Modeling the glucose regulatory system in extreme preterm infants

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Abstract

BACKGROUND
Premature infants represent a significant proportion of the neonatal intensive care population. Blood glucose homeostasis in this group is often disturbed by immaturity of endogenous regulatory systems and the stress of their condition. Hypo- and hyperglycemia are frequently reported in very low birth weight infants, and more mature infants often experience low levels of glycemia. A model capturing the unique fundamental dynamics of the neonatal glucose regulatory system could be used to develop better blood glucose control methods.

METHODS
A metabolic system model is adapted from adult critical care to the unique physiological case of the neonate. Integral-based fitting methods were used to identify time-varying insulin sensitivity and non-insulin mediated glucose uptake profiles. The clinically important predictive ability of the model was assessed by assuming insulin sensitivity was constant over prediction intervals of 1, 2 and 4 hours forward and comparing model-simulated versus actual clinical glucose values for all recorded interventions. The clinical data included 1,091 glucose measurements over 3,567 total patient hours, along with all associated insulin and nutritional infusion data, for N=25 total cases. Ethics approval was obtained from the Upper South A Regional Ethics Committee for this study.

RESULTS
The identified model had a median absolute percentage error of 2.4% [IQR: 0.9%-4.8%] between model-fitted and clinical glucose values. Median absolute prediction errors at 1, 2 and 4-hour intervals were 5.2% [IQR: 2.5%-10.3%], 9.4% [IQR: 4.5%-18.4%] and 13.6% [IQR: 6.3%-27.6%] respectively.

CONCLUSIONS
The model accurately captures and predicts the fundamental dynamic behaviors of the neonatal metabolism well enough for effective clinical decision support in glycemic control. The adaptation from adult to a neonatal case is based on data from literature. Low prediction errors and very low fitting errors indicate that the fundamental dynamics of glucose metabolism in both premature neonates and critical care adults can be described by similar mathematical models.

Introduction

Premature infants commonly demonstrate poor glycemic control. Physiologically, the neonate is in a transitional state from the complete dependence of the foetus to the complete independence of older infants and adults [1]. Hyperglycemia occurs in 40-80% of very low birth weight infants in the neonatal intensive care unit (NICU) [1, 2]. The incidence of hyperglycemia increases with degree of prematurity and lower birth weight. Hypoglycemia is also a commonly reported perturbation in glucose homeostasis in both very low birth weight infants and more mature neonates [3, 4]. An increasing body of literature links hyperglycemia to worsened outcomes in preterm neonates, but there have been no studies of sufficient power to demonstrate whether hyperglycemia itself is harmful, or is merely a reflection of disease severity. Associated morbidities include sepsis, increased ventilator dependence, retinopathy of prematurity, hospital length of stay, osmotic diuresis, electrolyte imbalance and intraventricular haemorrhage [5-11].

Conditions that cause stress to the infant increase the risk of hyperglycemia [12]. Increased secretion of counter-regulatory hormones due to the stress of their condition leads to a prominent rise in endogenously produced glucose and the rate of hepatic gluconeogenesis, as well as a reduction in insulin sensitivity. Nutritional support regimes with high carbohydrate content are also provided to increase neonate weight, but often compound the counter-regulatory response [10]. Additionally, lipids and lipid components in nutritional inputs, particularly free fatty acids, can promote hyperglycemia [13].

Hyperglycemic infants are often treated by glucose restriction [13-15]. However, prolonged severe glucose restriction may adversely affect the infant's nutritional status and may also be a reason for poor

growth observed in these infants [14]. Hence, there is a need to balance the adverse effects of hyperglycemia with the need to provide enough nutrition to promote growth. As a result, there is an increasing use of insulin to help maintain both normal glucose levels and glucose uptake [16, 17].

Insulin is an anabolic hormone and promotes growth, while lowering glucose levels. However, endogenous deficiency or lack of effect due to high insulin resistance will have a negative impact on glycemic levels [14]. Additionally, studies have shown reduced proteolysis, and thus preservation of muscle mass associated with insulin therapy [18, 19], independent of glucose infusion [20]. However, in the neonate, immature insulin processing can also produce excessive pro-insulin, which is approximately 16x less effective than regular adult insulin, which may also explain why some poor control is exhibited in this population [21].

Tight blood glucose control in an adult intensive care population has been shown to reduce morbidity and mortality by up to 45% for patients with stays greater than 2 days [22-24]. Several recent studies have associated hyperglycemia with increased morbidity and mortality in neonatal cohorts [7-9]. Ertl et al [5] and Garg et al [6] linked hyperglycemia with increased risk of retinopathy of prematurity. Limited trials of glucose control using insulin in neonates have been reported [14, 18, 25-30], and insulin therapy did help to improve glucose tolerance in these limited trials.

Model based glycemic control methods using both insulin and/or nutrition modulation have been employed successfully in the control of hyperglycemia in adult critical care populations, as reviewed in Chase et al [31]. Model based methods allow information about the metabolic state of the patient, and infant in this case, to be inferred from serial blood glucose measurements and records of nutrition and insulin administration [32, 33]. Therefore, a model capturing the fundamental dynamics of the neonatal

glucose regulatory system could be used to develop methods to better control blood glucose levels in this cohort, while also enhancing nutritional support and improving outcomes.

This paper presents the adaptation and validation of a metabolic system model for glucose control from adult critical care to the unique clinical and physiological case of the neonate.

Methods

Patient cohort

Retrospective data from 25 episodes of insulin therapy treatment in the Christchurch Women's Neonatal Intensive Care Unit was used in the study. These infants were not part of any clinical trial, and were selected based on receiving insulin as a standard treatment for hyperglycemia, as insulin infusion data is a requirement to accurately produce model fits. All infants received IV insulin mixed with 0.9% saline administered using similar infusion sets, and insulin tubing was flushed with concentrated insulin solution prior to use to minimize adsorption. Ethics approval for the collection and publication of data was obtained from the Upper South A Regional Ethics Committee.

The clinical details of the cohort are shown in Table 1. The 25 episodes of insulin usage comprised 21 individual patients representing 3,567 hours of patient data. The data set used for model fitting contained 1,091 blood glucose measurements, and totals of insulin and dextrose administered every hour. Gestational age at birth ranged from 23 to 28.9 weeks, and birth weight ranged from 600 to 1,280 grams. Inclusion criteria were birth weight less than 1,500 grams and a period of treatment with insulin of at least 12 hours. Insulin was commenced when blood glucose concentration was persistently above 10 mmol/L, at the discretion of the attending clinician, and insulin rate was titrated to blood glucose level. Dextrose infusion rates were determined by the attending clinician. The majority of blood glucose concentrations (74%) were measured with the Bayer 850 blood gas analyzer (Bayer AG, Leverkusen, Germany), with the remaining measurements taken using the bedside GluoCard (Arkray, Inc., Kyoto, Japan) and i-Stat (Abbott Laboratories, Illinois, USA) devices. The reported coefficients of variation for glucose measurements for the blood gas analyzer, GlucoCard and i-Stat devices were 4.9% [34], 2.4-6.3%[35, 36], and 2.0-3.5% [37] respectively.

System model

The system model used in this research is based on a clinically validated glucose regulatory system model for adult intensive care patients [32, 33]. The model has been modified to account for the main physiological differences based on available clinical data and kinetic studies in neonates. The overall model is defined:

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

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

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

Where $G(t)$ [mmol/L] is the total plasma glucose and $I(t)$ [mU/L] is the plasma insulin, exogenous insulin input is represented by $u_{ex}(t)$ [mU/min] and basal endogenous insulin secretion I_B [mU/L/min], with k_I [L/mU.min] 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/L], 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 effect are p_G [1/min] and S_I [L/(mU.min)], respectively. The parameter $V_{I,frac}$ [L/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 $P(t)$ [mmol/min], endogenous glucose production is denoted by P_{END} [mmol/kg/min] and $V_{G,frac}(t)$ [L/kg] represents the glucose distribution volume per kilogram of body weight. CNS [mmol/kg/min] represents non-insulin mediated glucose uptake by the central nervous system. 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.

Parameter values

Table 2 summarizes the parameters used in this model with supporting clinical references. For this study, k, n, α_I, α_G, *CNS*, I_B and $V_{I,frac}(t)$ are set to generic population values based on reported data. Prior clinical and model sensitivity studies with the similar adult model [33, 38] have shown this choice to be robust with respect to prediction of response to clinical interventions.

The distribution of fluids in the neonatal body is markedly different from children and adults. In particular, the extra-cellular fluid compartment is a much higher percentage of total body weight [39-41]. It can also decrease over time as very preterm neonates can pass through a diuretic stage in the first few days of life [40, 42], and this contraction of the extra-cellular fluid compartment may be a major contributor to weight loss in infants of this gestation and postnatal age [43]. Hence, a population-based, time-varying volume of glucose distribution as a proportion of body weight was created for the parameter $V_{G,frac}(t)$ based on the clinical data shown in Figure 1 [43, 44]. The distribution volume for insulin $V_{I,frac}$ was set to a neonatal plasma volume of approximately 4.5% of the body weight expressed in kilograms [44, 45]. The most recently measured body weight was used in parameter value calculations, and was generally updated every 2 to 3 days.

The parameter *CNS* represents non-insulin mediated glucose uptake by the central nervous system. In contrast to the adult case, the brain represents a major source of glucose uptake in infants, due to their larger brain-to-body weight ratio [20, 46]. Glucose metabolism by the brain is relatively constant [47] and independent of insulin concentration [1]. The value used for *CNS* in this study was 8.8μmol/min/100g brain weight (0.088 mmol/min/kg brain weight) based on [48], where the average brain weight of the preterm infant at the age used in this cohort was estimated at 14% of body weight [49].

With respect to saturation effects, Farrag et al [46] found no plateau in the rate of glucose uptake at several increasing levels of insulin infusion during clamp tests. This result suggests that insulin mediated glucose uptake does not saturate at the insulin delivery rates typically encountered in neonatal intensive care. Therefore, the parameter representing saturation of insulin mediated glucose uptake, α_G, was set to zero in this study. This lack of saturation effect is significantly different to the adult case, where the significant glucose uptake saturation can occur [38, 50-52].

The parameter n represents the disappearance of insulin from plasma. Factors influencing this parameter include transport into the interstitial space and removal by the liver and kidneys. Farrag, et al identified that the rate of insulin clearance was much higher in neonates compared to a group of healthy adults [46]. In this study, a value of $n = 0.9$ was used, compared to 0.16 in adults [33], as derived from neonatal insulin infusion studies [18, 19, 46, 53].

The parameter I_B represents basal insulin secretion in the presence of no exogenous insulin input. This parameter provides an estimate of basal insulin secretion to better model the actual physiological situation. It also makes the model robust to the sometimes frequent periods where no exogenous insulin is administered. This parameter was set to a population constant of 10 mU/L/min to achieve steady state basal insulin concentrations similar to reported clinical results [46, 53]. It is assumed that exogenous insulin administration suppresses endogenous insulin secretion and the parameter k_I broadly captures this suppression effect. Published clinical data was not available to quantify the effective life of insulin (k) and plasma insulin disappearance saturation parameters (α_I), and it was therefore assumed that these values do not significantly differ from adults [33]. It should also be noted that a constant excretion would be expected in the presence of relatively constant nutritional infusions. The resulting plasma insulin model was compared to reported plasma insulin concentrations from constant insulin infusion studies in neonates [18, 19, 46, 53, 54].

The parameter P_{END} represents endogenous glucose production, which can be measured in tracer studies [20, 53, 55-59]. Endogenous glucose production is decreased in the presence of increased blood glucose concentration and increased plasma insulin concentration [59, 60]. Because of the fragile nature of this population the true fasting rate of glucose production cannot be determined. In addition, almost all such studies are performed concurrently with parenteral nutrition to avoid underfeeding the low birth weight neonate. Figure 2 plots the average endogenous glucose production against blood glucose concentration for the available literature reporting tracer studies in preterm neonates [20, 53, 55-59]. At $G=0$, the p_G and S_I terms in Equation 1 become zero. Thus, the range of values for $P_{END} =$ [0.0172 to 0.0312 mmol/kg/min] suitable for this model formulation were obtained from Figure 2 at $G=0$ (the intercept with the y-axis). Bootstrapping with replacement (N=1000) was used to determine the mean intercept and the upper and lower 5% of possible intercepts that define this range.

Parameter identification and sensitivity analysis

The parameters P_{END}, p_G and S_I are the remaining parameters to explicitly determine from the data. As a result of using P_{END} at $G=0$, the parameters p_G and S_I incorporate the effects of insulin and blood glucose concentration to inhibit endogenous glucose production. Finally, the range of P_{END} in Figure 2 delimits the acceptable values for this parameter, but not a specific population of patient-specific value.

A grid search was performed to determine the optimal population values of P_{END} and p_G for this cohort. In particular, p_G was found to be relatively constant in an adult intensive care population [33], and is initially assumed so here.

To this end, the time-varying parameter S_I was fitted to the clinical data using several values of P_{END} held constant within the range of [0.01442 – 0.03396] mmol/kg/min based on Figure 2. The range of

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P_{END} assessed in simulation extends beyond the 5%-95% range shown in Figure 2 to more fully observe the effect of this model parameter. The value of p_G was also held constant within the range [0.0005 – 0.02] min^{-1}. This range of p_G is based on a range of adult results with no further data available for the neonate.

The insulin effect parameter, S_I, is allowed to vary every hour. The integral-based fitting method of Hann et al [33] was employed for identifying S_I over time using retrospective blood glucose concentrations (G), insulin administration ($u_{ex}(t)$) and nutritional infusion rates ($P(t)$). The resulting time-varying S_I profile smoothed using a 3-point moving average to reduce the effects of sensor noise. The smoothed S_I profile was then used to generate a model derived BG curve to compare to the clinical data and thus assess the model. A total of 2,000 such assessments were made over the ranges of p_G and P_{END} for the 25 patient cohort with S_I identified for each (p_G, P_{END}) set of values. The optimal P_G and P_{END} values are presented in the Results and Table 2.

The population constants α_G, α_I, CNS, k, n, V_G and V_I were then varied by -50%, -10%, +10% and +50% to address model sensitivity to a particular patient constant and the appropriateness of using a particular population-based constant. The retrospective cohort data was re-fitted for each parameter variation and model performance assessed using BG fit and prediction analyses.

The median and IQR of absolute fitting error and prediction error were the metrics used to compare the ability of the model to fit the data for any set of parameters. Fitting error was assessed by analyzing the absolute percentage difference between measured blood glucose concentration and identified model generated blood glucose concentration. Prediction error is clinically more important and was assessed over 1, 2, 3 and 4-hour intervals. Predictions were generated at each blood glucose measurement by holding all parameter values, in particular S_I, constant over the prediction interval and performing a

forward simulation of Equations (1)-(3). Only data up to that time point are used in forward predictions. This method reflects the use of this model in adult critical care trials. Prediction error was analyzed by comparing the error between the predicted blood glucose concentration and its measured value, or where a measurement was not available the prediction was compared to a linearly interpolated value between two appropriate blood glucose measurements. The optimal or best (p_G, P_{END}) values are thus those that provide the best outcomes in these fitting and prediction metrics.

Results

Plasma insulin model

Figure 3 shows the plasma insulin model and population constants are valid for a wide range of reported insulin concentrations from steady exogenous insulin infusions. Typical insulin infusion rates expected in neonatal control scenarios would occupy the left half of the range shown in Figure 3, below 0.3 U/kg/hr. Agus and colleagues [10, 11] used supra-physiological concentrations of insulin to determine the effects of insulin on protein breakdown. Thus, they provide further data points but at clinically irrelevant values.

Typical steady state insulin concentrations for the adult insulin model for similar weight-based rates of insulin infusion are shown in Figure 3. Neonatal plasma insulin concentrations are significantly lower than adults for similar weight-adjusted rates of exogenous insulin infusion [39]. This result may represent a much higher metabolic clearance rate of insulin in the neonate. To date, the specific mechanisms that create a higher metabolic clearance rate in neonates remain as open questions. The goal of this study was to generate a model designed for control purposes that matches observable insulin kinetics in the neonate and further investigation of physiological mechanisms of insulin transport is outside the scope of this research.

Parameter and sensitivity analysis

Figure 4 shows that fit error plateaus at minimum levels for values of $p_G \leq 0.01$ min^{-1} and $P_{END} \geq 0.02$ mmol/kg/min. These results suggests that a range of values for p_G and P_{END} will provide robust fitting and prediction performance. Figure 4 also shows the 1, 2, 3 and 4-hour prediction errors over these same ranges result in similar plateaus of minimal error for $p_G < 0.01$ min^{-1} and $P_{END} > 0.02$ mmol/kg/min.

The sum of the maximum five BG fitting errors per patient profile was used to choose the optimum values of p_G and P_{END}. The combination of $p_G = 0.003$ min^{-1} and $P_{END} = 0.02838$ mmol/kg/min provided the smallest sum of maximum fitting errors across the entire cohort. These final values are also shown in the lower part of Table 2. Thus, an example of the resulting model for a 750 gram infant born at 28 weeks gestational age, receiving an insulin infusion of 0.05 U/kg/hr and a dextrose infusion of 8 mg/kg/min may be found by inserting the value of Table 2 into Equations (1)-(3) to yield Equations (4)-(6). The system of equations may be solved and the S_I parameter fitted using the integral-based fitting method of Hann et al [33].

$$\dot{G}(t) = -0.003[\text{min}^{-1}].G(t) - S_I.G(t).Q(t)$$
$$+ \frac{0.033[\text{mmol/min}] + \left(0.02838[\text{mmol/kg/min}] \times 0.75[\text{kg}]\right) - 0.00924[\text{mmol/min}]}{0.56[L/kg] \times 0.75[\text{kg}]} \qquad (4)$$

$$\dot{Q}(t) = -0.0086[\text{min}^{-1}]Q(t) + 0.0086[\text{min}^{-1}]I(t) \qquad (5)$$

$$\dot{I}(t) = -\frac{0.90[\text{min}^{-1}].I(t)}{1 + 1.70 \times 10^{-3}[\text{min}^{-1}].I(t)} + \frac{0.625[\text{mU/min}]}{0.045[L/kg] \times 0.75[\text{kg}]}$$
$$+ e^{\left(0.1[L/(mU.\min)]\frac{0.625[mU/\min]}{0.045[L/kg] \times 0.75[kg]}\right)} \times 10[mU/L/\min] \qquad (6)$$

The results of the population constant sensitivity analysis shown in Figure 5 indicate that model performance is relatively insensitive to the variations in population constants introduced here. The volume of glucose distribution, V_G, created the greatest effect on model performance at -50% of the population value used here, which is a very large change for a typically well known or understood parameter. A reduction of V_G of 50% brings this volume closer to the value used for adults in proportion to body weight. Thus, recognizing the increased proportion of body weight taken up as extra-cellular fluid in neonates is seen to be relevant to accurate glucose control. This last result provides a further model validation, in that good model performance requires accurate neonatal physiology where such differences to adults are known to exist.

Model performance

The median cohort model fit error was 2.4% [IQR: 0.9% - 4.8%] or 0.2 mmol/L [IQR: 0.1 – 0.4 mmol/L] for the 3,567 hours of patient data. The smoothing process attempts to remove non-physiological sources of noise such as errors in BG measurements and recorded insulin/dextrose inputs, and results in a more physiological S_I parameter profile at the expense of a potentially greater fit error. A sample parameter identifications and model-generated BG fit is presented in Figure 6.

Table 3 shows the median fitting error for all patients and the retrospective lognormal blood glucose mean, multiplicative lognormal standard deviation, median insulin use and median dextrose delivered. The results show a relatively constant level of fitting error spanning cases of relatively unstable blood glucose, indicated by a higher standard deviation and/or higher mean blood glucose. They also show varying levels of insulin and glucose administration over these same results. Thus, the model can be seen to account for a range of different patient responses, which include a range of S_I parameter values indicating these patients can be highly dynamic metabolically.

Table 4 shows the median absolute percentage prediction error for 1, 2, 3 and 4-hour prediction intervals. Results are compared to blood glucose measurements or linearly interpolated between retrospective measurements where none are available for a given interval. The cohort median prediction error was 5.2% at 1 hour, 9.4% at 2 hours, 11.9% at 3 hours and 13.6% at 4 hours. Blood glucose prediction errors did not change over time for each patient. This result also emphasizes the importance of frequent blood glucose measurement to provide tighter continuous control. Figure 7 shows the distribution of absolute blood glucose prediction error, with increasing variance as the prediction interval increases.

Figure 8 shows part of the record for Patient 13. This episode is dominated by the BG measurement of 31.2 mmol/L at 7 hours. The gradual decrease in BG over the next 11 hours suggests this measurement was not due to errors in the measuring device. This patient had severe metabolic imbalances, was relatively clinically unstable and did not survive ICU. A glucose/insulin mixture was administered at 6 hours that contained 0.26U insulin in 8mL/kg of 50% dextrose. Interestingly, the model was able to account for this relatively extreme deviation in blood glucose concentration, and accurately captured the impact of this sudden large amount of added dextrose on BG concentration.

Figure 9 shows the cumulative distribution function of the identified time-varying S_I profile for each patient, with median and 5%-95% range overlaid. Each patient's insulin sensitivity profile is unique, yet there are no significantly outlying patient profiles. Figure 10 compares histograms of the empirical cumulative distribution functions of model-fitted S_I for the neonatal cohort of this paper to 393 adult intensive care patients totaling 44,386 hours of fitted data [16]. The median S_I for neonates was 0.68×10^{-3} L/(mU.min), compared to 0.24×10^{-3} L/(mU.min) for adults, and the 5%-95% data interval was $[0.17 - 1.70] \times 10^{-3}$ L/(mU.min) for neonates and $[0.06 - 0.79] \times 10^{-3}$ L/(mU.min) for adults respectively.

Finally, Figure 11 presents the model generated fit for Patient 23 and highlights a sustained period of low S_I and large swings in blood glucose concentration. This period of unstable glycemia contrasts with a more typical patient blood glucose time-course presented in Figure 6.

Discussion

Tight glycemic control without increased risk of hypoglycemia has proven difficult to achieve in intensive care in both adults [61] and neonates [62]. Moderately elevated blood glucose levels are recently more tolerated or recommended [63] because of the fear of hypoglycemia and higher nursing effort frequently associated with TGC [64]. A recent study by Alsweiler and colleagues [65] found that while all surveyed neonatal units would consider use of insulin for hyperglycemia, the threshold for commencing insulin infusions varied, as well as the choice of glycemic management using altered dextrose infusion rates. Most units reported little to no hypoglycemia, and these findings agreed with previous surveys that found a lack of consensus on the management of neonatal hyperglycemia, possibly reflecting the lack of data available in this area [65]. Most studies of hyperglycemia and outcomes in neonates are retrospective, and it is difficult to ascertain whether high glucose levels are a cause or a symptom of conditions such as sepsis [8]. Maintenance of normoglycemia with exogenous insulin has been found to improve innate immunity and reduce catabolism, acidosis and inflammation in rabbit models of critical illness [66], which may or may not hold in the neonatal case. More prospective studies are thus required to elucidate the link between tight glucose control and neonatal outcomes. Model-based control may be useful in exploring these relationships by providing targeted glucose control whilst concurrently minimizing the risk of hypoglycemia.

Insulin sensitivity can be measured in-vivo using the euglycemic hyperinsulinemic clamp test [60], where a euglycemic concentration of glucose is maintained at several different levels of insulinemia. This clinically intensive process also requires several blood samples and is thus difficult to perform in clinically fragile low birth weight infants who also possess a relatively very small blood volume for this procedure. Three euglycemic hyperinsulinemic clamps that incorporated glucose tracer measurements

on preterm infants were available in the literature [46, 53, 67]. An additional study [45] used a modified minimal model analysis to generate an insulin sensitivity index. Results in all cases showed a significant spread of insulin sensitivities for otherwise similar infants, similar to what is seen in this study.

Figure 9 shows location and spread of the S_I parameter for this NICU cohort and Figure 10 presents a comparison of the location and spread of S_I for NICU and adult ICU patients. The range and variation of model-fitted S_I has been studied in adult critical care populations using similar models [68, 69]. However, this is the first time this form of modeling has been applied to a neonatal cohort. Two reasons for this higher median S_I in neonates are higher rates of glucose turnover and higher metabolic clearance of insulin resulting in lower plasma insulin concentrations. More specifically, Farrag et al found greater peripheral sensitivity to insulin compared to adult controls [46]. Hertz et al [20] found their estimate of non-insulin mediated glucose uptake to be similar to that of normal adults. Thus, the lower insulin concentrations and greater peripheral sensitivity to insulin in neonates suggests higher numerical values of S_I compared to adults. However, this finding may also reflect differences in endogenous glucose and insulin production between the two cohorts.

More specifically, Figure 9 shows that each patient has a uniquely identified S_I parameter profile. The intra-patient variability of response to exogenous insulin is significant in the neonate, increasing the importance of accurate identification for control. Thus, noting the wider spread in Figure 10, NICU patients exhibit high inter-patient variation relative to adults. Thus, such differences must be accounted for when designing glucose control protocols for neonates, or adapting successful protocols from the adult critical care case. An adaptive control scheme must be able to dose insulin appropriately to the unique identified patient state. As a result, it can be seen that such an adaptive method will be required to provide tight control for all patients, rather than fixed clinical protocols.

The P_{END} term represents the regulatory response of the body to endogenously produce glucose to avoid hypoglycemia. To measure the true rate of endogenous glucose production, the neonate would be required to undergo a fast for several hours, which is generally not possible for clinical and ethical reasons [15]. The estimates of basal endogenous glucose production derived in this study are higher than the values seen in adults [20, 70]. The explanation for this difference is that the extra glucose is required in infants for growth and to supply the glucose requirements of the relatively large brain in the infant compared to total body weight [71].

In particular, it has been shown that endogenous glucose production (via glycogenolysis and gluconeogenesis, primarily from the liver) may not be suppressed in the preterm infant by exogenous glucose infusions [46, 55]. Specifically, Farrag et al [46] found a maximal suppression of endogenous glucose production of 58% of basal rates. This result is in marked contrast to the healthy adult who can effectively completely suppresses endogenous glucose production [46]. However, it is similar to the critically ill adult [31, 72]. In this paper, some of this effect is captured by the parameters p_G and S_I, which incorporate contributions of increased insulin concentration [20] and plasma glucose concentration [15] to decreasing net hepatic glucose output.

Several studies have reported that many neonates produce an inadequate glucose raising response to decreases in glucose infusion [58] and to a bolus of glucagon [73]. Additionally, it has been shown that many preterm infants have concentrations of hepatic glucose-6-phosphatase, the rate limiting enzyme in gluconeogenesis, below the limit of normal term infants [74]. Glycogen stores in premature infants to produce further glucose for use are also relatively sparse [16, 74]. Low birth weight infants therefore must be fed adequately to prevent long-term deficiencies in growth and development [75]. However, initiation of feeding has also been linked to hyperglycemia [10, 13]. Thus, control of hyperglycemia

whilst maintaining an adequate nutrition rate may be one factor of benefit for neonatal growth and development.

Hence, the goal of this model is to provide a vehicle for real-time blood glucose control. It is therefore desirable to minimize the number of patient-specific parameters to be identified to avoid identifiability issues with limited (glucose only) measurements. This issue is particularly important in this neonatal case where real-time tracer studies are not viable and control must be based upon a very minimal number and volume of blood samples compared to the adult case. This latter point is a salient difference from the critically ill adult case where the blood sampling frequency used is primarily a question of clinical burden. Therefore, the model must provide better longer term prediction performance at 2 or more hours forward, which is dependent on good identification.

The predictive ability presented is similar to other studies that have successfully applied similar models to control glycemia in adult intensive care patients [33]. The model sufficiently captures the varied dynamics of the neonatal cohort. Model prediction error was independent of length of accumulated data for each patient. This result possibly reflects that hour-to-hour changes in response to insulin are largely random, similar to variations in critical care adults [68, 69]. The parameter sensitivity analysis revealed the population parameter that appeared to have the most influence on model fit and prediction errors was the glucose volume of distribution, V_G. Outside this parameter, the low sensitivity of model performance to the remaining parameters is similar to the adult case [33]. This result may imply that, with the right neonatal parameters, models of similar structure give similar fit and prediction performance in adults and neonates, which may be unexpected given the differing external clinical management of metabolism in these patient groups.

It should be noted that the frequency of measurement of retrospective data can influence the accuracy of blood glucose predictions, where some dynamics may be missed by sparse data collection. This issue is especially evident in the relatively poor prediction results for Patient 23. Figure 11 shows a part of the record for Patient 23, highlighting a period of rapid change in blood glucose. This patient experienced much more rapid swings in blood glucose compared to the rest of the cohort. This period of glycemic instability coincided with steroid and antibiotic administration, very unstable respiratory periods requiring resuscitation, a number of new IV lines, and some BG measurements taken using a GlucoCard glucometer, rather than the typical blood gas analyzer. In general, more frequent blood glucose measurements would enable the model to more accurately capture such periods of rapid change in glucose concentration, as well as provide insight to the contribution to unstable glucose due to patient condition and noise from measurement devices.

Published data was not available to directly estimate the insulin removal saturation parameter α_I, so this parameter was held at the same value as the adult case. Figure 3 shows that the effect of α_I is only relevant at very high insulin infusion rates, and that the value employed provides a good fit to the supra-physiological results of [18, 19]. The insulin model in adults exhibits instability for insulin infusion rates greater than approximately 18 U/hr for a typical 70kg adult due to the insulin removal saturation term α_I. The adult model was designed for use for insulin in the range of 0 - 8 U/hr (0 - 0.11 U/kg/hr). The dynamics of the neonatal model allow stability for a insulin infusion rates up to 1.4 U/hr for a typical 1kg infant, and represents an infusion rate approximately 3x - 9x higher than would be used for control.

The major assumption used in the predictions made in this study is that the in S_I parameter is constant over the prediction interval. Hence, longer intervals will subsequently show potentially greater variation as patient condition has a longer time and thus more opportunity to evolve. However, Figure 8

shows the mode of the error distribution remains relatively constant at approximately 4-7% over all four 1-4 hour prediction intervals. Thus, the increasing likelihood of changes over time in S_I are evident, as seen previously in the adult population [33, 68, 76]. Stochastic modeling of the S_I parameter [77], as applied in adult critical care patients [68], could provide a more accurate forecast of future S_I values and thus create confidence intervals for predicted blood glucose concentrations that account for this variation and would thus provide better clinical guidance.

Conclusions

A model of the glucose regulatory system has been adapted from adult critical care to the neonatal case. Model fits of the S_I parameter were generated for 25 patient records and 3,567 hours of retrospective data. Adaptation of several physiological model parameters, including insulin clearance rate, endogenous production rate and volumes of distribution, resulted in an average fitting error of 2.4%. The predictive ability of the model was assessed by assuming parameters were constant over the interval. Prediction error at 1, 2 and 4-hour intervals were 5.2%, 9.4% and 13.6% respectively. The model performance is within variations that would also account for dynamic patient evolution. The model thus provides a first *in-silico* result for modeling the metabolic dynamics of the low-birth weight preterm infant. It also creates a platform towards better metabolic clinical management of glycemia in neonates.

Conflict of interest statement

The authors state they have no outstanding conflicts of interest.

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Table 1: Patients and/or episodes selected for long-term data collection. Cohort summaries are presented as median [range].

Patient	Gestation age at birth (weeks)	Age at start of data (days)	Weight at birth (grams)	Gender	Duration of insulin usage (days)	Average BG frequency of measurements (per day)
1	23	< 1	600	F	12.7	8.6
2	24.4	4	650	F	13.9	5.5
3	23.7	< 1	625	M	8.8	6.0
4	25.4	< 1	800	F	12	5.5
5	26.6	7	840	F	5.9	6.2
6	25	< 1	900	F	3.9	10.9
7	26.3	7	810	M	4.6	5.3
8	26.6	6	825	F	4.3	4.9
9	26.6	3	915	M	3.8	6.0
10	27.9	3	1280	F	2.7	6.9
11	28.1	< 1	1275	F	4.9	7.5
12	28.6	< 1	845	F	1.4	10.4
13	27.7	< 1	860	F	2.4	10.4
14	24.9	3	735	M	7.6	7.1
15	26.9	2	880	F	8.6	6.7
16	29.9	< 1	865	F	1.8	9.2
17	26.4	7	990	M	1.9	5.9
18	26.6	3	920	M	3.8	5.5
19	28.6	4	930	M	1.8	11.4
20	26.6	4	860	F	4.7	6.0
21[a]	26.6	20	860		5.8	8.0
22	25.4	2	800	F	11.8	10.0
23[b]	25.4	22	800		12.7	9.2
24[b]	25.4	41	800	F	5.9	8.0
25[b]	25.4	56	800		1.3	7.1
Cohort	26.6 [23.0 – 28.9]	3.0 [< 1 – 56]	845 [600 – 1,280]		4.7 [1.3 – 13.9]	7.0 [4.9 – 11.4]

[a] = Second episode of insulin usage for Patient 21
[b] = Subsequent episodes of insulin usage for Patient 23

Table 2: Constant model parameter values

Parameter	Value	References
k	0.0086 min^{-1}	[33]
n	0.90 min^{-1}	[18, 19, 46, 53]
α_I	1.70 x 10^{-3} L/mU	[33]
α_G	0 L/mU	[46]
CNS	0.088 mmol/kg/min	[48]
m_{brain}	0.14 * m_{body} kg	[49]
I_B	10 mU/L/min	[46, 53]
k_I	0.1 L/(mU.min)	
$V_{I,frac}$	0.045 L/kg	[44, 45]
$V_{G,frac}$	ECF proportion^a L/kg	[39-42]
P_{END}	0.02838 mmol/kg/min	[20, 53, 55-59], From sensitivity study
p_G	0.003 min^{-1}	From sensitivity study

^{a}ECF proportion derived from Figure 1

Table 3: Quality of fit per-patient compared to model inputs. $BG_{geo,mean}$ and $BG_{geo,SD}$ represent the lognormal geometric mean and standard deviation respectively.

Patient	Median fit error	$BG_{geo,\,mean}$ [mmol/L]	$BG_{geo,\,SD}$ [mmol/L]	Median insulin [U/kg/hr]	Median dextrose	
					[mg/kg/min]	[kcal/kg/day]
1	2.6%	6.8	1.70	0.091	8.9	51.2
2	2.0%	7.8	1.26	0.053	10.4	59.7
3	2.7%	7.5	1.38	0.050	9.0	51.6
4	1.5%	7.6	1.32	0.026	8.2	47.5
5	3.0%	8.0	1.37	0.037	10.5	60.6
6	3.6%	7.3	1.44	0.037	4.9	28.1
7	2.1%	7.9	1.28	0.092	11.8	68.0
8	1.6%	7.7	1.28	0.031	10.7	61.4
9	1.0%	8.5	1.23	0.026	9.7	56.1
10	2.6%	6.9	1.40	0.025	9.9	56.9
11	1.3%	9.1	1.57	0.047	5.9	34.2
12	0.6%	6.2	1.86	0.047	5.3	30.3
13	2.1%	5.6	1.77	0.025	4.0	23.1
14	1.3%	8.9	1.28	0.029	10.0	57.7
15	2.1%	7.9	1.37	0.053	9.2	52.8
16	1.8%	8.2	1.38	0.040	5.0	28.6
17	4.5%	6.3	1.46	0.059	11.4	65.4
18	1.5%	7.7	1.22	0.025	8.3	47.5
19	2.4%	8.3	1.45	0.050	11.3	65.2
20	2.3%	8.4	1.30	0.030	14.1	81.4
21	2.2%	9.3	1.46	0.022	10.3	59.5
22	2.2%	7.5	1.32	0.027	8.5	49.2
23	6.2%	8.2	1.54	0.077	8.8	50.6
24	3.1%	8.0	1.57	0.017	10.0	57.6
25	0.6%	9.6	1.31	0.030	9.6	55.1

Table 4: Median prediction errors compared to linearly interpolated BG value.

Prediction interval	Cohort prediction error	
	Median	IQR
1 hour	5.2%	[2.5% - 10.3%]
2 hours	9.4%	[4.5% - 18.4%]
3 hours	11.9%	[5.1% - 23.7%]
4 hours	13.6%	[6.3% - 27.6%]