Intensive Control Insulin-Nutrition-Glucose Model Validated in Critically Ill Patients

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Abstract: A comprehensive, more physiologically relevant Intensive Control Insulin-Nutrition-Glucose (ICING) Model is presented and validated using data from critically ill patients. Glucose utilisation and its endogenous production in particular, are more distinctly expressed. A more robust glucose absorption model through ingestion is also added. Finally, this model also includes explicit pathways of insulin kinetics, clearance and utilisation. Identification of critical constant population parameters is carried out parametrically, optimising one hour forward prediction errors, while avoiding model identifiability issues. The identified population values are $p_G = 0.006$ min^{-1}, $EGP_b = 1.16$ mmol/min and $n_I = 0.003$ min^{-1}, all of which are within reported physiological ranges. Insulin sensitivity, S_I, is identified hourly for each individual. All other model parameters are kept at well-known population values or functions of body weight or surface area. A sensitivity study confirms the validity of limiting time-varying parameters to S_I only. The model achieves median fitting error <1% in data from 173 patients (N = 42,941 hrs in total) who received insulin while in the Intensive Care Unit (ICU) and stayed for more than 72 hrs. Most importantly, the median per-patient one-hour ahead prediction error is a very low 2.80% [IQR 1.18, 6.41%]. It is significant that the 75^{th} percentile prediction error is now within the lower bound of typical glucometer measurement errors of 7–12%. This result further confirms that the model is suitable for developing model-based insulin therapies, and capable of delivering tight blood glucose control, in a real-time model based control framework with a tight prediction error range.

Keywords: model-based control, tight blood glucose control, TGC, blood glucose, insulin therapy, insulin sensitivity, critical care, predictive performance

1. INTRODUCTION

Since the landmark study in surgical intensive care unit (ICU) patients by Van Den Berghe et al. (2001), which reduced mortality 18-45% using tight glycaemic control (TGC), the attitude towards tolerating hyperglycaemia in critically ill patients has changed. However, repeating the results of Van Den Berghe et al. (2001) has been difficult, and the role of TGC in ICU and suitable glycaemic ranges have been under scrutiny in recent years (e.g. Schultz et al., 2008; Preiser, 2009; Vanhorebeek et al., 2007; Moghissi et al., 2009). However, conclusions are varied with both success (Van Den Berghe et al., 2006; Chase et al., 2008; Krinsley, 2004), failure, (The NICE-SUGAR Study Investigators, 2009) and, primarily, no clear outcome (e.g. Griesdale et al., 2009; Wiener et al., 2008).

Although allowing excessive hyperglycaemia and its associated effects is becoming unacceptable (Preiser and Devos, 2007), moderately elevated blood glucose levels are tolerated or recommended (Moghissi et al., 2009) because of the fear of hypoglycaemia and higher nursing effort frequently associated with TGC (Preiser and Devos, 2007; Vanhorebeek et al., 2007). Interestingly, some, but not all, TGC studies that reported a mortality reduction also had reduced and relatively low hypoglycaemic rates (Chase et al., 2008; Krinsley, 2004), whereas almost all other reports had increased and often excessive hypoglycaemia (e.g. The NICE-SUGAR Study Investigators, 2009; Brunkhorst et al., 2008).

Many studies have developed glucose-insulin models with varying complexity for a wide range of uses, primarily in research studies of insulin sensitivity (e.g. Chase et al., 2007; Mari and Valerio, 1997; Bergman et al., 1981; Parker and Doyle, 2001; Hovorka et al., 2007). For a model to be successful in TGC, it needs to reflect observable physiology and known biological mechanisms. In addition, it should be uniquely identifiable given the limitated clinically available data. Finally, the most important aspect for a model in model-based TGC is its predictive ability, where most studies provide only fitting error as validation (e.g. Hovorka et al., 2007; Parker and Doyle, 2001).

This paper presents a more physiologically relevant and comprehensive model, ICING (Intensive Control Insulin-Nutrition-Glucose Model), for TGC particularly in the ICU. The model addresses several incomplete or implicit physiological aspects from prior models by Chase et al. (2007) and Lotz et al. (2008). The new model is validated using clinical data from ICU patients and assessed for both its fitting, and more critically, predictive performance.

2. GLUCOSE-INSULIN PHYSIOLOGY MODEL

Two clinically validated glucose-insulin models set the basis of this study. The model from Chase et al. (2007) was developed and validated for TGC in the ICU. This model captures the fundamental dynamics seen in ICU patients, yet has a relatively simple mathematical structure enabling rapid identification of patient-specific parameters (Hann et al., 2005). This model only requires measurements in blood glucose levels (BG), therefore it can be used clinically for real-time identification and control.

The second model from Lotz et al. (2008) was developed for insulin resistance diagnosis. The modeled insulin sensitivity has high correlation to the euglycaemic hyperinsulinemic clamp (EIC) and high repeatability. However this model cannot be readily applied to TGC because it requires non-real-time plasma insulin and C-peptide assays.

Both models perform very well for their specific applications. However, neither is generic enough to be readily applied to different clinical settings. The model in Chase et al. (2007) lacks diffusive mechanism between interstitial and plasma insulin compartments, making it unsuitable for modeling relatively low doses of insulin infusion. The lack of a generic dextrose absorption model also limits its application. The model in Lotz et al. (2008) does not include insulin receptor saturation, limiting its use to low-dose insulin administration. The Intensive Control of Insulin-Nutrition-Glucose (ICING) Model is developed by combining the best aspects of these two models:

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

$$\dot{Q} = n_I(I(t) - Q(t)) - n_C\frac{Q(t)}{1+\alpha_G Q(t)} \quad (2)$$

$$\dot{I} = -n_K I(t) - \frac{n_L I(t)}{1+\alpha_I I(t)} - n_I(I(t) - Q(t)) + \frac{u_{ex}(t)}{V_I} + (1-x_L)\frac{u_{en}}{V_I} \quad (3)$$

$$\dot{P}1 = -d_1 P1 + D(t) \quad (4)$$

$$\dot{P}2 = -min(d_2 P2, P_{max}) + d_1 P1 \quad (5)$$

$$P(t) = min(d_2 P2, P_{max}) + PN(t) \quad (6)$$

$$u_{en}(t) = k_1 e^{-\frac{I(t)^{k_2}}{k_3}} \quad \text{when C-peptide data is not available} \quad (7)$$

The nomenclature for this model is listed in Table 1.

Table 1. Nomenclature for the ICING Model

G	Blood glucose level	[mmol/L]
Q	Interstitial insulin level	[mU/L]
I	Plasma insulin level	[mU/L]
EGP	Endogenous glucose production	[mmol/min]
EGP_b	Basal endogenous glucose production	[mmol/min]
CNS	Central nervous system glucose uptake	[mmol/min]
p_G	Insulin independent glucose removal (excluding CNS) and the suppression of EGP from EGP_b with respect to G	[min^{-1}]
S_I	Insulin mediated glucose removal and the suppression of EGP from EGP_b with respect to G and Q	[L/mU/min]
α_G	Saturation parameter for insulin mediated glucose removal	[L/mU]
V_G	Plasma glucose distribution volume	[L]
$P(t)$	Glucose appearance in plasma from dextrose intake	[mmol/min]
n_I	Plasma-interstitium insulin diffusion rate	[min^{-1}]
n_C	receptor-bound insulin degradation	[min^{-1}]
n_K	insulin clearance through kidneys	[min^{-1}]
n_L	insulin clearance through liver	[min^{-1}]
α_I	Saturation parameter for insulin clearance through liver	[L/mU]
$u_{ex}(t)$	Exogenous insulin	[mU/min]
$u_{en}(t)$	Endogenous insulin	[mU/min]
V_I	Insulin distribution volume	[L]
x_L	First pass hepatic clearance	
$P1$	Glucose level in stomach	[mmol]
$P2$	Glucose level in gut	[mmol]
d_1	Glucose absorption rate from stomach	[min^{-1}]
d_2	Glucose absorption rate from gut	[min^{-1}]
$D(t)$	Enteral dextrose intake	[mmol/min]
$PN(t)$	Parenteral dextrose intake	[mmol/min]
P_{max}	Maximal glucose flux from gut to plasma	[mmol/min]
k_1	Basal endogenous insulin production	[mU/min]
k_2, k_3	Generic constants for exponential suppression of u_{en} with elevated I	

Equation (1) is revised from the glucose compartment in Chase et al. (2007). Insulin independent glucose removal (excluding CNS) and the suppression of EGP from EGP_b with respect to $G(t)$ are compounded and represented by p_G. Insulin mediated glucose removal and the suppression of EGP from EGP_b are similarly compounded and represented by S_I. Consequently, S_I effectively represents the whole-body insulin sensitivity, which includes tissue insulin sensitivity and the action of Glucose Transporter-4 (GLUT-4). The action of GLUT-4 is associated with the compounding effect of receptor-binding insulin and blood glucose, and its signaling cascade is also dependent on metabolic condition and can be affected by medication (Bryant et al., 2002). Therefore, S_I is time varying and can reflect evolving patient condition. Its variation through time can be significant, particularly for highly dynamic, critically ill patients (Lin et al., 2008).

Equations (2) and (3) define the insulin pharmacokinetics, and are revised from Lotz et al. (2008). Insulin clearance from plasma is saturable, so is its degradation after receptor binding in the interstitium (Duckworth et al., 1998). The receptor-bound insulin $Q/(1+\alpha_G Q)$ is also the portion effective for glucose removal to cells. Hence this term also appears in Equation (1) for glucose dynamics.

Equations (4)–(6) present the gastric absorption of glucose. This dextrose absorption model is generic, whereas the equations in Chase et al. (2007) require relatively infrequent adjustments in enteral feeding rate. Equation (7) is a generic representation of endogenous insulin production if C-peptide data is not available from the patient for specific identification of its production.

In summary, the ICING model has added CNS and EGP_b in the glucose compartment, and a generic gastric absorption model compared to Chase et al. (2007). The insulin kinetics is similar to Lotz et al. (2008), but with added insulin receptor saturation. The generic expression of endogenous insulin production is also a new addition, and reflects observed physiology (Duckworth et al., 1998). Overall, this model is more comprehensive in physiology compared to the models from Chase et al. (2007) and Lotz et al. (2008). The more generic expressions of the compartments, as oppose to protocol specific, also makes the ICING model more suitable for testing or designing different insulin-nutrition protocols.

3. METHODS

Validation of the ICING Model is performed using data from 173 patients (42,941 total hours) that were on the SPRINT TGC protocol for ≥3 days, which cohort also had a statistically significant hospital mortality reductions (Chase et al., 2008). These patients also had long enough stays to exhibit periods of both dynamic evolution and metabolic stability. The median APACHE II score for this cohort is 19 [IQR 16, 25] and the median age is 64 [IQR 49, 73] yrs old. The percentage of operative patients is 33%.

The introduction of EGP_b and its relationship with p_G and S_I in the ICING Model requires EGP_b, p_G and S_I to be identified, rather than adapted from Chase et al. (2007). Amongst parameters associated with insulin kinetics, n_I also needs to be identified independently because of its influence on the shape of Q, linking I and G (note that n_C can be calculated from n_I (Lotz et al., 2008)). Parameter identification and model validation were performed in two stages to avoid identifiability issues, because G is the only compartment measured in ICU patients.

The first stage focuses on glucose dynamics and identifies p_G and EGP_b as model constants in Equation (1). Because n_I is yet to be identified, insulin kinetics equations and associated constant parameter values from Chase et al. (2007) are used during this stage:

$$\dot{Q} = -kQ(t) + kI(t) \tag{8}$$

$$\dot{I} = -\frac{nI(t)}{1+\alpha_I I(t)} + \frac{u_{ex}(t)}{V_I} \tag{9}$$

The model at this stage is referred to as the "Intermediate Model". The second stage focuses on insulin kinetics and uses the complete model as defined by Equations (1)–(7). Identification of n_I is performed in this stage. Figure 1 illustrates the parameter identification process and the model stages.

Insulin sensitivity, S_I, the critical dynamic parameter, is identified hourly using an integral based method (Hann et al., 2005) while a grid search of p_G and EGP_b values

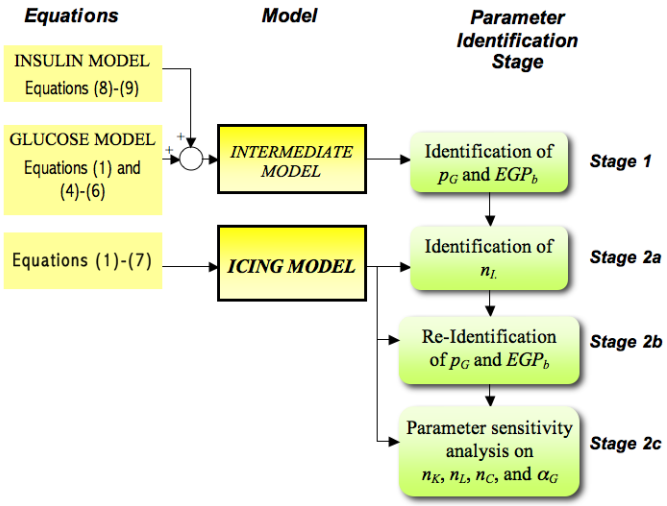


Fig. 1. Parameter identification process.

was performed in *Stage 1*. A similar grid search of n_I then follows in *Stage 2a*. During grid searches, one constant value for each parameter is applied across the whole cohort. Optimal population constant parameter values for p_G, EGP_b and n_I are chosen from all the combinations analysed according to the model's goodness of fit and, more importantly, the one hour forward prediction accuracy, by assuming the current fitted hourly S_I for the next hour. Grid search of p_G and EGP_b is performed again with the complete ICING model to confirm these values in *Stage 2b*. Finally, a sensitivity study (*Stage 2c*) is performed on the other parameters treated as population constants (n_K, n_L, n_C, and α_G). This step verifies the validity of using population constants for these parameters.

4. RESULTS

4.1 p_G and EGP_b Identified in the Intermediate Model – Stage 1

The per-patient median prediction and fitting errors over the ranges $p_G = 0.001 \rightarrow 0.1$ [min^{-1}] and $EGP_b = 0 \rightarrow 3.5$ [mmol/min] generally increase diagonally from low p_G-low EGP_b region to high p_G-high EGP_b region. The area where low fitting and prediction errors occur also have the least number of large outlying errors. The "per-patient" analysis weights each patient equally and eliminates any bias from having different lengths of patient data. The per-patient analysis also provides an idea of the cohort characteristic and inter-patient variability.

Given that low p_G and low EGP_b produced generally low per-patient fitting and prediction error well within the typical measurement error of 7–12%, cohort-wise errors were evaluated to determine the most suitable p_G-EGP_b combination. Figure 2 shows the cumulative distribution function of the fitting error for 3 selected combinations of p_G and EGP_b values. These values provided equally good per-patient fitting and prediction errors, as well as cohort-wise prediction errors. The best fitting errors, with the least number of hourly error over measurement error, is achieved with $[p_G, EGP_b] = [0.006, 1.16]$. Both values are within the reported physiological ranges (e.g. Tappy

et al., 1999; Chambrier et al., 2000; McDonald et al., 2000; Pillonetto et al., 2002).

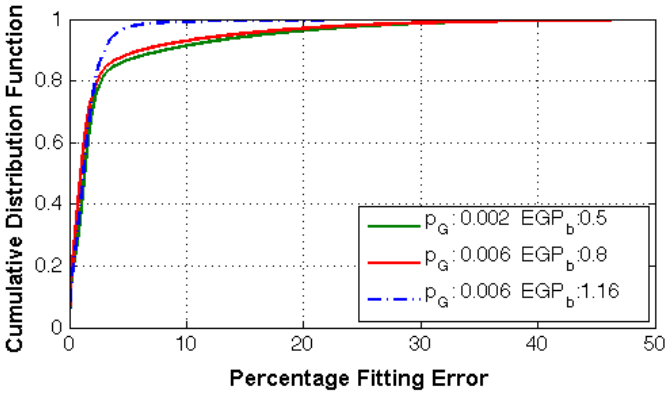
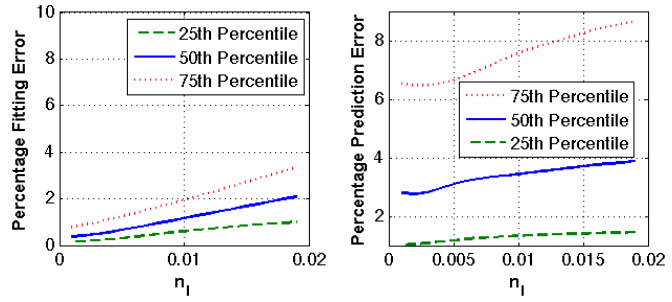


Fig. 2. Cumulative distribution functions of fitting errors with different combinations of p_G and EGP_b.

4.2 Insulin Kinetics Parameters identified in the ICING Model – Stage 2a

The median of the 25^{th}, 50^{th} and 75^{th} percentile fitting and prediction errors for each patient across $n_I = 10^{-4} \rightarrow 0.02$ min^{-1} in the full ICING Model are shown in Figure 3. It can be seen that $n_I = 0.003$ min^{-1} provides the best predictive performance while fitting error is low through the entire range. This value corresponds to a half-life within the reported ranges (Mari and Valerio, 1997; Natali et al., 2000).



(a) Fitting Error (%) (b) Prediction Error (%)

Fig. 3. Fitting and Prediction Error from n_I grid search.

Patient 5004 is shown in Figure 4 as an example of typical model fit using the fully identified ICING Model (*Stage 2a* in Figure 1). The model is capable of capturing the patient's highly variable dynamics during critical illness, particularly from the 50^{th} hour to the end of stay, where the insulin requirement varied significantly from hour to hour. Note that in Figure 4, only hourly insulin levels in plasma and interstitial are plotted for readability.

The improvements in model performance from the model of Chase et al. (2007) through Intermediate Model, and finally the fully identified ICING Model in Equations (1)–(7) are shown in Table 2. Results are shown on both per-patient and by cohort basis to highlight any inter-patient variability in model performance.

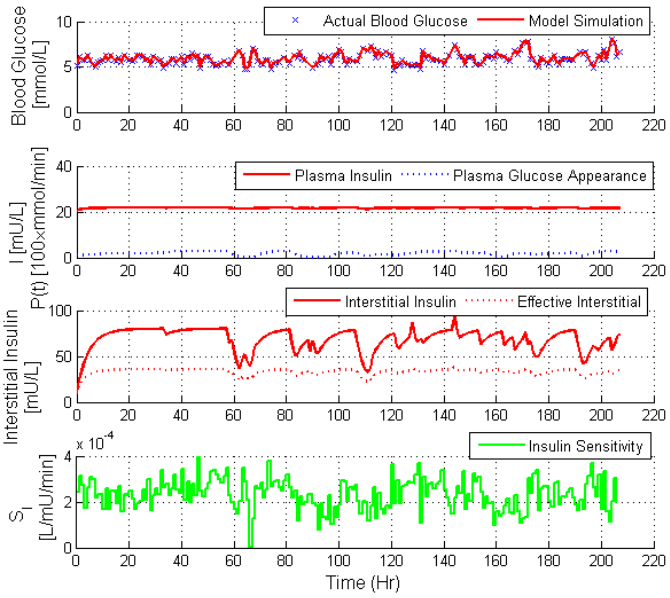


Fig. 4. Simulation results on Patient 5004 using the fully identified ICING Model. In the top panel, the solid line (–) illustrates the blood glucose model simulation while crosses (×) represents the actual BG measurements. The second panel demonstrates the plasma insulin appearance (–) and plasma glucose appearance (···). The third panel shows the interstitial insulin (–) and the receptor-bound interstitial insulin (···). Model fitted S_I is displayed in the bottom panel.

Main results in Table 2 show:

(1) Intermediate Model reduces **intra-patient** variability with lower per-patient upper quartile prediction.
(2) Finalized ICING Model reduces **inter-patient** variability with lower upper quartile cohort prediction errors.

Table 2. Comparison of Median and IQR for Prediction and Fitting Error Between Models

	Chase Model[#]	*Intermediate Model*	*ICING Model*
Prediction Error (%) median [IQR]			
pp[*]	5.90 [4.75,7.51]	5.23 [4.20,6.36]	**2.80 [1.18,6.41]**
bc[+]	5.59 [2.46,10.64]	5.02 [2.11,10.34]	**2.81 [1.08,6.47]**
Fitting Error (%) median [IQR]			
pp[*]	1.11 [0.84,1.63]	0.86 [0.58,1.18]	**0.50 [0.21,0.99]**
bc[+]	1.02 [0.41,1.94]	0.71 [0.23,1.44]	**0.47 [0.20,0.97]**
S_I (10^{-3} L/mU/min) median [IQR]			
pp[*]	0.25 [0.11,0.45]	0.21 [0.13,0.41]	**0.31 [0.23,0.40]**
bc[+]	0.24 [0.14,0.40]	0.21 [0.14,0.32]	**0.31 [0.20,0.48]**

[#]model from Chase et al. (2007),
[*]pp = per-patient, [+]bc = by cohort

4.3 Re-Identification of p_G and EGP_b – Stage 2b

Grid search for the re-identification of p_G and EGP_b near the previously identified [p_G, EGP_b] = [0.006, 1.16] from Section 4.1 re-affirm these values. This combination of p_G and EGP_b values provides very low fitting and prediction errors in the grid search region, and does not require adjustments.

Table 3. Sensitivity analysis on prediction error, fitting error and S_I

	Baseline	n_K		n_L		n_C		α_G	
		+50%	−50%	+50%	−50%	+50%	−50%	+50%	−50%
Prediction Error (%)	2.81	2.82	2.78	2.88	2.73	2.93	2.75	2.74	3.02
median [IQR]	[1.08,6.47]	[1.09,6.49]	[1.05,6.46]	[1.12,6.51]	[1.03,6.43]	[1.13,6.52]	[1.04,6.46]	[1.03,6.40]	[1.17,6.55]
Fitting Error (%)	0.47	0.51	0.43	0.54	0.39	0.54	0.42	0.41	0.62
median [IQR]	[0.20,0.97]	[0.22,1.02]	[0.18,0.90]	[0.24,1.08]	[0.17,0.84]	[0.24,1.08]	[0.18,0.88]	[0.17,0.87]	[0.28,1.17]
S_I (10^{-3}L/mU/min)	0.31	0.35	0.28	0.37	0.26	0.35	0.29	0.39	0.25
median [IQR]	[0.20,0.48]	[0.22,0.53]	[0.18,0.43]	[0.24,0.58]	[0.17,0.38]	[0.22, 0.54]	[0.19,0.42]	[0.26,0.57]	[0.16,0.40]

*Baseline is the model performance when no change is made to the constant parameters, and is the same as in Table 2 for the ICING Model.

4.4 Parameter Sensitivity – Stage 2c

The parameter sensitivity study results for n_K, n_L, n_C and α_G are shown in Table 3. Changes of ±50% from their final parameter values for the ICING Model have no clinically (as opposed to statistically) significant effect on simulation results in terms of prediction error, fitting error and identified insulin sensitivity, S_I. These results suggest n_K, n_L, n_C and α_G can be fixed at their current population values without over simplifying the model.

5. DISCUSSION

The ICING Model presented in this study is an integration and improvement of two clinically validated glucose-insulin physiological models (Chase et al., 2007; Lotz et al., 2008). This new model has more explicit physiological relevance without increasing the number of patient-specific parameters to be identified. The insulin kinetics is expressed with distinctive routes for clearance and transport from plasma, reflecting biological mechanisms. A generic model for gastric glucose absorption is also introduced.

Parameters for endogenous glucose removal p_G, and basal endogenous glucose production EGP_b trade off each other. Therefore, it is important that they are identified as a pair. The definition for EGP_b implies this parameter stays constant for any given patient. The decision to keep p_G as a constant is based on its relatively constant behaviour in ICU patients (Hann et al., 2005). Grid analysis for the identification of p_G and EGP_b as constants population parameters found the most suitable combination of parameter values within reported physiological ranges.

Glucose uptake is highly correlated with interstitial insulin (Poulin et al., 1994). However, interstitial insulin concentrations and dynamics are difficult or impossible to measure experimentally. This study attempted to find a realistic description of interstitial insulin by linking plasma insulin and BG response through known biological mechanisms and parameter identification. The diffusion rate between plasma and interstitium n_I, is the critical parameter linking I and G, and its population value is chosen using an exhaustive grid search in a physiological range. The chosen parameter value provided low fitting and prediction error in BG, and particularly reduced inter-patient variability in prediction error.

An important issue also addressed in this study is model identifiability. Given the limited data available at the bedside, it is crucial to maintain a model that is uniquely identifiable with bedside (glucose) measurements. Although the model presented in this study requires many population assumptions, and resulted in a much simpler structure compared to many others (e.g. Parker and Doyle, 2001; Hovorka et al., 2007), it is able to accurately capture the highly dynamic response in critical illness. Given all the parameters kept as population constants have been carefully studied and their sensitivity analysed, this paper presents a clinically applicable yet comprehensive glucose-insulin model that is uniquely identifiable for each patient at any given time.

However, all models have limitations and this model would benefit from further investigation into some parameters. The critical parameters are those that influence the shape of $Q/(1 + \alpha_G Q)$, as this level is the ultimate unknown (being unmeasurable) and the critical link between insulin and BG response. These parameters are effectively n_I and α_G, as the parameters that only appear in the plasma insulin equation (Equation (3)) can be more readily identified given insulin and C-peptide measurements.

6. CONCLUSIONS

A new, more comprehensive glucose-insulin model is presented and validated using data from ICU patients. The model is capable of accurately capturing long term dynamics of a ICU patient's glucose-insulin response. Insulin sensitivity S_I is the only parameter that is identified hourly for each individual. Its identification is guaranteed to be unique given the integral fitting method used in this study. Population constant parameters p_G, EGP_b and n_I have been identified in steps to avoid model identifiability issues. Parameter sensitivity analysis further confirms the validity of limiting time-varying parameters to S_I only. The model achieved low fitting and, most importantly, low prediction error when validated on ICU patients. Fitting errors and the 75^{th} percentile prediction errors were all well below measurement error for 42,941 hours of data from 173 patients. The new model outperforms its predecessors, and has greater physiological relevance. This model therefore offers a platform to develop robust insulin therapies for tight glycaemic control.

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