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ORIGINAL ARTICLE

On the Problem of Patient-Specific Endogenous Glucose Production in Neonates on Stochastic Targeted Glycemic Control

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Abstract

Background:

Both stress and prematurity can induce hyperglycemia in the neonatal intensive care unit, which, in turn, is associated with worsened outcomes. Endogenous glucose production (EGP) is the formation of glucose by the body from substrates and contributes to blood glucose (BG) levels. Due to the inherent fragility of the extremely low birth weight (ELBW) neonates, true fasting EGP cannot be explicitly determined, introducing uncertainty into glycemic models that rely on quantifying glucose sources. Stochastic targeting, or STAR, is one such glycemic control framework.

Methods:

A literature review was carried out to gather metabolic and EGP values on preterm infants with a gestational age (GA) <32 weeks and a birth weight (BW) <2 kg. The data were analyzed for EGP trends with BW, GA, BG, plasma insulin, and glucose infusion (GI) rates. Trends were modeled and compared with a literature-derived range of population constant EGP models using clinically validated virtual trials on retrospective clinical data.

Results:

No clear relationship was found for EGP and BW, GA, or plasma insulin. Some evidence of suppression of EGP with increasing GI or BG was seen. Virtual trial results showed that population-constant EGP models fit clinical data best and gave tighter control performance to a target band in virtual trials.

Conclusions:

Variation in EGP cannot easily be quantified, and EGP is sufficiently modeled as a population constant in the neonatal intensive care insulin–nutrition–glucose model. Analysis of the clinical data and fitting error suggests that ELBW hyperglycemic preterm neonates have unsuppressed EGP in the higher range than that seen in literature.

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Abbreviations: (BG) blood glucose, (BW) birth weight, (CNS) central nervous system, (EGP) endogenous glucose production, (ELBW) extremely low birth weight, (GA) gestational age, (GI) glucose infusion, (IQR) interquartile range, (NICU) neonatal intensive care unit, (NICING) neonatal intensive care insulin–nutrition–glucose, (STAR) stochastic targeting, (TPN) total parenteral nutrition

Keywords: endogenous glucose production, extremely preterm infants, glycemic control, insulin therapy, physiological modeling

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Introduction

Hyperglycemia, elevated blood glucose (BG) levels, is a common complication of prematurity in neonatal intensive care units (NICUs) and is associated with increased morbidity and mortality,[1] worsened outcomes,[2] and increased risk of severe infection[3] and multiple organ failure.[4] Conversely, hypoglycemia, a frequent result of insulin therapy,[5,6] is associated with negative outcomes and mortality.[7]

Endogenous glucose production (EGP) is the formation of glucose by the body from substrates and is a physiological function that normally assists in self-regulation of BG levels and the avoidance of hypoglycemia. It encapsulates two main metabolic processes: (1) gluconeogenesis, a metabolic pathway generating glucose from noncarbohydrate carbon substrates, and (2) glycogenolysis, by which the body generates glucose through the breakdown of glycogen to glucose.

Endogenous glucose production can be measured by tracer studies.[8–10] However, because of the inherent fragility of the extremely low birth weight (ELBW) cohort, the true fasting rate of EGP cannot be explicitly determined, introducing significant uncertainty to models that rely on its value. Studies measuring unfasted EGP are relatively few, so what literature data there are for similar cohorts must be extrapolated. In addition, interpatient variability has led to significant variation between results and conclusions in these studies.

Stochastic targeting (STAR) is a model-based glycemic control framework for insulin therapy that reduces hyperglycemia and directly quantifies and mitigates the risk of hypoglycemia.[11] Model-based glycemic control has been effective in reducing morbidity and mortality.[11–15] Stochastic targeting has also been used in the NICU, where it has proven to be effective at controlling to a target normal range.[16] Furthermore, STAR did not increase the incidence of hypoglycemia,[16] as seen in other NICU insulin therapy studies.[5,6]

Stochastic targeting uses a time-varying clinically validated model-based insulin sensitivity (S_I) to quantify patient variability.[13] Once a current S_I is identified using a clinical measurement, forecast S_I outcome bounds are generated based on population models.[17–19] These bands allow clinical interventions to be made that best overlap a range of predicted BG outcomes with a target BG range.[11] A treatment can be selected such that the maximum theoretical likelihood of future BG below a clinically specified lower target is 5%. Thus, STAR safely controls BG with a quantified risk of moderate hypoglycemia.

This study aims to quantify variation in EGP for the purposes of improving the performance and safety of STAR glycemic control. An analysis of EGP within the model-based glycemic control framework is augmented by a review and analysis of relevant literature data.

Methods

The analysis utilizes both literature review and clinical data. A literature review was carried out for the purposes of gathering data and examining reported trends. From identified trends, EGP models were created, and their efficacy was analyzed with respect to control outcomes in simulation. EGP population constants based on literature distributions were used to examine the effect of EGP on control in a clinical patient cohort across the entire range of possible EGP values. These methods can be found summarized in **Figure 1**.

Literature Review

Inclusion Criteria

A literature search was carried out using search criteria of "glucose," "production," "preterm," and "neonate" in the PubMed database. Studies were excluded if they were associated with maternal or fetal diabetes, subjects were not human, subjects were full-term or older, or studies were unrelated to glucose metabolism. Studies were chosen from the remaining literature on the basis that they reported sufficient data, including the rate of EGP, the current BG, birth

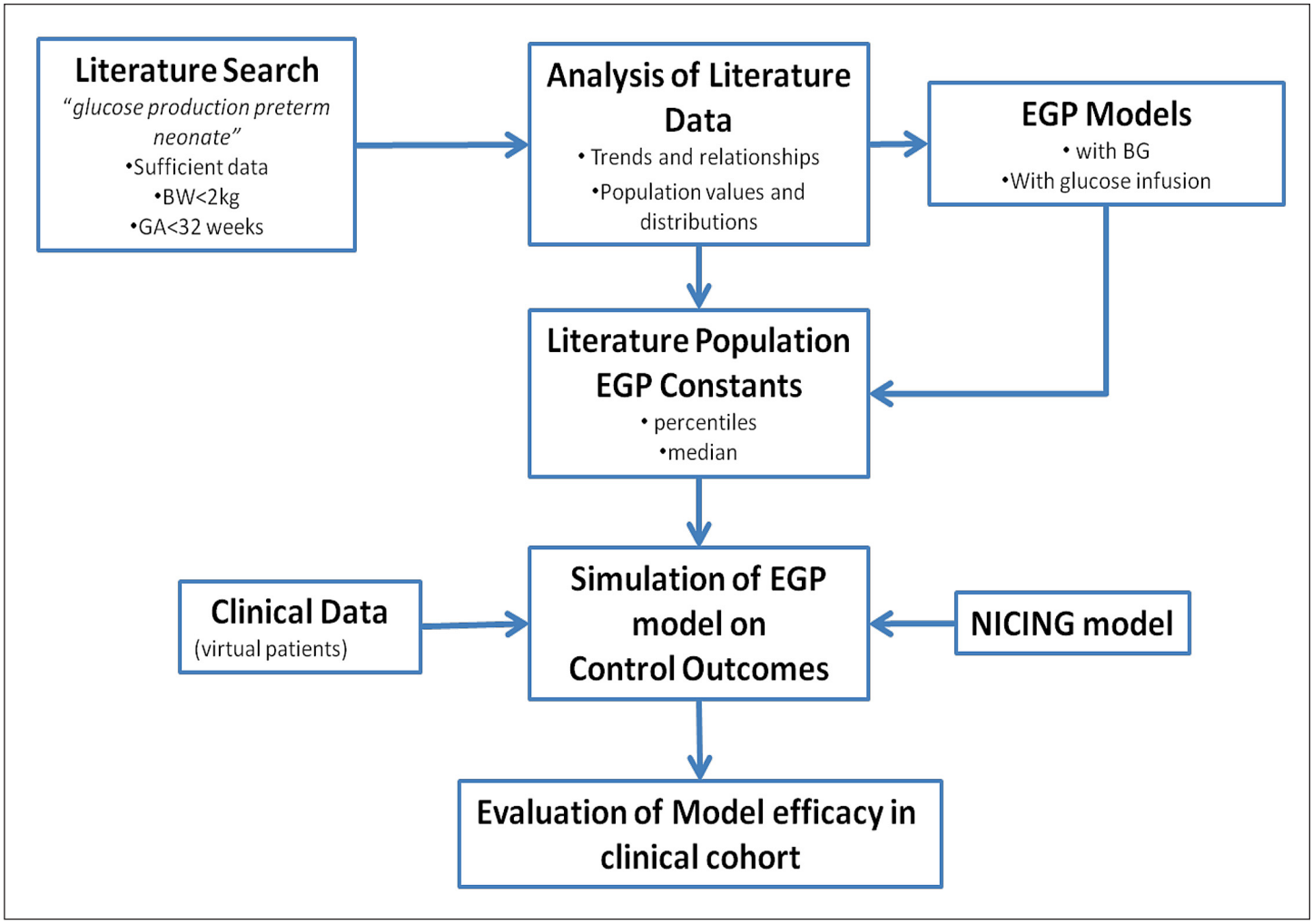

Figure 1. Summary of methodological approach.

weight (BW) <2 kg, gestational age (GA) <32 weeks, and glucose infusion (GI) feed regimes. A total of 177 data points were collected from 21 studies. Study methods and primary conclusions are summarized in **Table 1**. Endogenous glucose production is shown in **Figure 2** as a function of BG.

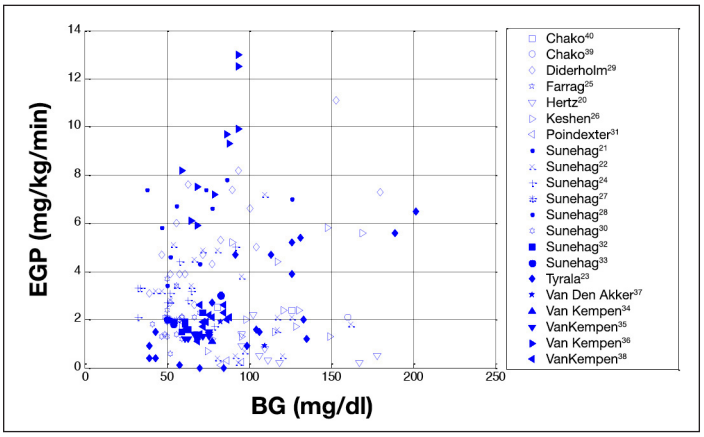

Figure 2. Endogenous glucose production as a function of BG over the literature cohort of 177 data points.

Data Analysis and Trend Generation

Endogenous glucose production was analyzed for trends with respect to BW, GA, GI, and BG. A linear function was then fit using least squares for EGP versus GI, the strongest correlated pair of parameters. A piecewise linear function was also used to describe the suppression of EGP with increasing BG. The piecewise linear model was chosen because of the high variation shown in the data in **Figure 2**. It was clear that EGP was often higher at lower BG and lower at higher BG, but no trend or consistent value was evident between these BG levels. Upper and lower limits were chosen as representative of the average EGP response over that glucose range, and linear trend was fit between.

Table 1.
Overview of Literature Studies

Study (first author)	Methods		Study conclusion(s)
	Tracers	Tracer infusion duration	
Hertz[20]	[6-6-d_2] glucose	Primer dose, 5 min Study period, 4 h	• Clinically stable, extremely premature infants suppress glucose production and increase glucose utilization in response to increased GI. • Increasing the rate of glucose delivery results in no change in whole body proteolysis in these infants.
Sunehag[21]	[6-6-d_2] glucose	Primer dose, 10 min Study period, 2 h	• Infants born at <28 gestational weeks have a capacity to produce glucose on their first day of life at rates close to or even exceeding those reported in term infants.
Sunehag[22]	[6-6-d_2] glucose	Primer dose, 5 min Study period, 160–180 min	• Very immature newborn infants have an incomplete and varying capacity to respond to GI with suppression of glucose production. • Insulin seems to be more important than plasma glucose in the regulation of glucose homeostasis in these infants.
Tyrala[23]	[6-6-d_2] glucose	Primer dose, 1 min Study period, 2 h	• Infants who weigh <1100 g utilize 3–4 times more glucose per kg of body weight than adults, reflecting their higher brain-to-body weight. • EGP provided only approximately one-third of the glucose required.
Sunehag[24]	[6-6-d_2] glucose [2-^{13}C] glycerol	Primed 2 h	• Extremely preterm infants are capable of generating glycerol at a rate within the range reported for term and near-term newborns. • The infants were also capable of converting part of this glycerol to glucose, providing a contribution to hepatic glucose production comparable to that found in more mature newborns.
Farrag[25]	—	—	• Adult-like response to insulin requires maturation beyond the neonatal period. • Ontogeny of glucose utilization responsiveness to insulin occurs before that of glucose production.
Keshen[26]	[U-^{13}C] glucose	4 h	• Neonates whose BW is less than 1200 g have a particularly high glucose production rate secondary to enhanced gluconeogenesis.
Sunehag[27]	[U-^{13}C] glucose [2-^{13}C] glycerol	10 h	• During TPN, gluconeogenesis accounts for one-fourth to one-third of glucose Ra after 8–10 h of reduced glucose supply.
Sunehag[28]	[U-^{13}C] glucose [2-^{13}C] glycerol	8 h	• In very-low-birth-weight infants receiving TPN, gluconeogenesis is maintained equally well by endogenous or exogenous amino acid supply.
Diderholm[29]	[6-6-d_2] glucose [2-^{13}C] glycerol	3.5 h	• No significant change in plasma glycerol concentrations, glycerol production, and the fraction of glycerol converted to glucose after theophylline administration. • The percentage of glucose derived from glycerol increased.
Sunehag[30]	[U-^{13}C] glucose [2-^{13}C] glycerol [6-6-d_2] glucose	11 h	• In very-low-birth-weight infants receiving TPN, normoglycemia was maintained during reduced GI by glucose production primarily derived from gluconeogenesis. • Glycerol was the principal gluconeogenic substrate.
Poindexter[31]	[6-6-d_2] glucose + unlabeled glucose	3 h	• In response to amino acid, infusion rates of EGP were unchanged.
Sunehag[32]	[U-^{13}C] glucose	8 h	• In very premature infants, parenteral glycerol enhances gluconeogenesis and attenuates time-dependent decrease in glucose production.
Sunehag[33]	[2-^{13}C] glycerol	10 h	• In parenterally fed very premature infants, lipids play a primary role in supporting gluconeogenesis.
Van Kempen[34]	[6-6-d_2] glucose [2-^{13}C] glycerol	6 h	• Preterm infants can only partly compensate a decline in exogenous glucose supply by increasing EGP rate. • The ability to maintain the plasma glucose concentration after a decrease in exogenous supply is better preserved in infants >30 weeks owing to more efficient adaptation of peripheral glucose utilization.
Van Kempen[35]	[6-6-d_2] glucose [2-^{13}C] glycerol	6 h baseline (unlabeled) infusion Study period, 3 h	• Administration of alanine does not stimulate gluconeogenesis in preterm infants.

continued →

Table 1. Continued

Study (first author)	Methods		Study conclusion(s)
	Tracers	Tracer infusion duration	
Van Kempen[36]	[6-6-d_2] glucose [2-^{13}C] glycerol	6 h baseline Study period, 1h	• Increase in glucose production after glucagon was similar in appropriate-for-GA and small-for-GA infants, mainly due to an increase in glycogenolysis. • Based on the assumption that glycogenolysis is an indicator of liver glycogen content, our data do not support the hypothesis that liver glycogen content is lower in preterm small-for-GA compared with appropriate-for-GA infants after the first postnatal day.
Van Den Akker[37]	[U-^{13}C] glucose	6–7 h	• The anabolic state resulting from amino acid infusion in the immediate postnatal period resulted from increased protein synthesis and not decreased proteolysis. • Energy required for additional protein synthesis was not derived from increased glucose oxidation.
Van Kempen[38]	[6-6-d_2] glucose [2-^{13}C] glycerol	9 h	• Intralipid enhanced glucose production by increasing gluconeogenesis in preterm infants.
Chacko[39]	[6-6-d_2] glucose	Primer $^2H_20$ Study period, 8 h	• Gluconeogenesis is sustained in preterm infants receiving routine TPN, providing glucose at rates exceeding normal infant glucose turnover rates and accounting for the major part of residual glucose production. • Gluconeogenesis is not affected by the GI rate or BG concentration.
Chacko[40]	[U-^{13}C] glucose	11 h	• In ELBW infants receiving TPN, gluconeogenesis is a continuous process that is not affected by infusion rates of glucose or concentrations of glucose or insulin.

Clinical Data and Model Fit

Clinical Patient Cohort

The clinical patient cohort, see **Table 2**, consists of data from 21 retrospective patients (25 patient episodes) and 40 patients (8 short-term, 32 long-term, 53 patient episodes total) from prospective BG control studies using STAR.[16,41] Patients who received no insulin or had no BG measurements for greater than 8 hours were separated into different patient episodes. Typically, subsequent patient episodes were separated by more than 24 h.

Table 2.
Clinical Patient Summary Statistics

	Short-term (n = 8)		Long-term (n = 45)		Retrospective (n = 25)	
	Median	(IQR)	Median	(IQR)	Median	(IQR)
GA at birth (weeks)	25.6	(24.9–26.4)	25.7	(25.0–28.4)	26.6	(25.4–27.7)
Weight at birth (g)	745	(681–814)	770	(627–972)	845	(800–904)
Age at start of trial (days)	6.6	(3.6–7.7)	4	(1.0–10.3)	—	

The median GA and BW of the literature cohort are higher than that of the clinical data but within the interquartile range (IQR). The average BG for the literature data is significantly lower than that of the clinical data, as shown in **Table 3**.

Neonatal Intensive Care Insulin–Nutrition–Glucose Model

The clinically validated NICING (neonatal intensive care insulin–nutrition–glucose) model[42] describes glucose–insulin dynamics in the extremely preterm neonate. The model is described by the ordinary differential equations given in **Equations (1)–(7)**. Pictorial representation and parameter origins are given in **Appendix A**.

The rate of change of BG (G), in mg/dl/min, is defined in **Equation 1**:

$$\dot{G} = -p_G G(t) - S_I G(t) \frac{Q(t)}{1 + \alpha_G Q(t)} + \frac{P_{ex}(t) + EGP * m_{\text{body}} - \text{CNS} * m_{\text{brain}}}{V_{g,\text{frac}}(t) * m_{\text{body}}} \quad (1)$$

Insulin-mediated glucose clearance is determined by insulin sensitivity (S_I), units (liter/mU/min) and non-insulin-mediated uptake includes a clearance term ($p_G = 0.0030\ \text{min}^{-1}$), including kidney clearance, and a central nervous system (CNS) uptake (CNS = 15.84 mmol/kg/min). "Glucose sources include exogenous glucose ($P_{ex}(t)$ [mmol]) and endogenous production (EGP = 5.11 mg/kg/min). m_{body} is the body mass, and m_{brain} is the brain mass (approximated as 14% of m_{body}). The rate of change of plasma (I) and interstitial (Q) insulin (units [mU/liter/min]) are defined in **Equations (2)–(4)**:

$$\dot{I} = -\frac{n_L I(t)}{1 + \alpha_I I(t)} - n_K I(\text{t}) - n_I (I(\text{t}) - Q(t)) + \frac{u_{ex}(t)}{V_{I,frac} * m_{body}} + (1 - x_L) u_{en} \quad (2)$$

$$u_{en} = I_B e^{\frac{-k_I u_{ex}}{V_I}} \quad (3)$$

$$\dot{Q} = n_I (I(t) - Q(t)) - n_C \frac{Q(t)}{1 + \alpha_G Q(t)} \quad (4)$$

Plasma insulin is cleared via the liver (n_L = 1/min), the kidney (n_K = 0.150/min), and transport into interstitial fluid (n_I = 0.003/min). Insulin enters the system exogenously (u_{ex} [mU/min]) or endogenously [u_{en} (mU/min)] through pancreatic secretion, as described in **Equation (3)** (basal secretion I_B = 15 mU/liter/min, interstitial transport rate $k_I = 0.1\ \text{min}^{-1}$). Insulin leaves the interstitial fluid through degradation (n_c = 0.003/min).

Table 3.
Summary of Patient Metrics between the Literature Data and Our Clinical Data Cohorts

	Cohort medians		
Cohort (first author)	GA (weeks)	BW (g)	BG (mg/dl)
Hertz[20]	25.5	8900	109.8
Sunehag[21]	26	796	63
Sunehag[22]	27	1196	86.4
Tyrala[23]	Range, 23–28	Mean, 858	101.7
Sunehag[24]	26	865	55.8
Keshen[26]	28	1110	117
Sunehag[27]	Mean, 27	Mean, 1020	Mean, 55.8
Sunehag[28]	27.6	1060	3.8
Diderholm[29]	28.5	1160	68.4
Sunehag[30]	27	1050	50.4
Farrag[25]	—	677	70.2
Poindexter[31]	32	1500	86.4
Sunehag[32]	28	1030	63
Sunehag[33]	27.5	995	54
Van Kempen[34]	29.1	1140	70.2
Van Kempen[35]	<32	Appropriate for GA	70.2
Van Kempen[36]	30.5	1244	82.8
Van Den Akker[37]	27.4	946	97.2
Van Kempen[38]	29.4	1335	75.6
Chacko[39]	Mean, 26.5	Mean, 955	Mean, 160.2
Chacko[40]	25.4	820	73.8
Median literature data (IQR)	27.5 (26–29)	1080 (921–1315)	73.8 (68.4–97.2)
Median clinical data (IQR)	25.9 (25.0–27.0)	805 (640–930)	138.4 (126–155)
P-values of median measurements	<0.0001	<0.0001	<0.0001

Appearance of glucose via the enteral route is modeled by two intermediate compartments, the stomach (P_1 [mg]) and the gut (P_2 [mg]), and is described by **Equations (5)–(7)**:

$$\dot{P}_1 = -d_1 P_1 + P(t) \quad (5)$$

$$\dot{P}_2 = -\min(d_2 P_2, P_{\max}) + d_1 P_1 \quad (6)$$

$$\dot{P}_{ex}(t) = \min(d_2 P_2, P_{\max}) + PN(t) \quad (7)$$

Transport rates between the stomach and gut and gut and blood (d_1 = 0.0347/min and d_2 = 0.0069/min, respectively) are limited to a maximum flux (P_{max} [mg/min]). Solutions to **Equations (1)–(7)** (giving profiles for G,I,Q,P_1, and P_2) are generated simultaneously in the time domain using a Runga–Kutta 4-based ordinary differential equation solver.

S_I is patient specific and time varying, describing a patient's current metabolic state. It is fit using integral-based fitting methods[43] on a retrospective hour-to-hour basis and assumed constant over an hour-long period. In addition to being a marker of peripheral insulin sensitivity, S_I also incorporates uncertainty around patient-specific endogenous insulin and glucose production. A S_I of 1×10^{-7} liter/mU/min, which is very close to zero, represents the lower physiological bound in insulin sensitivity, where no glucose is leaving the blood plasma via the insulin-mediated uptake path.

Fitting Error

Accuracy of model fit to clinical data was one metric used to evaluate the effect of the new EGP models. This fitting error is defined as the average percentage difference between the real and modeled BG levels at BG measurements. When using an integral-based fitting method,[43] the identified S_I must remain positive to be physiologically correct; the lower limit of S_I was set to a lower limit of 1×10^{-7} liter/mU/min.

In cases where fitting error was poor, with modeled BG failing to reach clinical measurements, a negative S_I had been forced to a lower limited value of 1×10^{-7} liter/mU/min. In such cases, **Equation (1)** was rearranged and EGP was then solved under the assumption of S_I 1×10^{-7} liter/mU/min. The resulting EGP_{min} values gave an indication of the magnitude of minimum EGP required in the NICING model to adequately fit clinical data under the assumption of minimum peripheral insulin sensitivity. These results should thus show the minimum level of interpatient variability.

Control-Based Analysis

Control Performance with Endogenous Glucose Production Models

Modeling EGP as a population constant was examined through the use of a range of EGP values from literature data (**Table 2**). This range is based on percentiles of the literature data, defined in **Table 4**. Other EGP values between the median and 95th percentile were included for completeness.

Table 4.
Values of Constant Endogenous Glucose Production Used to Investigate Effect on Control

Percentile	EGP (mg/kg/min)
5th	0.29
25th	1.40
50th	2.1
75th	4.6
95th	7.7
Currently used: Lin and coauthors[19]	5.11
Other EGP:	5.50, 6.00, 6.50, 7.00, and 7.50

For each EGP value, S_I was identified for the whole cohort and a new stochastic model generated. Control was tested using clinically validated virtual trial methods,[13,41] and the control protocol selected insulin such that the predicted outcome likelihood of BG <79 mg/dl (4.4 mmol/liter) was 5%.[44]

Control Performance Metrics

Percentage time in band (BG between 72 and 144 mg/dl) evaluated the performance of control, while the number of severe hypoglycemic patients (BG < 47 mg/dl) evaluated safety.

Results

Literature Analysis

Studies have attempted to quantify variability EGP, with mixed results. Gluconeogenesis has been shown to persist in infants receiving total parenteral nutrition (TPN).[39] Endogenous glucose production has been shown to remain unaffected by amino acid administration,[28,31,35] but lipids have been shown to support[33] or enhance EGP.[38] Glycerol has been shown to enhance gluconeogenesis[32] and to be a principal gluconeogenetic substrate.[32,45] Furthermore, the extremely

preterm infant is capable of generating glycerol at a rate similar to much larger, term infants.[21,24] Preterm infants have been shown to produce glucose at a rate similar to[21,24] or exceeding[23,26,39] that of term infants, or adults, and there is evidence of some relationship between GA and EGP[39,46] or weight and EGP.[26]

Some studies conclude that glucose production has been regulated by BG levels,[9,20] but the majority report the reverse.[39,40,47,48] Preterm infants display varying ability to suppress EGP with increasing GI, with complete,[20] incomplete,[22,34] and failed[39] suppression reported. Although one study suggests that insulin plays an important role in EGP regulation,[22] other studies show that EGP is not suppressed by plasma insulin levels.[21,39,40,47]

Endogenous Glucose Production with Respect to Patient Metrics

Comparing reported values of EGP with BW and GA showed little or no correlation in **Figure 3**. High interpatient variability between similar patients is seen in the large scatter of EGP across all metrics. Similarly, as shown in **Figure 4**, there is no distinct correlation between BG and EGP or plasma insulin and EGP. Across all literature studies, a suppression of EGP with increasing GI can be seen. However, at any given GI rate, there is significant variation in EGP, with no clear distribution with BW or GA. A piecewise linear trend of GI and EGP from **Figure 4** is defined as follows:

$$\text{EGP (GI)} = \begin{cases} -0.55 \times \text{GI} + 4.96, & 0 < \text{GI} \leq 7 \\ 1.11, & \text{GI} > 7 \end{cases} \quad (8)$$

where EGP and GI have units of mg/kg/min.

Endogenous Glucose Production and Blood Glucose

Within the literature, a subcohort of studies show some degree of increase in EGP with BG. These studies are plotted in **Figure 5A**, with each study showing a different trend in the magnitude of EGP with respect to BG. All studies show high variation, as reflected in the R^2 values from 0.2–0.5. If all the remaining studies are considered, a suppression of EGP with increasing BG can be seen. This suppression exists to varying degrees among and between studies, shown in **Figure 5B**.

From **Figure 5B**, a suppressed EGP with BG can be modeled. The EGP variation with BG is modeled as follows:

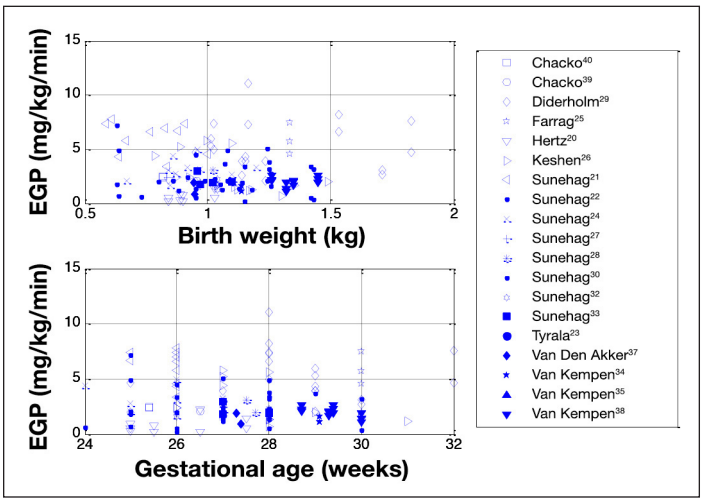

Figure 3. Relationships between EGP with BW and GA.

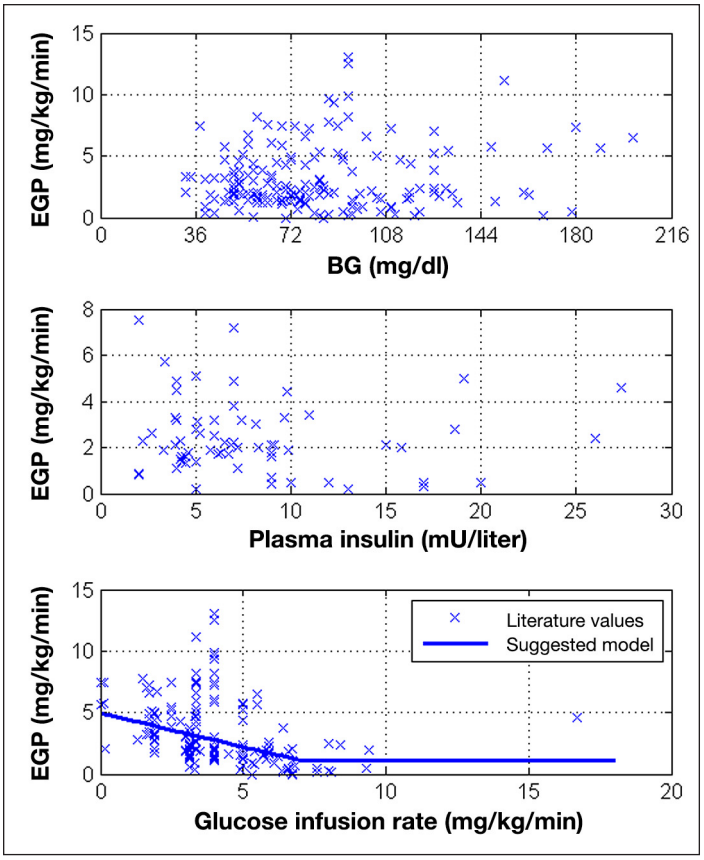

Figure 4. Relationships between EGP and BG, plasma insulin, and GI.

$$\text{EGP (BG)} = \begin{cases} 4, & \text{BG} < 36 \\ 5.75 - 0.049 * \text{BG}, & 36 < \text{BG} \leq 108 \\ 0.5, & \text{BG} > 108 \end{cases} \quad (9)$$

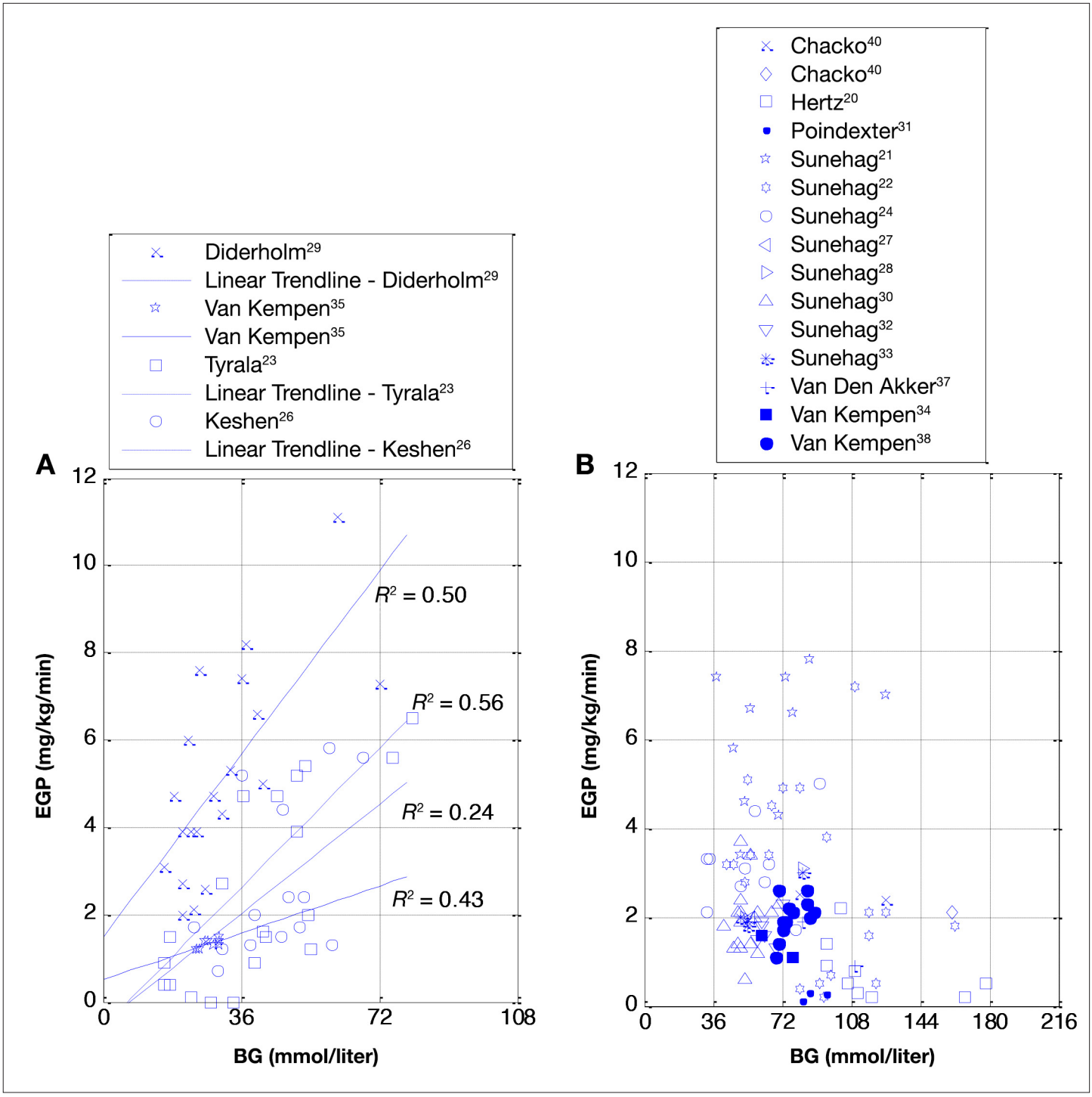

Figure 5. Subcohorts of studies which show **(A)** increasing EGP with BG and **(B)** suppression of EGP with BG.

Endogenous glucose production has units of mg/kg/min and BG mg/dl. With the suppression of EGP with BG, there was a fitting error of 3.77% over the whole cohort. However, many patients had one or more instances where S_I was constrained to a lower limit of $S_I = 1 \times 10^{-7}$ liter/mU/min without fitting the data, indicating insufficient EGP production in the model. To estimate patient-specific EGP over these periods, the EGP was reverse calculated using an assumption of minimum S_I, giving EGP_{min}, as in **Figure 6**. These minimum values suggest that EGP in hyperglycemic infants is generally higher than the literature data and not suppressed by elevated BG. EGP_{min} is also highly scattered across the cohort, with a far wider spread than the literature data.

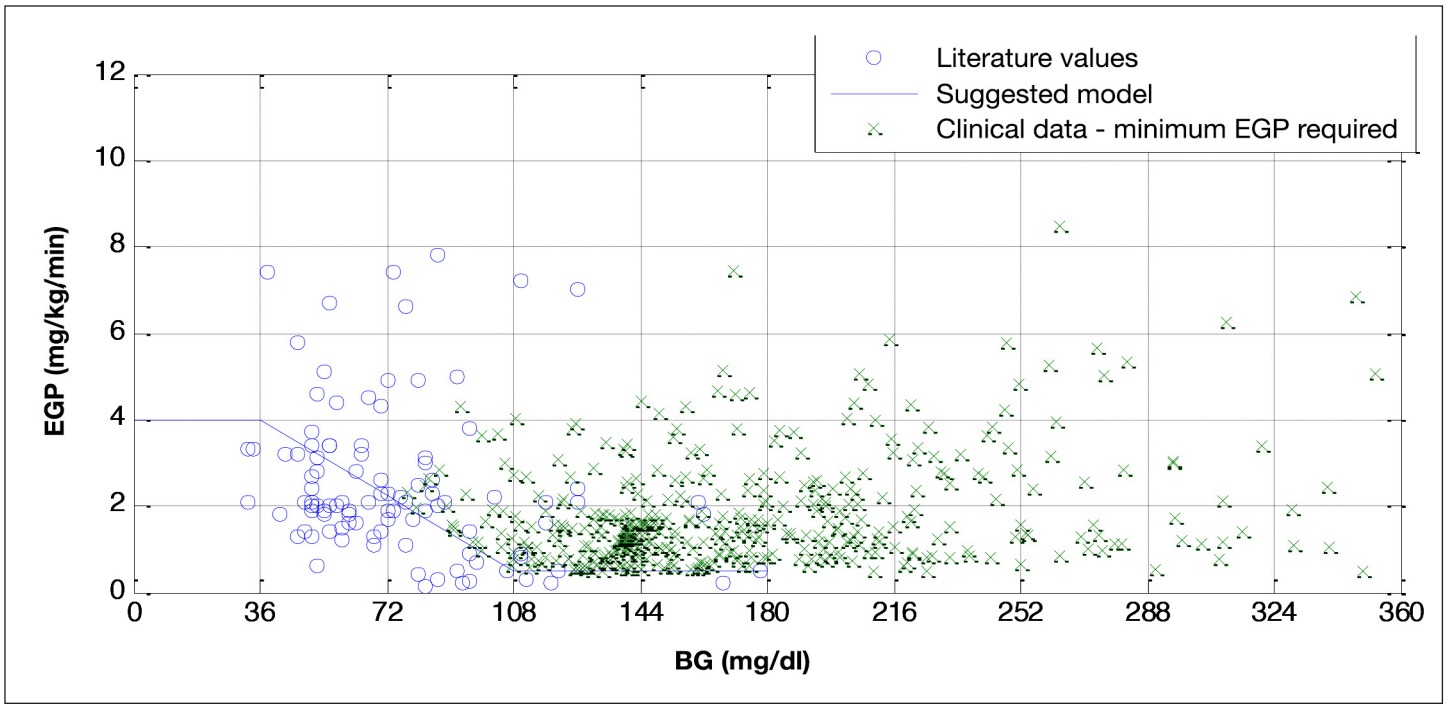

Figure 6. Comparison of literature-based model of EGP with BG and EGP_{min}: estimated from clinical data.

Effect of Endogenous Glucose Production on Control

The fitting and virtual trial control performance metric results for different EGP models are shown in **Table 5**. Endogenous glucose production as a function of GI and EGP as a function of BG both preformed worse than the currently used constant of EGP = 5.11 mg/kg/min.[19] In the first case, fitting error was increased, and in both cases, the percentage time in band and number of patients with hypoglycemic events increased.

Due to high variation in EGP in **Figures 1** and **6**, a range of constant EGP values were investigated. **Table 5** shows that EGP values below 2 mg/kg/min had high fitting error due to insufficient EGP to reach clinically measured BG levels, and during simulation, EGP was insufficient to maintain a positive BG. Increasing EGP decreased fitting error and increased the performance and safety of STAR-model-based glycemic control. However, all fitting errors for EGP >2 mg/kg/min are within measurement error. Thus, compared with BG values in **Figure 1**, the current value of EGP = 5.11 mg/kg/min appears reasonable. From a control standpoint, EGP = 6.0 mg/kg/min provides the best compromise across all key metrics in **Table 5**; however, this improvement is unlikely to be clinically significant.

Discussion

The piecewise linear models of suppressed EGP with increasing BG and EGP with GI resulted in poor fitting and control performance, mainly because EGP values in the literature were too low during hyperglycemia to sustain the BG values measured clinically. These results suggest that hyperglycemic ELBW premature infants often fail to suppress or otherwise regulate EGP with BG or GI, compared with normal infants.

Literature data and EGP_{min} data points did not overlap, as shown in **Figure 6**. The literature BG data was in the normal range, so it is likely that the majority of these infants were healthy and therefore representative of normal EGP dynamics. In contrast, the clinical data are based on hyperglycemic infants, with higher average BG levels, suggesting this cohort is less healthy. This result implies that EGP may be higher in these preterm and hyperglycemic infants, which is physiologically intuitive, as BG is likely high at least in part due to elevated or unsuppressed EGP due to the stress of their condition. These results mimic the adult intensive care unit situation[49,50] and, again, suggest that hyperglycemic infants have less ability to suppress EGP with high BG or GI.

Table 5.
Comparison of Model Fit and Control Performance across Different Endogenous Glucose Production Models

Case	Fitting	Control			
EGP (mg/kg/min)	Fitting error	Time in band (72 – 144 mg/dl)	Hyperglycemic (BG > 180 mg/dl)	Mild hypoglycemic (BG < 72 mg/dl)	Severe hypoglycemic (BG < 47 mg/dl)
Suppressed EGP (BG)	2.77%	EGP too low to sustain modeled BG levels, indicating inability of the EGP model to replicate clinical results.			
0.3 (5th)	4.78 %				
1.40 (25th)	3.07 %				
2.1 (50th)	2.58 %	74.8 %	8.08 %	2.25 %	6
4.20	2.16 %	77.3 %	7.10 %	2.05 %	3
4.6 (75th)	2.11%	78.0 %	6.69%	2.05 %	3
5.11[a]	2.11 %	78.4 %	6.52 %	2.14 %	2
5.50	2.10 %	78.6 %	6.61 %	2.10 %	1
6.00[b]	2.09 %	79.2 %	6.35 %	2.23 %	1
6.50	2.09 %	79.5 %	6.42 %	2.38 %	2
7.00	2.08 %	79.8 %	6.34 %	2.56 %	1
7.50	2.08 %	79.9 %	6.17 %	2.67 %	1
7.7 (95th)	2.08%	80.7%	5.86%	2.60%	1
EGP (GI(t))	2.28%	73.7 %	8.24 %	2.1 %	8

[a] Currently in use with EGP = 5.11 mg/kg/min.[19]
[b] Optimum.

In support of these outcomes, the clinical data patients are typically younger (lower GA), lighter (lower BW), and generally start hyperglycemic, unlike literature data. Clinical data had a median starting BG of 176.4 mg/dl (IQR, 149.4–221.4 mg/dl) compared with the literature median BG of 73.8 mg/dl (IQR, 68.4–97.2 mg/dl). These statistics, summarized in **Table 3**, reflect a limitation in the use of the literature data to describe EGP model in hyperglycemic ELBW infants. However, no other data for EGP in this cohort exists. Due to the practical difficulty of measuring EGP in this cohort, literature data provides a valid basis for extrapolation.

Figure 5A suggests that some neonates are at higher BG levels because of a physiological inability to regulate EGP. In the case of deficient EGP, regulation BG is a complex function of EGP, endogenous insulin secretion, insulin therapy, and nutritional treatments. Thus it is extremely difficult to define a direct cause-and-effect relationship between BG and EGP. This is partially reflected in the low R^2 values shown in **Figure 5A**. Higher EGP with increased BG, as seen in the subcohort of studies in **Figure 5A**, was not modeled, as this created a positive feedback system within the simulation software, which inhibited the controller's ability to regulate BG to a target band.

No strong relationship was found with EGP and BW, plasma insulin, or GA over the entire literature data. Keshen and coauthors[26] have reported decreasing EGP with increasing body weight in babies less than 31 weeks GA and with a postnatal age of 4–9 days, but these data remain unconfirmed by any other literature study and were contradicted by the findings of Chacko and Sunehag[39] in a study with a similar patient cohort. Van Kempen and coauthors[34] have reported that the ability of neonates to maintain basal BG levels with a decrease in exogenous insulin is greater in neonates older than 30 weeks GA, but no studies have specifically investigated EGP over a range of GA, although preterm infant EGP has been shown to be similar or exceed that of term infants.[21,51]

As the overall result of this study, we conclude that a population constant of EGP = 5.11 mg/kg/min is adequate for use in control. The population constant model best accounts for and reflects uncertainty due to variability between patients. Increases in controller performance at higher assumed EGP values are unlikely to be clinically significant.

A 2002 study in adults by Tigas and coauthors[52] suggests that using an isotope infusion period of 5 h or longer can reduce error in EGP measurements by at least 80% due to the time required for isotopes and substrates to equilibrate. As a result, some of the studies undertaken before 2002, where infusion periods tend to be shorter than 5 h, may have inherent error in EGP. However, using only literature with an infusion period of 5 h or greater changed none of the trends of EGP and did little to reduce the variation in EGP across all metrics.

With respect to limitations, the CNS glucose uptake is also a population constant based on literature data. It is possible that CNS in this population is lower, which would be reflected in this study as a higher EGP. In addition, a higher EGP term could result from a need for reduced endogenous insulin production. High variability in EGP seen in the literature may also suggest that model dynamics such as CNS and endogenous insulin secretion are not adequately modeled, setting a direction for future work.

Finally, this analysis is only relevant in the context of this model. The model itself has been validated by very successful, safe, and prolonged use in neonates.[16,53] The same model framework and *in silico* control modeling approach have been validated in adult cases where more independent data are available.[13] Thus, it is felt that the overall results showing enhanced EGP with elevated BG is realistic.

Conclusions

A wide range of literature studies have been found that report EGP. The studies themselves are divided in their conclusions, and no definitive relationship between EGP and BG, plasma insulin, or patient metrics such as weight and GA exists. Over all studies, EGP was shown to be highly variable between patients and studies. Endogenous glucose production was seen to decrease with increasing GI over all literature studies examined. Additionally, two trends were seen with glucose production and BG: the first saw higher EGP at higher BG and the second saw suppression of glucose production at higher BG. Both tends are physiologically reasonable. Stochastic targeted glycemic control was found to perform best when EGP was modeled as a population constant. Results indicate that hyperglycemic ELBW infants produce glucose at a higher rate than healthy counterparts.

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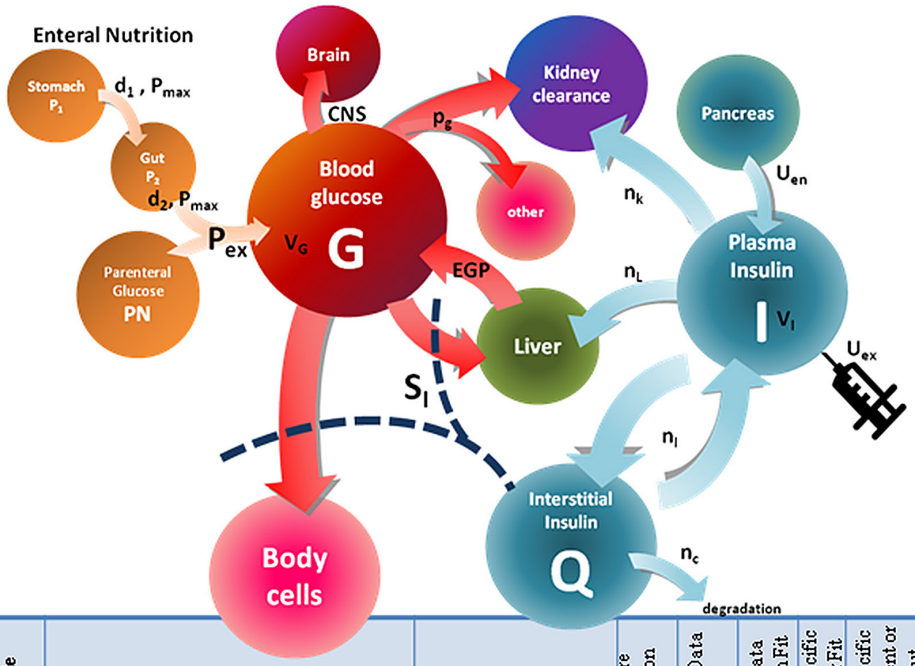
Appendix A. Model Parameter Origins



Variable	Description	Values	Literature Population	Literature Data Fit	Clinical Data Population Fit	Patient Specific Parameter Fit	Patient Specific Measurement or given input	Model Output
G	Blood glucose	(mmol/L)					√	√
I, Q	Plasma Insulin, Interstitial Insulin	(mU/L)						√
p_G	Endogenous glucose clearance	0.0030 (min^{-1})			√			
α_G/α_I	Saturation gluose/insulin clearance	0.0017 (L/mU)	√					
S_I	Insulin sensitivity	(L/mU/min)				√		
EGP	Endogenous glucose production	0.0284 (mmol/kg/min)	√					
CNS	Central nervous system glucose uptake	0.088 (mmol//kgmin)	√					
P_{ex}	Exogenous glucose appearance	(mmol/min)						√
P, PN	Enteral nutrition, parenteral nutrition	(mmol/min)					√	
P_{max}	Maximal glucose flux from gut to plasma	6.11 (mmol/min)	√					
P_1, P_2	Glucose in stomach and gut	(mmol)						√
V_G	Plasma glucose distribution volume	0.5961 (L)	√					
k_I	Interstitial insulin transport rate	0.1 (min^{-1})	√					
I_B	Basal endogenous insulin production	15 (mU/L/min)		√				
n_I	Rate of transport between plasma and interstitial insulin compartments	0.003 (min^{-1})	√					
n_K	Renal insulin clearance	0.150 (min^{-1})		√	√			
n_L	Hepatic insulin clearance	1 (min^{-1})		√	√			
n_C	Interstitial insulin degradation	0.003 (min^{-1})		√	√			
x_L	First-pass hepatic insulin clearance	0.67		√	√			
$u_{ex}(t)$	Exogenous insulin	(mU/min)					√	
$u_{en}(t)$	Endogenous insulin production	(mU/min)		√				
V_I	Plasma insulin distribution volume	0.0450 (L)	√					
d_1	Glucose absorption rate from stomach	0.0347 (min^{-1})	√					
$d2$	Glucose absorption rate from gut	0.0069 (min^{-1})	√					
m_{body}	Body mass	(kg)					√	
m_{brain}	Brain mass= 14% body mass	(kg)				√		