JS. Glycemic variability: a strong independent predictor of mortality in critically ill patients. Crit Care Med. 2008;36(11):3008–13.
17. Beardsall K, Vanhaesebrouck S, Ogilvy-Stuart AL, Vanhole C, Palmer CR, van Weissenbruch M, Midgley P, Thompson M, Thio M, Cornette L, Ossuetta I, Iglesias I, Theyskens C, de Jong M, Ahluwalia JS, de Zegher F, Dunger DB. Early insulin therapy in very-low-birth-weight infants. N Engl J Med. 2008;359(18):1873–84.
18. Collins JW Jr, Hoppe M, Brown K, Edidin DV, Padbury J, Ogata ES. A controlled trial of insulin infusion and parenteral nutrition in extremely low birth weight infants with glucose intolerance. J Pediatr. 1991;118(6):921–7.
19. Vaucher YE, Walson PD, Morrow G III. Continuous insulin infusion in hyperglycemic, very low birth weight infants. J Pediatr Gastroenterol Nutr. 1982;1(2):211–7.
20. Binder ND, Raschko PK, Benda GI, Reynolds JW. Insulin infusion with parenteral nutrition in extremely low birth weight infants with hyperglycemia. J Pediatr. 1989;114(2):273–80.
21. Ng SM, May JE, Emmerson AJ. Continuous insulin infusion in hyperglycaemic extremely-low-birth-weight neonates. Biol Neonate. 2005;87(4):269–72.
22. Ostertag SG, Jovanovic L, Lewis B, Auld PA. Insulin pump therapy in the very low birth weight infant. Pediatrics. 1986;78(4):625–30.
23. Kanarek KS, Santeiro ML, Malone JI. Continuous infusion of insulin in hyperglycemic low-birth weight infants receiving parenteral nutrition with and without lipid emulsion. JPEN J Parenter Enteral Nutr. 1991;15:417–20.
24. Beardsall K, Ogilvy-Stuart AL, Frystyk J, Chen JW, Thompson M, Ahluwalia J, Ong KK, Dunger DB. Early elective insulin therapy can reduce hyperglycemia and increase insulin-like growth factor-I levels in very low birth weight infants. J Pediatr. 2007;151(6):611–7.
25. Vlasselaers D, Milants I, Desmet L, Wouters PJ, Vanhorebeek I, van den Heuvel I, Mesotten D, Casaer MP, Meyfroidt G, Ingels C, Muller J, Van Cromphaut S, Schetz M, van den Berghe G. Intensive insulin therapy for patients in paediatric intensive care: a prospective, randomised controlled study. Lancet. 2009;373(9663):547–56.
26. Hey E. Hyperglycaemia and the very preterm baby. Sem Fetal Neonatal Med. 2005;10(4):377–87.
27. Bottino M, Cowett RM, Sinclair JC. Interventions for treatment of neonatal hyperglycemia in very low birth weight infants. Cochrane Database Syst Rev. 2009;(1):CD007453.
28. Hume R, Burchell A, Williams FL, Koh DK. Glucose homeostasis in the newborn. Early Hum Dev. 2005;81(1):95–101.
29. Avery GB, Fletcher MA, MacDonald MG. Neonatology: pathophysiology and management of the newborn. 4th ed. Philadelphia: Lippincott; 1994.
30. Mena P, Llanos A, Uauy R. Insulin homeostasis in the extremely low birth weight infant. Semin Perinatol. 2001;25(6):436–46.
31. Hay WW Jr, Lucas A, Heird WC, Ziegler E, Levin E, Grave GD, Catz CS, Yaffe SJ. Workshop summary: nutrition of the extremely low birth weight infant. Pediatrics. 1999;104(6):1360–8.
32. Chase JG, Shaw GM, Wong XW, Lotz T, Lin J, Hann CE. Model-based glycaemic control in critical care—a review of the state of the possible. BSPC. 2006;1(1):3–21.
33. Wong XW, Chase JG, Shaw GM, Lin J, Lotz T, Hann CE. Clinical trials of active and adaptive insulin and nutrition control to control hyperglycaemia in critically ill patients. Presented at Canterbury Health Research Conference, Christchurch, 2005.
34. Plank J, Blaha J, Cordingley J, Wilinska ME, Chassin LJ, Morgan C, Squire S, Haluzik M, Kremen J, Svacina S, Toller W, Plasnik A, Ellmerer M, Hovorka R, Pieber TR. Multicentric, randomized, controlled trial to evaluate blood glucose control by the model predictive control algorithm versus routine glucose management protocols in intensive care unit patients. Diabetes Care. 2006;29(2):271–6.
35. Chase JG, Shaw GM, Lotz T, Le Compte A, Wong J, Lin J, Lonergan T, Willacy M, Hann CE. Model-based insulin and nutrition administration for tight glycaemic control in critical care. Curr Drug Deliv. 2007;4(4):283–96.
36. Hann CE, Chase JG, Lin J, Lotz T, Doran CV, Shaw GM. Integral-based parameter identification for long-term dynamic verification of a glucose-insulin system model. Comput Methods Programs Biomed. 2005;77(3):259–70.
37. Lotz TF, Chase JG, McAuley KA, Lee DS, Lin J, Hann CE, Mann JI. Transient and steady-state euglycemic clamp validation of a model for glycemic control and insulin sensitivity testing. Diabetes Technol Ther. 2006;8(3):338–46.
38. Le Compte A. Modelling the glucose-insulin regulatory system for glycaemic control in neonatal intensive care. In: Mechanical engineering. Christchurch: University of Canterbury; 2009.
39. Hovorka R, Shojaee-Moradie F, Carroll PV, Chassin LJ, Gowrie IJ, Jackson NC, Tudor RS, Umpleby AM, Jones RH. Partitioning glucose distribution/transport, disposal, and endogenous production during IVGTT. Am J Physiol Endocrinol Metab. 2002;282(5):E992–1007.
40. Wong XW, Chase JG, Shaw GM, Hann CE, Lotz T, Lin J, Singh-Levett I, Hollingsworth LJ, Wong OS, Andreassen S. Model predictive glycaemic regulation in critical illness using insulin and nutrition input: a pilot study. Med Eng Phys. 2006;28(7):665–81.
41. Farrag HM, Nawrath LM, Healey JE, Dorcus EJ, Rapoza RE, Oh W, Cowett RM. Persistent glucose production and greater peripheral sensitivity to insulin in the neonate vs. the adult. Am J Physiol. 1997;272(1 Pt 1):E86–93.

42. Poindexter BB, Karn CA, Denne SC. Exogenous insulin reduces proteolysis and protein synthesis in extremely low birth weight infants. J Pediatr. 1998;132(6):948–53.

43. Powers WJ, Rosenbaum JL, Dence CS, Markham J, Videen TO. Cerebral glucose transport and metabolism in preterm human infants. J Cereb Blood Flow Metab. 1998;18(6):632–8.

44. Ho KC, Roessmann U, Hause L, Monroe G. Newborn brain weight in relation to maturity, sex, and race. Ann Neurol. 1981;10(3):243–6.

45. Cassady G. Plasma volume studies in low birth weight infants. Pediatrics. 1966;38(6):1020–7.

46. Leipälä JA, Talme M, Viitala J, Turpeinen U, Fellman V. Blood volume assessment with hemoglobin subtype analysis in preterm infants. Biol Neonate. 2003;84(1):41–4.

47. Simpson J, Stephenson T. Regulation of extracellular fluid volume in neonates. Early Hum Dev. 1993;34(3):179–90.

48. Lorenz JM, Kleinman LI, Ahmed G, Markarian K. Phases of fluid and electrolyte homeostasis in the extremely low birth weight infant. Pediatrics. 1995;96(3 Pt 1):484–9.

49. Hartnoll G, Bétrémieux P, Modi N. Body water content of extremely preterm infants at birth. Archives Dis Child Fetal Neonatal Ed. 2000;83(1):F56–9.

50. Bidiwala KS, Lorenz JM, Kleinman LI. Renal function correlates of postnatal diuresis in preterm infants. Pediatrics. 1988;82(1):50–8.

51. Kalhan SC, Oliven A, King KC, Lucero C. Role of glucose in the regulation of endogenous glucose production in the human newborn. Pediatr Res. 1986;20(1):49–52.

52. Hertz DE, Karn CA, Liu YM, Liechty EA, Denne SC. Intravenous glucose suppresses glucose production but not proteolysis in extremely premature newborns. J Clin Invest. 1993;92(4):1752–8.

53. Cowett RM, Oh W, Schwartz R. Persistent glucose production during glucose infusion in the neonate. J Clin Invest. 1983;71(3):467–75.

54. Sunehag AL, Haymond MW, Schanler RJ, Reeds PJ, Bier DM. Gluconeogenesis in very low birth weight infants receiving total parenteral nutrition. Diabetes. 1999;48(4):791–800.

55. Tyrala EE, Chen X, Boden G. Glucose metabolism in the infant weighing less than 1100 grams. J Pediatr. 1994;125(2):283–7.

56. Van Kempen AA, Romijn JA, Ruiter AF, Ackermans MT, Endert E, Hoekstra JH, Kok JH, Sauerwein HP. Adaptation of glucose production and gluconeogenesis to diminishing glucose infusion in preterm infants at varying gestational ages. Pediatr Res. 2003;53(4):628–34.

57. Lonergan T, Le Compte A, Willacy M, Chase JG, Shaw GM, Wong XW, Lotz T, Lin J, Hann CE. A simple insulin-nutrition protocol for tight glycemic control in critical illness: development and protocol comparison. Diabetes Technol Ther. 2006;8(2):191–206.

58. Wong XW, Chase JG, Hann CE, Lotz TF, Lin J, Le Compte AJ, Shaw GM. Development of a clinical type 1 diabetes metabolic system model and in silico simulation tool. J Diabetes Sci Technol. 2008;2(3):424–35.

59. Peet AC, Kennedy DM, Hocking MD, Ewer AK. Near-patient testing of blood glucose using the Bayer Rapidlab 860 analyser in a regional neonatal unit. Ann Clin Biochem. 2002;39(Pt 5):502–8.

60. Chen ET, Nichols JH, Duh SH, Hortin G. Performance evaluation of blood glucose monitoring devices. Diabetes Technol Ther. 2003;5(5):749–68.

61. Lin J, Lee D, Chase JG, Shaw GM, Hann CE, Lotz T, Wong J. Stochastic modelling of insulin sensitivity variability in critical care. BSPC. 2006;1(3):229–42.

62. Lin J, Lee D, Chase JG, Shaw GM, Le Compte A, Lotz T, Wong J, Lonergan T, Hann CE. Stochastic modelling of insulin sensitivity and adaptive glycemic control for critical care. Comput Methods Programs Biomed. 2008;89(2):141–52.

63. McCowen KC, Malhotra A, Bistrian BR. Stress-induced hyperglycemia. Crit Care Clin. 2001;17(1):107–24.

64. Thorell A, Rooyackers O, Myrenfors P, Soop M, Nygren J, Ljungqvist OH. Intensive insulin treatment in critically ill trauma patients normalizes glucose by reducing endogenous glucose production. J Clin Endocrinol Metab. 2004;89(11):5382–6.

65. Lind L, Lithell H. Impaired glucose and lipid metabolism seen in intensive care patients is related to severity of illness and survival. Clin Intensive Care. 1994;5(3):100–5.

66. Basi S, Pupim LB, Simmons EM, Sezer MT, Shyr Y, Freedman S, Chertow GM, Mehta RL, Paganini E, Himmelfarb J, Ikizler TA. Insulin resistance in critically ill patients with acute renal failure. Am J Physiol Renal Physiol. 2005;289(2):F259–64.

67. Pagano G, Cavallo-Perin P, Cassader M, Bruno A, Ozzello A, Masciola P, Dall'omo AM, Imbimbo B. An in vivo and in vitro study of the mechanism of prednisone-induced insulin resistance in healthy subjects. J Clin Invest. 1983;72(5):1814–20.

68. Nicod N, Giusti V, Besse C, Tappy L. Metabolic adaptations to dexamethasone-induced insulin resistance in healthy volunteers. Obes Res. 2003;11(5):625–31.

69. Langouche L, Vander Perre S, Wouters PJ, D'Hoore A, Hansen TK, van den Berghe G. Effect of intensive insulin therapy on insulin sensitivity in the critically ill. J Clin Endocrinol Metab. 2007;92(10):3890–7.

70. Egi M, Bellomo R, Stachowski E, French CJ, Hart G. Variability of blood glucose concentration and short-term mortality in critically ill patients. Anesthesiology. 2006;105(2):244–52.

71. Chase JG, Andreassen S, Jensen K, Shaw GM. Impact of human factors on clinical protocol performance: a proposed assessment framework and case examples. J Diabetes Sci Technol. 2008:2(3):409–16.

72. Mackenzie I, Ingle S, Zaidi S, Buczaski S. Tight glycaemic control: a survey of intensive care practice in large English hospitals. Intensive Care Med. 2005;31(8):1136.

73. Hartnoll G. Basic principles and practical steps in the management of fluid balance in the newborn. Semin Neonatol. 2003;8(4):307–13.

74. Hewson M, Nawadra V, Oliver J, Odgers C, Plummer J, Simmer K. Insulin infusions in the neonatal unit: delivery variation due to adsorption. J Paediatr Child Health. 2000;36(3):216–20.

75. Fuloria M, Friedberg MA, DuRant RH, Aschner JL. Effect of flow rate and insulin priming on the recovery of insulin from microbore infusion tubing. Pediatrics. 1998;102(6):1401–6.

76. Alsweiler JM, Kuschel CA, Bloomfield FH. Survey of the management of neonatal hyperglycaemia in Australasia. J Paediatr Child Health. 2007;43(9):632–5.

77. Lucas A, Morley R, Cole TJ. Adverse neurodevelopmental outcome of moderate neonatal hypoglycaemia. BMJ. 1988;297(6659):1304–8.

78. Rizza RA, Mandarino LJ, Gerich JE. Dose-response characteristics for effects of insulin on production and utilization of glucose in man. Am J Physiol. 1981;240(6):E630–9.