Insulin kinetics and the Neonatal Intensive Care Insulin-Nutrition-Glucose (NICING) model

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Abstract

Background: Models of human glucose-insulin physiology have been developed for a range of uses, with similarly different levels of complexity and accuracy. STAR (Stochastic Targeted) is a model-based approach to glycaemic control. Elevated blood glucose concentrations (hyperglycaemia) are a common complication of stress and prematurity in very premature infants, and have been associated with worsened outcomes and higher mortality. This research identifies and validates the model parameters for model-based glycaemic control in neonatal intensive care.

Methods: C-peptide, plasma insulin, and BG from a cohort of 41 extremely pre-term (median age 27.2 [26.2 - 28.7] weeks) and very low birth weight infants (median birth weight 839 [735 – 1000] g) are used alongside C-peptide kinetic models to identify model parameters associated with insulin kinetics in the NICING (neonatal intensive care insulin-nutrition-glucose) model. A literature analysis is used to determine models of kidney clearance and body fluid compartment volumes. The full, final NICING model is validated by fitting the model to a cohort of 160 glucose, insulin, and nutrition data records from extremely premature infants from two different NICUs (neonatal intensive care units).

Results: 6 Model parameters related to insulin kinetics were identified. The resulting NICING model is more physiologically descriptive than prior model iterations, including clearance pathways of insulin via the liver and kidney, rather than a lumped parameter. In addition, insulin diffusion between plasma and interstitial spaces is evaluated, with differences in distribution volume taken into consideration for each of these spaces. The NICING model was shown to fit clinical data well, with a low model fit error similar to that of previous model iterations.

Conclusions: Insulin kinetic parameters have been identified, and the NICING model is presented for glycaemic control neonatal intensive care. The resulting NICING model is more complex and physiologically relevant, with no loss in bedside-identifiability or ability to capture and predict metabolic dynamics.

Keywords: *physiological modelling, glucose, insulin, premature infant, glycaemic control*

Introduction

Mathematical models of glucose-insulin physiology have been developed with differing levels of complexity for a wide range of scientific and clinical applications. Models developed for the determination of model-based measures of physiology (e.g. [1, 2]), such as insulin sensitivity, tend to be more complex and comprehensive, requiring higher data density and/or measurement of multiple metabolic species. Other models are designed for specific clinical applications, such as glycaemic control in intensive care (e.g. [3-6]), or Type 1 Diabetes cohorts (e.g.[7]). These models tend to be less complex, as metabolic measurements are minimised in clinical or outpatient settings due to clinical and patient factors such as cost, availability, or comfort. In general, physiological models must have appropriate resolution, be mathematically identifiable [8], as well as practically applicable within their chosen application [9].

While glucose-insulin models for adult intensive care applications are more widely documented [9, 10] virtually no work has looked at neonatal intensive care unit (NICU) applications. Elevated blood glucose levels (BG) (Hyperglycaemia) is a common complication of prematurity and stress in neonatal intensive care, and while definitions and thresholds vary [11], studies show that 30-70% of very/extremely low birth weight infants have at least one BG> 8 mmol/L [12-16]. Hyperglycaemia is associated with increased mortality [15-17], and morbidity/complications in this cohort [15-21], but there is still debate over whether hyperglycaemia causes increased morbidity, or is reflective of worsened condition.

There is no best practice method for the treatment of hyperglycaemia in this cohort. Use of insulin has been shown to increase glucose tolerance [22-27], resulting in increased weight gain [23, 25, 27], but also commonly results in increased incidence of hypoglycaemia (low blood glucose concentration) [28-30], which is also dangerous. In adult intensive care even a single hypoglycaemic episode has been associated with increased risk of mortality [31-33], while in neonatal intensive care hypoglycaemia as been associated with adverse neurological outcomes [34, 35]. Model-based methods for glycaemic control have been little investigated, due in part to the extremely fragile nature

of this cohort and the subsequent limitations on invasive procedures and blood sample collection [36] that thus also limit the ability to identify parameters to validate more physiologically relevant and complex models.

The aim of this study is twofold. First, this paper presents a clinically applicable and physiologically relevant model of glucose-insulin physiology in hyperglycaemic very/extremely premature infants (gestational age <32 weeks), and secondly it aims to identify insulin kinetic parameters for this model. With regards to the first aim, it combines a previous, simpler, model iteration in this cohort [37] with a more physiologically descriptive model currently utilised for glycaemic control in the adult intensive care unit [5]. Specifically, this model is more descriptive with regards to modelled insulin kinetics and dynamics [38], necessary for safe and effective glycaemic control.

Related to the second aim, this paper also focuses on parameter identification of modelled insulin kinetics. While the key glucose dynamics have been previously published [39, 40], this study uses a previously published methodology from adults [41] and a novel data set of C-peptide concentrations from a very low birth weight (<1500g) cohort to evaluate diffusion of insulin between plasma and the interstitial fluid, and total liver and kidney clearance of insulin. In addition, the assumptions around insulin distribution volumes in the plasma and interstitial compartments are examined, and kidney glomerular filtration rate (GFR) is used to provide a patient specific value for renal clearance of insulin. The revised kinetics model is then used to create a new more physiologically relevant and complex, yet equally identifiable, glucose-insulin model, which is validated using clinical data.

2.0 Models and Methods

2.1 NICING Model of Glucose-Insulin Physiology

The NICING (Neonatal Intensive Care Insulin-Nutrition-Glucose) model for glycaemic control in very/extremely preterm neonates is developed from a previous NICU model [37] and the ICING (Intensive Care Insulin-Nutrition-Glucose) model for adult intensive care [5]. The values given, with the exception of those derived in this study, are predominantly derived from literature, and are originally presented and discussed in [37, 39].

In the new NICING model, blood glucose ($G \in \mathbb{R} : G \geq 0$), plasma ($I \in \mathbb{R} : I \geq 0$) and peripheral ($Q \in \mathbb{R} : Q \geq 0$) insulin kinetics are described:

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

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

$$\dot{Q} = n_I \frac{V_P}{V_Q}\big(I(t) - Q(t)\big) - n_C \frac{Q(t)}{1 + \alpha_G Q(t)} \quad (3)$$

Where G has units of mmol/L/min, and I and Q have units of mU/L/min. Clearance of glucose includes both insulin mediated and non-insulin mediated routes. Insulin mediated uptake is modulated by insulin sensitivity ($s_I \in \mathbb{R} : s_I \geq 10^{-7}$), while non-insulin mediated routes include a brain-mass (m_{brain} ~14% whole body mass, m_{body}) dependant [40] central nervous system uptake (CNS = 0.088 mmol/kg/min), and a concentration dependant pathway capturing other glucose clearances such as from the kidney (p_G = 0.003 /min). As p_G trades off mathematically with S_I and cannot be directly measured in this cohort, the adult value of 0.003/min is assumed. Glucose enters the system via exogenous (P_{ex}) inputs (parenteral and enteral) and endogenous glucose production (EGP = 0.033 mmol/kg/min) by the liver [39]. $V_{g,frac}$ is the volume of distribution of glucose in plasma in litres and is based on gestational age [37]. Saturation of insulin mediated glucose uptake in adults is modulated

with a Michaelis-Menten function, characterised by the parameter α_G. For neonates no saturation has been observed [42], so this value is $\alpha_G = 0$.

Liver clearance of insulin occurs in two main processes, a first pass hepatic clearance of endogenously secreted insulin (x_L) and clearance of insulin from circulating blood (rate constant: n_L). This hepatic clearance is a receptor-mediated process resulting in saturation of clearance at high insulin concentrations [43, 44], and so is modelled with a Michaelis-Menten function, characterised by the parameter α_I. Saturation of liver clearance and first pass hepatic clearance of insulin cannot be measured in premature infants, or indirectly determined in this analysis, so the adult value of $\alpha_I = 0.0017\ L/mU$ and x_L = 0.67 are used [5, 45].

Kidney clearance of insulin (rate constant: n_K) includes both glomerular filtration of insulin, and proximal tubal reabsorption. Insulin movement between the plasma and interstitial fluid, (rate constant: n_I) is likely diffusion based, as it is not reported to be saturated [46, 47]. Insulin degradation by cells (rate constant: n_C) is a complex, receptor-mediated process. Receptor bound insulin can either be released back into the extracellular fluid space or internalised by the cell [43]. As insulin-binding and insulin-receptor mediated glucose uptake are related, both share the saturation parameter $\alpha_G = 0$. Insulin is secreted (u_{en}) or is exogenously delivered (u_{ex}), with units of mU/min. Insulin secretion can be calculated using C-peptide [48, 49], a molecule secreted in equimolar quantities to insulin with simpler clearance kinetics. If C-Peptide measurements are not available, insulin secretion is modelled [49, 50]:

$$u_{en} = \begin{cases} \max(4.2, -1.5 + 1.9 * G) & \text{if female} \\ \max(2.2, -0.37 + 0.86 * G) & \text{if male} \end{cases} \quad (4)$$

The volume of distribution of plasma insulin is assumed to be the blood plasma volume (V_P). The volume of distribution of insulin in the peripheral compartment is approximated as the interstitial fluid volume (V_Q).

2.2 C-peptide Kinetic Model

C-peptide is a protein secreted in equimolar quantities with insulin. However, unlike insulin, it is only cleared by the kidney. Therefore, the relatively simple kinetics of C-peptide provide a means to estimate insulin secretion. The well known 2 compartment kinetics model [48] is used due to its overall physiological relevance:

$$\frac{d\hat{C}}{dt} = \hat{S} - (k_1 + k_3)\hat{C} + k_2\hat{Y} \tag{5}$$

$$\frac{d\hat{Y}}{dt} = k_1\hat{C} - k_2\hat{Y} \tag{6}$$

Where $\hat{C}$ ($\hat{C} \in \mathbb{R} : \hat{C} \geq 0$ [pmol]) is the amount of C-peptide in the central compartment of plasma (and tissues in rapid equilibrium with the plasma), and $\hat{Y}$ ($\hat{Y} \in \mathbb{R} : \hat{Y} \geq 0$ [pmol]) is the amount of C-peptide in the peripheral extra vascular compartment. $\hat{S}$ is the rate at which C-peptide, and thus insulin, is secreted into the central compartment [pmol/min]. Assuming the same diffusive properties between compartments gives $k_2 = k_1(V_P/V_Q)$, and considering the concentrations of C-peptide in central and peripheral compartments ($C, Y \in \mathbb{R} : C, Y \geq 0$) with units [pmol/L], allows the model to be rewritten:

$$\frac{dC}{dt} = S - n_{I_{cp}}(C - Y) - n_{k_{cp}}C \tag{7}$$

$$\frac{dY}{dt} = n_{I_{cp}}\frac{V_P}{V_Q}(C - Y) \tag{8}$$

Where:

$$n_{I_{cp}} = k_1 \tag{9}$$

$$n_{k_{cp}} = k_3 \tag{10}$$

The rate parameter $n_{I_{cp}}$ describes the rate of transport of C-peptide from the central to the peripheral compartment, and vice versa, and assumes that $k_2 = k_1(V_P/V_Q)$, in the model presented in [48]. The parameter $n_{k_{cp}}$ describes irreversible removal of C-peptide from central compartment via the kidney. Rate parameters in Equation 9 are renamed to allow consistency with the NICING model structure,

and reflect the assumption that the rates of forward and reverse diffusion between compartments are equal.

Since no studies have been performed in preterm or term neonates to determine the C-peptide kinetics, adult data and methodology [48, 51] was used as a reasonable approximation since the kinetic compartments and their functional physiology are the same. The values for these parameters are given in Table 1, and were adapted to this cohort using the methods in [48] and an age of 0 years, according to the equation:

$$long\ half\ life\ (min) = 0.14 * age\ (years) + 29 \tag{11}$$

$$k_2 = F\ (b - a) + a \tag{12}$$

$$k_3 = \frac{a\ b}{k_2} \tag{13}$$

$$k_1 = a + b - k_2 - k_3 \tag{14}$$

where a = log(2)/(short half life), and b = log(2)/(long half life). This age-based extrapolation from adult data does not utilise the model within the limits of the cohort it was originally validated in. This extrapolation was necessary, as C-peptide kinetic data is not available for the premature neonate. However, all parameters fall within the adult ranges (Van Cauter et al., 1992, Polonsky et al., 1986) and were these parameters to scale differently in neonates, it would simply offset SI without changing underlying dynamics. As such, these values within the adult range are considered a justifiable estimation of neonatal behaviour.

Table 1: C-peptide model parameter values

Parameter	Value [1/min]
k_1	0.0478
k_2	0.0516
k_3	0.0644

Sampling constraints due to limited blood volume in this cohort meant frequent, serial measurements of C-peptide were not possible. Assuming steady state conditions, it follows from Equation 8 that the rate of C-peptide entering and leaving the peripheral compartment must be equal. Hence, substituting this equality into Equation 5 and rearranging yields:

$$S = n_{k_{cp}} C = k_3 C \tag{15}$$

Since insulin is secreted in equimolar quantities alongside C-peptide, then under steady state conditions the rate of secretion of insulin, u_{en}, can be estimated from the rate of excretion of C-peptide from the central compartment.

2.3 Insulin Kinetic Parameter Identification

2.3.1 Insulin Clearance Parameters

Insulin clearance kinetics were determined using the model-based method of [41], which used C-peptide kinetics in combination with the ICING model and patient data to determine appropriate insulin clearance parameter values. The diffusion constant for insulin between the plasma and interstitial compartments is modelled as the C-peptide transfer rate scaled by molar mass [41]:

$$n_I = n_{I_{CP}} \frac{m_c}{m_I} = k_1 \frac{m_c}{m_I} \tag{16}$$

Where $m_c = 3.02kDa$ and $m_I = 5.8kDa$ are the molecular masses of C-Peptide and Insulin, respectively. Diffusion can be complex to characterise, so sensitivity to this parameter was tested by multiplying the mass ratio by powers of 1/3 to 1/1, with the former power based on Einstein's theory for diffusion of molecules in solution [52].

To determine n_C, steady state is assumed and Equation 3 re-arranged to yield:

$$n_C = n_I \frac{V_P}{V_Q}\left(\frac{I_{ss}}{Q_{ss}} - 1\right) \tag{17}$$

In adults, studies indicate that the steady state interstitial to plasma insulin ratio (Q_{ss}/I_{ss}) is between 0.4 and 0.6 [53-56]. In this study, a ratio of 0.5 is used.

If steady state conditions are also applied to Equation 2 then the sum of the kidney and liver clearances can be estimated:

$$n_K + n_L \approx \frac{-n_I(I_{ss} - Q_{ss}) + \frac{u_{ex}(t)}{V_P * m_{body}} + (1 - x_L)u_{en}}{I_{ss}} \quad (18)$$

2.3.2 Kidney Clearance of Insulin

It is estimated that 30-80% of insulin in the systemic circulation is removed by the kidneys [57]. Renal clearance of insulin occurs via two pathways: glomerular filtration, and absorption from the peritubular capillaries. Glomerular filtration compromises about 60% of total insulin clearance by the kidney [57]. Creatinine and inulin clearance are two common molecules used to estimate glomerular filtration rate (GFR). The rate of glomerular filtration of insulin is approximately 90% that of inulin determined GFR [58]. As such, total insulin clearance via the kidney can be estimated:

$$n_k = \frac{1}{V_P} \times \frac{0.9\ GFR_{inulin}}{0.6} \quad (19)$$

Where GFR_{inulin} is in units of ml/min, and V_P is the distribution volume of insulin. For this cohort, GFR_{inulin}can be estimated using [59]:

$$GFR_{inulin} = 0.45 + 0.24m_{bw} + 0.18A_{PN} \quad (20)$$

Here m_{bw} is the birth is weight, and A_{PN} is the postnatal age in weeks.

2.3.3 Insulin Volumes of Distribution

Previously it was indirectly assumed that interstitial and blood plasma fluid volumes of distribution for insulin were essentially equal [37]. This assumption is not correct for neonates, and a literature search in PubMed was carried out to determine how plasma and interstitial fluid volumes change over time or between patients. As interstitial fluid volume is the extracellular fluid volume (ECV) minus the plasma volume (V_P), extracellular fluid volumes were also included in the search. Key search terms included: plasma, extracellular, interstitial, fluid volume, and neonate. Exclusion criteria included lack of reported values, non-human or adult fluid volumes reported. Fluid volumes were analysed in units of mL/kg. Results were plotted against postnatal age and reported standard deviations were included as error bars.

2.4 Clinical Data and Model Validation

2.4.1 C-peptide Data

The clinical data used here has been described in detail elsewhere [49, 50]. In summary, three to four blood samples were taken from 88 hyperglycaemic (two BG measures >8.5 mmol/L more than 4 hours apart) very preterm (born at <32 weeks gestation) and/or very low birth weight (<1500g) infants enrolled in a randomised trial of glycaemic control (the HINT trial [28], Auckland, New Zealand). Blood samples were taken at randomisation (0-5 days post natal age) and at approximately 7, 14 and 21 days after randomisation.

Plasma insulin (Azsym system auto-analyzer, Abbott Laboratories, Abbott Park, IL) and glucose (glucose oxidise method, ABL 700, Radiometer Ltd, Copenhagen, Denmark) concentrations were determined as part of the study, and remaining blood from the samples was frozen. Of the original cohort of 88, 41 were of GA<32 weeks and had 1 or more samples with sufficient remaining blood volume available for retrospective C-peptide analysis. C-peptide concentrations were determined using immunometric assays (Elecsys 2010, Roche Diagnostics, Germany). Table 2 provides demographic data over the sample cohort, as well raw sample results.

2.4.2 Model Validation Cohorts

The model was validated through retrospective fitting to clinically charted glycaemic data from two New Zealand NICU cohorts. The Christchurch Women's Hospital (CWH) cohort consists of 67 very/extremely premature patients who received insulin either under sliding scale-based or model-based protocols [60]. The HINT cohort [28] was derived from detailed BG, insulin and nutrition data charted during the HINT trial in Auckland, NZ. This is the same cohort from which the C-peptide data was obtained, but those one-off weekly blood samples did not always appear in the clinical BG record. Of a total of 88 patients in the trial, 55 had sufficiently detailed data (BG measured at least 6 hourly, generally more frequently) to extract one or more glycaemic episodes per subject. A glycaemic episode is defined as ≥ 12 hours of insulin therapy, and at least 4 BG (max 6 hours apart)

measurements during this time. These criteria resulted in a total of 243 patient episodes across both cohorts, with all details in Table 3.

S_I profiles were fit to clinical data from the CWH and HINT validation cohorts using the integral based fitting method [60] and Equations 1-4. Ordinary differential equation solutions for Equations 1 - 3 (*G*,*I*,*Q*) were generated using a Runga-Kutta 4 based method (Matlab®, ode45). Insulin kinetic parameter values determined in this analysis ($n_L, n_k, n_I, n_c, V_P, V_Q$) were used to generate the plasma and interstitial insulin concentrations (*I*,*Q*). The identified S_I must remain positive to be physiologically correct, so the lower limit of S_I was set to $1x10^{-7}$ L/mU/min (near 0, where a typical S_I is 10^{-4} – 10^{-3} L/mU/min). For comparison, S_I profiles were also fit, and BG and insulin profiles generated, using the original NICU model [37]. Fitting and prediction error were compared between the older NICU model iteration and the new NICING model as a measure of validation to show similar performance to a working, clinically effective standard.

Table 2: Clinical and sample characteristics. Numbers are presented as median [IQR] or number (% of total).

Number of Patients	
Total	41
Control	21
Tight Glycaemic Control	20
Male (%)	20(49%)
Age	
Gestational, weeks	27.2 [26.2 - 28.7]
Post natal, days	9.5 [4 -17]
Birth weight	
grams	839 [735 – 1000]
Z score	-0.19[-1.03 - 0.14]
Small for gestational age	6
Ethnicity	
Asian	9 (22%)
Caucasian	11 (27%)
Maori	17 (41%)
Pacific Island	4 (10%)
Sample results	
Number of Samples	54
Day after randomisation*	7 [0 - 14]
BG, mmol/l	7.5 [5.1 – 10.5]
Plasma insulin concentration, pmol/L	59.0 [99.3 – 181.9]
Plasma C-peptide concentration, nmol/L	2.3 [1.1 - 4.2]

*Samples were taken on day of randomisation 0, 7, and 14.

Table 3: Patient cohort characteristics, presented as number of patients, or median [inter-quartile range].

	HINT	CWH
Patients		
Total Number	55	67
Control/TGC	33/22	22/45
Male/female	27/28	
Age		
Gestational age, weeks	25 [24–26]	27 [25–28]
Post natal age, days	4 [3–8]	2 [0–5]
Birth weight		
grams	690 [740–890]	865 [690-960]
Z score	0.02 [-0.85–0.58]	-0.67 [-1.2–0.27]
SGA	9	13
Total Episodes	160	83
Control/TGC	57/103	25/48
Total hours	4673	8455
Total BG measurements	1389	2951
Median time between measurements (hours) [IQR]	4.0 [3.5–4.8]	3.3 [2.8–3.9]
Median BG [mmol/L]	7.10 [4.90–9.40]	7.10 [5.70–9.00]
Median insulin rate [IQR] (U/kg/hr):	0.060 [0.033–0.080]	0.036 [0.026–0.051]

2.4.3 Fitting and Prediction Error

Fitting error was calculated as the percentage difference between the model solution at a measurement time and the actual measured value. Where fitting error is high, the model fails to fit clinical data and is therefore inappropriate. However, for appropriately constructed model dynamics, fitting error saturates at some lower value as the fitted insulin sensitivity ensures model fit over a reasonable range of parameter values [60]. For this reason, prediction error is also analysed.

Prediction error is calculated as the percentage difference between the actual measured BG and a 1 hour forward prediction, where 1 hour is the minimum resolution of S_I in this framework. The prediction from time t_n to t_{n+1} is based on S_I from t_{n-1} to t_n and the 50th percentile (median likely outcome) of observed outcomes based on statistical models of a base population [61]. Lower prediction error indicates that dynamics previously reflected in S_I are now more comprehensively modelled. As a result, there is improved ability of the model to forward predict median likely changes in BG for a given insulin-nutrition treatment, which is essential for accurately assessing future patient-specific state, and thus for effective control.

3.0 Results

3.1 Fluid Volume Analysis

A total of 10 studies (n = 18 – 32, exception [62] with n = 5) examined typical fluid volumes in preterm neonates with an average study cohort gestation age <33 weeks and birth weight <2kg. Of these, 7 reported ECV values [62-67] and 4 reported V_P [62, 68-70]. Figure 1 shows a significant drop in ECV over the first 1-2 weeks post natal age (PNA), followed by a relative plateau. Although a lot of variability is seen between study mean values, most studies fall within one standard deviation of each other.

Given this data, a power law function (R^2 = 0.44) was fit to capture the rapid decrease in ECV over the first few days and subsequent ECV plateau:

$$ECV = 492 \times PNA^{-0.09} \quad (17)$$

Figure 2 shows that plasma volume does not significantly change over the first couple of weeks of life. While Ussher and Lind [70] show a very slight decrease over time (R^2 = 0.04), Bauer et al [62] shows a slight increase. Therefore, V_P could be assumed to remain essentially constant over time, with an average volume of 47 mL/kg. The interstitial fluid volume is thus:

$$V_Q = 492 \times PNA^{-0.09} - V_P \quad (18)$$

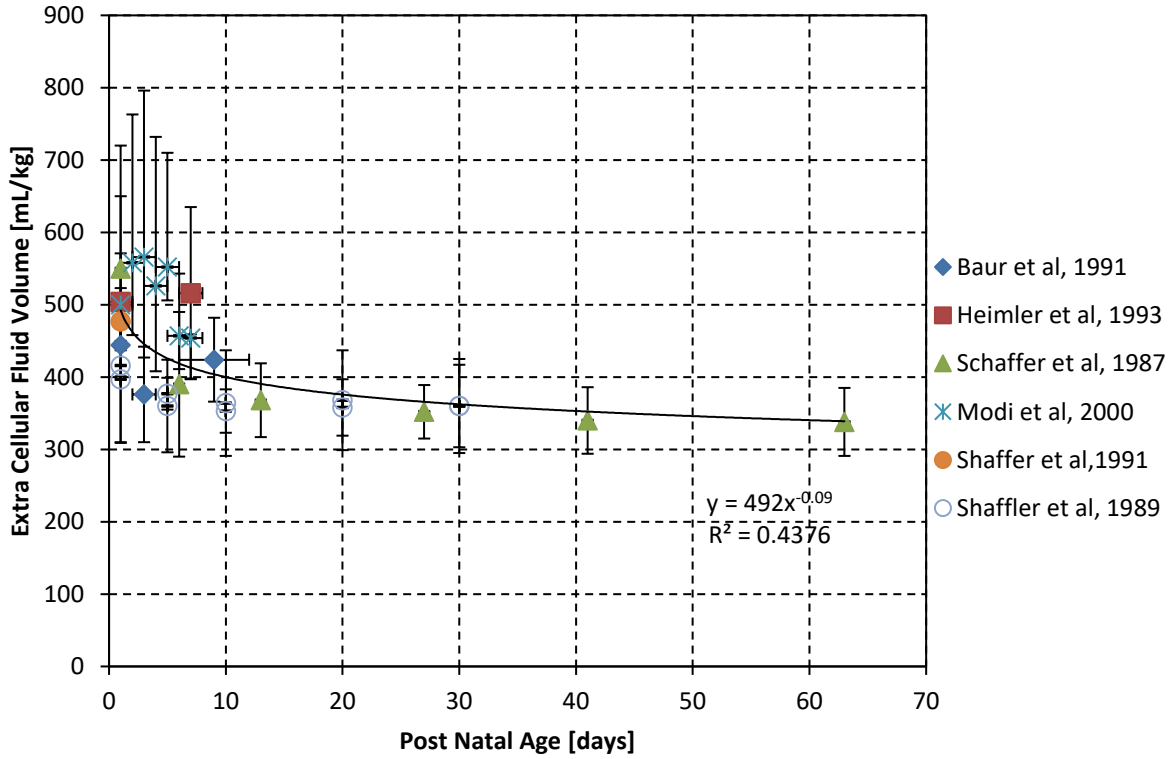

Figure 1: Decrease of ECV with postnatal age. Vertical Error bars are 1 standard deviation; horizontal error bars cover the range of days. For the Modi et al data, the median and range is plotted.

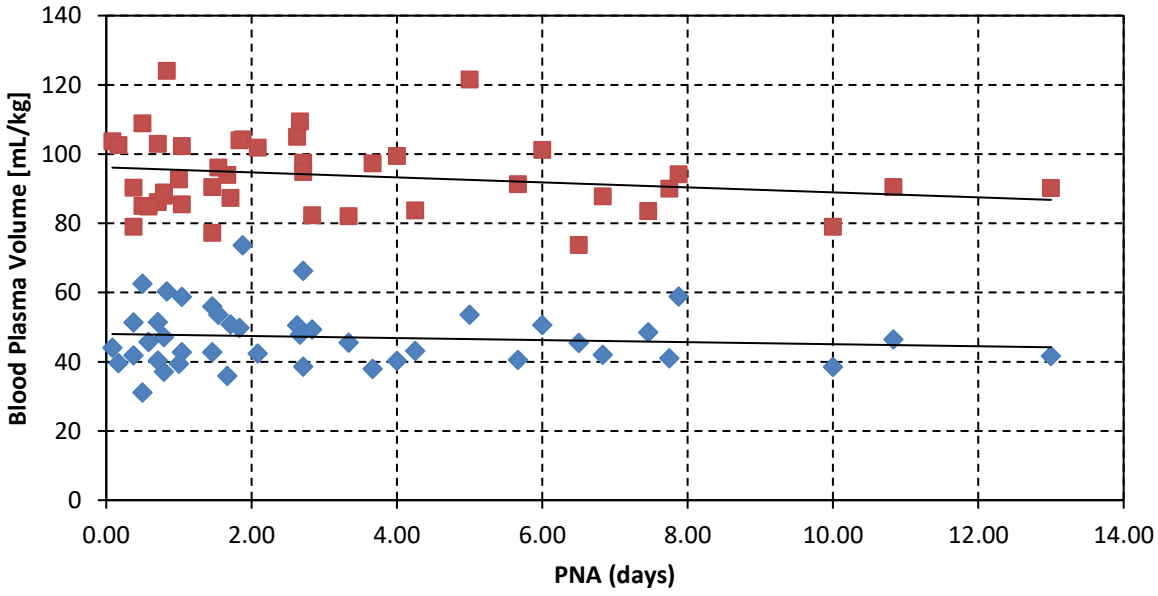

Figure 2: Plasma (♦) and blood volume (■) changes over time. Data used is patients with BW<2KG from Ussher et al [70].

3.2 Inference of Insulin Clearance Parameters

The results from the evaluation of Equations 14-18, using C-peptide data to estimate insulin secretion, are presented in Table 4 and Figure 3. It should be noted that n_C is scaled by the ratio of plasma volume to interstitial volume, as per Equation 17. The parameter n_K is made patient specific and dependant on a birth weight and postnatal age dependant model of GFR, according to Equations 19-20. The distribution of patient specific values for liver clearance, n_L, calculated using Equation 18, is shown in Figure 3, with a median clearance of 0.39 min^{-1}.

Sensitivity to assumptions around diffusion between compartments and hepatic insulin clearance was tested and results are shown in Figure 4. As n_I is an order of magnitude smaller than n_L, changes in n_I had very little effect on patient specific results for n_L. Figure 4 shows that within the sensitivity range, n_I had little effect on modelled plasma insulin concentrations. Model fit error was not affected, as the small change in peripheral insulin concentration, Q, resulted in a scale offset in S_I. The hepatic insulin clearance parameter, n_L, is much more sensitive, as evidenced in Figure 4 b). This aligns with expectations from Figure 3, where liver clearance was observed to be highly patient specific.

Table 4: Clearance Parameters based on HINT C-peptide analysis and physiological ranges in adult subjects. Unless otherwise state, results are presented as Median [IQR]

Parameter	Value [1/min]	Physiological range for adults [Lotz] Median (Range) [71]
n_I	0.025	0.28 [0.22-0.36] **[L/min]** 0.0052 [0.0041 – 0.0119] **[1/min]***
n_K	0.034 [0.030-0.039]	0.06 (0.053-0.064)
n_L	0.39 [0.15-0.70]	0.15 (0.1-0.21)
$n_c \frac{V_Q}{V_P} = n_I \left(\frac{I_{ss}}{Q_{ss}} - 1\right)$	0.025	-

* From [72]

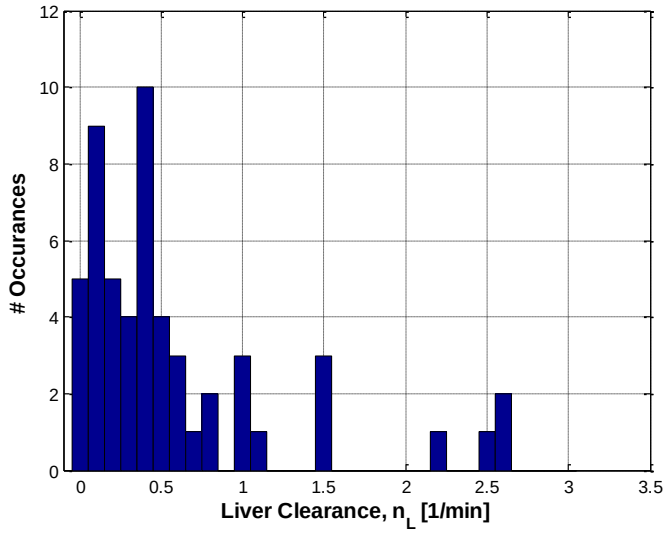

Figure 3: Liver clearance parameter, n_L, distribution derived from HINT data.

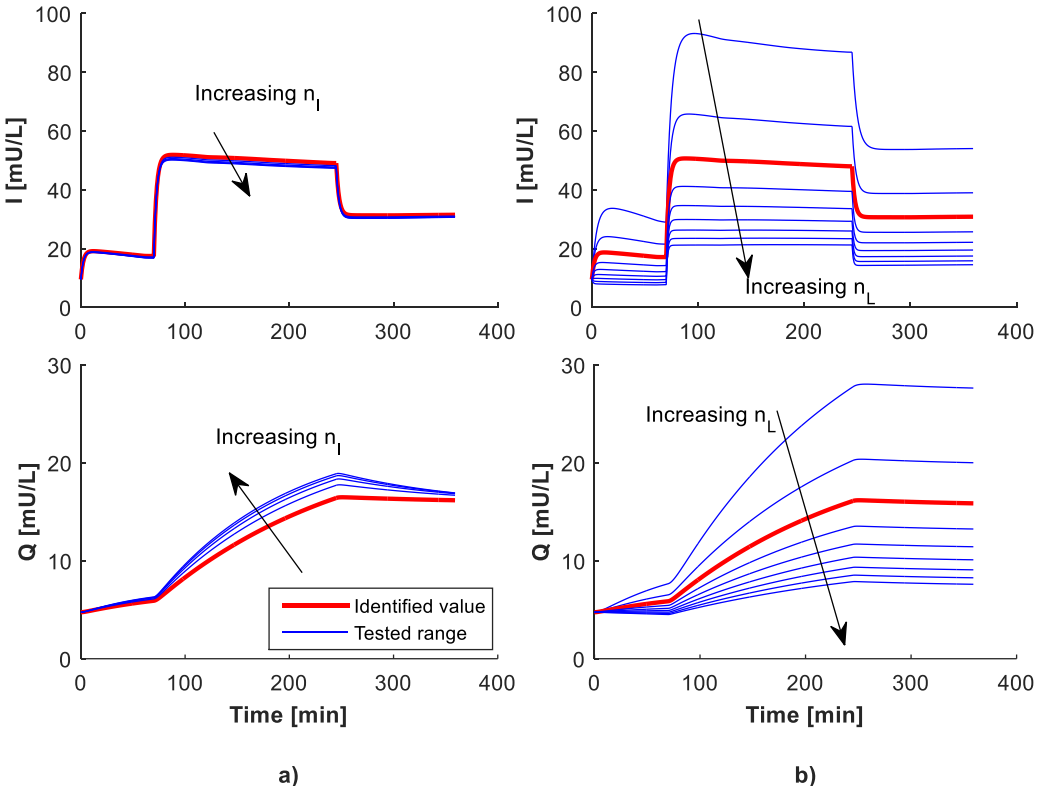

Figure 4: Sensitivity analysis of on a) diffusion of insulin between compartments (n_I), and b) hepatic insulin clearance n_L. Increasing n_I was achieved by multiplying the mass ratio of Equation 12 by a power of [1/1, 1/1.5, 1/2, 1/2.5, 1/3], giving n_I in the range 0.025 – 0.038 1/min. n_L was varied across the range: [0.20:0.10:1] 1/min.

Table 5 presents the fitting and prediction error results over the HINT and CWH patient cohorts for both the new NICING and the previous NICU [45] models. There was no difference in fitting error between the two models in the CWH cohort, and prediction error was slightly increased. In the HINT cohort, both fitting and prediction error were slightly decreased with the NICING model. All changes were very small relative to typical measurement errors. Figure 5 shows two examples fits to clinical data. Model fit is good, with only a very small undershoot on some peaks.

Table 5: Fitting and Prediction error for the NICING and NICU models

	CWH Cohort	**HINT Cohort**
NICING model		
Fitting Error	2.1%	2.7%
Prediction Error	12.6 [5.2-24.7] %	18.3 [7.3-34.0] %
NICU model		
Fitting Error	2.1%	2.9%
Prediction Error	11.7 [5.1-23.5] %	18.8 [8.1-37.0] %

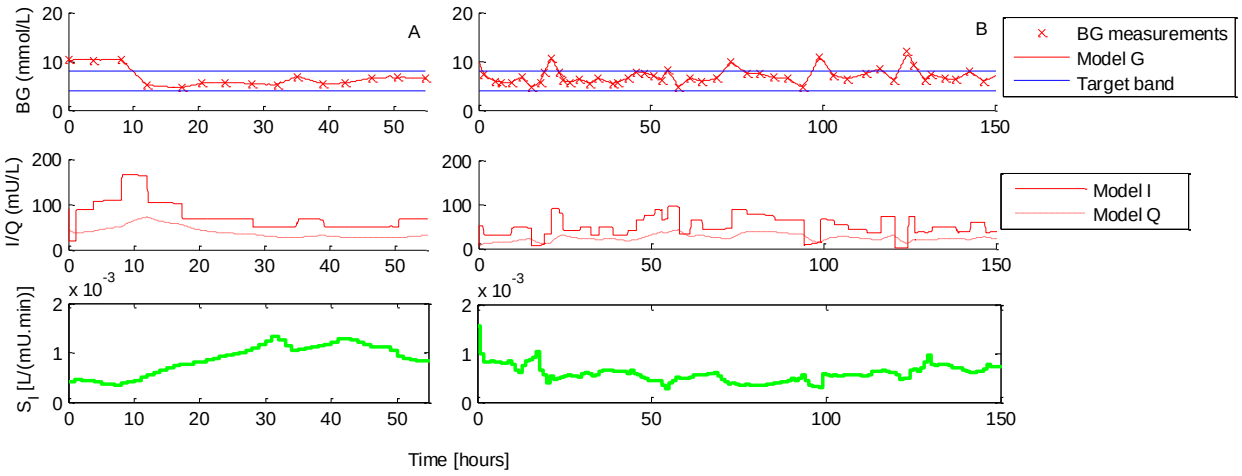

Figure 5: Model fit in A: a very stable shorter-stay patient, and B: long-stay dynamic patient.

4.0 Discussion

This study presents a more physiologically descriptive glucose-insulin model for the purposes of glycaemic control in premature infants. In particular, it focuses on the kinetics of insulin, which are necessary to obtain accurate estimates of patient-specific metabolic state, and thus accurate control. Previously in the NICU model [45], insulin clearance via the liver, kidney, and receptor-bound degradation was modelled by a single clearance parameter determined from literature data and minimisation of model fitting error. The NICING model separates out these clearances, adding a degradation term to the interstitial compartment, saturable liver clearance, and kidney clearance [38]. Birth weight and age based modelling of plasma volumes and GFR allow inter-compartment transport and renal clearances to be-patient appropriate.

After these changes, the full NICING model system has similar or better ability to fit two cohorts of clinical data when compared to a simpler and less physiologically relevant previous iteration of the model, as evidenced by the unchanged fitting error in the CWH cohort and the reduction in the HINT cohort. This reflects the model's ability to capture time-varying dynamics in the wider HINT cohort from which the insulin clearance parameters were derived, as well as in a separate, independent cohort to test whether the new model parameters were effective in capturing observed clinical dynamics. Prediction error was increased by ~1% in the CWH cohort, and decreased by ~1% in the HINT cohort, suggesting that the NICING model overall is likely to perform in a very similar manner to the NICU model. Clinical results to date using the old NICU model in model-based control [73, 74] suggest that it is robust, safe, and effective for use in glycaemic control in a NICU setting [74-76].

The NICING model is used in a risk-based decision framework [74, 77]. Hourly identification of S_I allows changes in insulin sensitivity to be observed. Stochastic modelling is used to predict future changes in insulin sensitivity, resulting in a distribution of likely BG outcomes for a given intervention. Insulin interventions are chosen such that this range of likely BG outcomes overlaps with the desired clinical targets. Specifically, we set a maximum risk threshold for mild hypoglycaemia (BG<4.0 mmol/L) at 5%. New results to date using the NICING model show further

significant improvement in control and safety [73] over the previous NICU model, indicating that the new model more accurately captures underlying dynamics, beyond what can be evaluated using fitting and prediction error.

Most of the insulin clearance parameters lie within the reported physiological range for adults, suggesting these volume normalised values are reasonable. Insulin diffusion between the plasma and peripheral compartments, n_I, is an order of magnitude faster than the adult ICING model ($n_I = 0.003\,\mathrm{min}^{-1}$). The associated half life of action for n_I is ~150 minutes, and when n_C is also considered, the combined time to half maximal interstitial insulin for an IV insulin infusion is ~70 minutes, which is similar to results from studies in lean and obese adults (46 and 72 minutes respectively) [56]. Given that that the ICING model value for n_I was chosen based on extensive grid search and fitting error minimisation [5], it is likely that the NICING value is more physiologically real.

Insulin kinetic parameters were assumed to be independent of nutritional intake. Previous work saw no clear trend or effect of nutrition on insulin secretion [49, 50], which is known in adults to be more directly affected by nutritional intake and resulting hormone signalling.

Hepatic liver clearance was found to be highly patient specific (Figure 3), and 2-3 times higher than adult values [71]. The wide range of clearance values found are a reflection of the model's sensitivity to this parameter (Figure 4), where, having calculated all other parameters, n_L was fit such that the model fit the samples plasma insulin concentration. This variability could also result from accumulated patient-specific deviation from other model parameters, however given kidney clearance (n_K) and diffusion between compartments (n_I) are an order of magnitude smaller, this effect is not likely to be significant. The high variability in the results is similar to the large variability in endogenous glucose production seen in previous work [39], and likely a reflection of patient condition and metabolic maturity in this very premature cohort. Patient-specific deviations in hepatic insulin clearances may thus result in a bias in the overall S_I profile for some patients, but are not likely to affect short-term changes in S_I.

The higher liver clearance constant in this premature infant cohort could be a reflection of overall higher hepatic metabolism and/or the relatively larger proportional mass of the infant liver. However, this is speculative as no studies specifically examine hepatic insulin kinetics in the premature infant. Premature infants have larger proportional organ mass and higher basal metabolic rate in proportion to total body mass than adults [78]. Previous reviews of literature show that endogenous glucose production (EGP) is generally higher in premature infants (median 2.2 mg/kg/min [39] vs. mean ~ 1.4 mg/kg/min in unfasted adults [79], EGP is higher at ~ 4 mg/kg/min in fasted adults [79]) and is also unsuppressed at higher BG and/or glucose infusion rate in premature infants [80]. Infants born less than 27 weeks gestation lack glycogen stores, so intravenous/frequent exogenous nutrition is required to meet energy needs. Thus, the premature liver may utilise and eventually clear more insulin than its adult counterpart, and for this reason liver clearance of insulin may be higher.

Birth weight and age based modelling of plasma volumes and GFR allow inter-compartment transport and renal clearances to be patient-appropriate. This approach is in contrast to the adult case, where these volumes are held constant. In addition, during the first week of life there is significant weight loss in the premature infant as the extracellular fluid compartment contracts. Modelling this contraction will prevent long term bias in identified S_I profiles, thus providing more accurate S_I estimates for use in glycaemic control.

Insulin degradation is being modelled as a process that is unsaturated at high insulin concentrations. [42] observed insulin mediated glucose uptake was not saturated with insulin concentration. Insulin mediated glucose uptake is a receptor-mediated process, and receptor-bound insulin is either released back into the extracellular space, or internalised by the cell [43]. As such, the same saturation parameter is applied to both insulin-mediated glucose uptake and insulin degradation. In this case it has been set to zero, due to the lack of observed saturation of insulin-mediated glucose uptake.

Glycaemic control using the ICING model in the adult intensive care unit has proven safe and effective, with low incidence of hypoglycaemia and around 90% time in a clinically targeted range of 4.0-8.0mmol/L [3]. The NICING model is based on the ICING model, and should thus allow

consistency with existing adult ICU glycaemic control protocols and T1DM/T2DM orientated models [81]. The greater physiological descriptiveness of the NICING model in comparison to the old NICU model additionally allows it to be more easily customised to the infant case using clinical C-peptide data, when available, and future metabolic studies.

Study limitations include the assumption of steady state kinetics in the analysis of C-peptide concentrations. Due to the inherent extreme fragility of this premature neonatal cohort, serial blood samples are not practically or ethically possible, so the more detailed model based analysis of C-peptide and insulin kinetics seen in adult studies [48, 82] are not possible. Such steady-state assumptions are not unreasonable in this cohort, as the majority of nutrition is given via parenteral infusion, or enteral feeds, which do not tend to change dramatically from hour to hour. In addition, none of the samples were taken within 2 hours of an infant starting insulin infusion. Hence, the assumption of steady state conditions is both reasonable and a necessity in this cohort.

Further, no kinetic parameters are available for C-peptide dynamics specific to this cohort, so adult kinetic parameters, adjusted for age, were used. Patient specific parameters for neonates cannot be determined due to the demands of the procedure. While it is understandably not desirable to use age to extrapolate these adult parameters this far beyond the cohort for which they were originally validated, the resulting normalised parameter values fall within ranges reported in studies on adults [48, 51]. This outcome provides a level of qualitative validation that the assumption used is not poor. In addition, using adult kinetic population constants, particularly under the assumption of steady state, is not likely to change any of the underlying trends observed, and scale differences are absorbed by the model in an overall shift in S_I without altering control outputs. Thus, as long as S_I forecasting models are scaled consistently, relative changes in S_I, enabling BG prediction, are accounted for. If this model were to be used in a more detail-oriented setting (e.g. like the metabolic analysis of [1, 2]), or if patient-specific insulin parameters (e.g. liver clearance), were to be identified in real time for control, this assumption may require revisiting and further examination. This study highlights the need for data and studies to validate any significant differences in neonatal kinetics that would affect this assumption, as well as, more generally, the potential value of pursuing such studies in this cohort.

A limitation of the HINT data used in validation is that all nutritional data was recorded as daily totals. It was assumed that daily totals were delivered as a constant infusion over the course of the day, which is not unreasonable in this cohort. However, the slightly higher fitting error in this cohort is likely caused in part by this assumption.

5.0 Conclusions

A physiological model of glucose-insulin kinetics for use in glycaemic control in very premature infants is presented. The insulin kinetics model is more physiologically descriptive than previously, and parameters identified using a novel set of C-peptide concentrations from very premature infants. Cohort and infant-specific insulin clearance parameters were identified for clearance through the liver, the kidneys, and peripheral degradation. Saturation of liver clearance at high insulin concentration is modelled, and kidney clearance is modelled according to changes in kidney function with birth weight and gestational age. Estimations of insulin distribution values based on fluid compartments are found from literature data, and the post-natal contraction of the extracellular fluid compartment is also captured. Fitting error between the model and clinical validation data across two clinical data sets indicate that this model has a similar or better ability to fit clinical data compared to a previous, less physiologically detailed and relevant NICU model, and tight glycaemic control performance is significantly improved.

6.0 Acknowledgements and conflicts of interest

The authors declare that there are no conflicts of interest associated with this work. Clinical data from the HINT trial was provided by Dr Jane Alsweiler, and analysed independently from the original trial. Additional C-peptide analyses on existing blood samples was funded by Health Research Council of New Zealand. Clinical data from Christchurch Women's Hospital was collected as part of ongoing research between the University of Canterbury and Christchurch Women's Hospital. The main body of this work and manuscript was carried out by Jennifer Dickson, who was funded by a Canterbury PhD Scholarship.

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