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MATHEMATICAL MODELLING OF GLUCOSE-INSULIN SYSTEM BEHAVIOUR IN HOSPITAL TENGKU AMPUAN AFZAN INTENSIVE CARE UNIT PATIENTS

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ABSTRACT

Mathematical modelling of glucose-insulin system is significantly important to understand the body regulation control, to analyze experimental data based on clinical trials, to identify and quantify relevant physiological parameters, to design proper clinical trials and to assess diabetes therapies. In general, critically ill patients with blood glucose concentrations between 10.0 to 12.2 mmol/l is identified to develop an acute *hyperglycaemia* or high blood glucose (BG). Thus, to monitor *hyperglycaemia* among critically ill patients, this study is focused on observing the glucose-insulin system behaviour based on 40 patients' clinical data collected in Hospital Tengku Ampuan Afzan, Kuantan, Pahang with clinically validated mathematical glucose-insulin model. By using this model, a critical model-based parameter known as insulin sensitivity (*SI*) that illustrates patient's severity were identified hourly for all patients whose on insulin infusion therapy protocol for average four to six days. The results show that a BG normal distribution is attained with median kurtosis of 2.72. While, the 40 patient-specific *SI* indicate that an outliers-prone distribution occurred as kurtosis 3.96. Thus, abrupt changes in *SI* is basically due to chaotic interaction between blood glucose and insulin concentrations in bloodstreams. Also, the glucose-insulin behaviour pattern among these 40 critically ill patients might be varied due to their main diagnostics illness such as acute kidney failure, cardiovascular disease, etc. Overall, these results might assist clinicians and researchers to understand the glucose-insulin behaviour based on patient's severity illness and helps to inform glycaemic control protocol development in a larger group of critically ill patients.

Keywords: glucose-insulin system, mathematical modelling, insulin sensitivity, blood glucose, critical care.

INTRODUCTION

The glucose-insulin system is defined as interaction between insulin produced in pancreas once food is consumed. This system is important to maintain blood glucose levels in a stable condition (*homeostasis*). To sustain homeostasis, blood glucose concentrations are regulated by negative feedback where the concentrations are monitored by β-cells in the pancreas to produce insulin (Ferrannini and Mari, 2004). The production of insulin acts as the body's feedback signal to manage blood glucose storage (i.e. body fat) and transportation needs that determines the glucose utilisation as energy (Whyte *et al.*, 2010).

Since 19th century, mathematical models have been developed to study glucose metabolism, insulin production and insulin-glucose system (Akerman, Gatewood, Rosevear, and Molnar, 1965; Insel *et al.*, 1974). These models which defined by model parameters represent explicit physiology effects/processes of the true behaviour have been successfully simulated the mechanisms governing by glucose-insulin system (Chase, Le Compte, Suhaimi, *et al.*, 2011). Thus, any changes in observed behaviour can be interpreted in terms of changing parameter values where the model can be used to provide a physiological explanation for the observed dynamic effects (Chase, Le Compte, Preiser, *et al.*, 2011; Chee, Fernando, Savkin, and van Heeden, 2003; Mari, 2002). It also helps to understand the changes in physiological parameters can actually affect the changes in the uptake of substance by various organs in the body.

Nowadays, the potential of mathematical models in managing blood glucose levels in critically ill is becoming realized as these patients are sensitively prone to *hyperglycaemia* (high blood glucose) condition where extra cautions need to be taken during this stage. There are several mathematical model-based control protocols have been developed by researchers to aid clinicians (Chase, Le Compte, Preiser, *et al.*, 2011; Chee *et al.*, 2003; Mari, 2002) in managing this situation. However, only few models have been clinically validated. For most models, the primary form of validation has been a simple fitting model to match clinical data (Lotz, 2007). Although few studies have used more rigorous predicition validation that tests the models ability to predict the outcome based on clinical data (Lonergan *et al.*, 2006), only a few clinically validated models can predict within clinically acceptable ranges (Lin *et al.*, 2011).Thus, it is essential to ensure that any mathematical models that represent the true physiology is validated and clinically tested before it can be utilised by clinicians to manage blood glucose levels especially in critically ill patients.

For example, a simple model-based glycaemic control protocol has been successfully developed and piloted (Lin *et al*., 2011). This model-based method can identify evolving patient-specific parameters and customize clinical therapy based on patient's condition. The prinicipal of model-based control uses a physiological model that relies on a single, time-varying parameter, i.e. insulin sensitivity (*SI*) to capture the patient-specific blood glucose response to insulin. *SI* is an indicator as a function of the model ability's to accurately capture the dynamics of insulin kinetics over time in the highly variable critically ill patients. Thus, this study is mainly focused on observing the glucose-insulin system behaviour based on the insulin sensitivity of the critically ill patients to underlying the true physiological parameters that might potentially affect glucose-insulin system.

SUBJECTS AND METHODS

Insulin infusion therapy

The development of an insulin infusion protocol was initiated by a team of nurses, dietitians, pharmacists and physicians. The protocol included contraindications for use in specific clinical settings, i.e. under surgical or medical observations (Chase, Le Compte, Suhaimi, *et al*., 2011). In critical care unit, the blood glucose concentration goal was set at 4.4 - 7.8 mmol/l (generally 6.1 mmo/l) (Fisk, Le Compte, Shaw, and Chase, 2012) would be feasible. This range of blood glucose would allow the patient to receive the benefits of preventing *hyperglycaemia* while helping to decrease the risk of *hypoglycaemia* (low blood glucose).

The intensive insulin infusion in the intensive care unit (ICU) is aimed to maintain blood glucose level (BGL) within 5.1 - 8.0 mmol/l. Once patient is admitted in the ICU, BGL will be monitored in 2-hourly timeframe. However, BGL can be monitored less frequently when patient is stable with minimum of 1 reading per day. If BGL is > 8.0 mml/l, patient will be re-checked again within an hour. Then, if BGL still >8.0 mmol/l, IIT will be commenced. The initial insulin infusion rate is presented in Table-1. Meanwhile insulin is infused to the patient, start or maintain 10% dextrose infusion at 25 ml/h until Enteral Nutrition (EN) tolerated (i.e. 40 ml/h with 200 ml aspirate) or Total Parenteral Nutrition (TPN) started. The check BGL hourly and adjust infusion rate until 2 consecutive hours require no rate change, then check BGL within 2 to 4 hourly. If adjusting the insulin infusion rate or changing between dextrose/EN/TPN, revert to hourly BGL monitoring.

Table-1. Insulin infusion rate.

BGL (mmol/l)	**Infusion Rate** (U/h)
8.1 – 11.0	2
11.1 – 15.0	3
>15.0	4

Patients demographic

The table below represents 40 critically ill patient demographics.

Table-2. Patient demographics.

Gender	Number of patients	Age, yr Median [90%CI]	Weight, kg Median [90% CI]	Height, m Median [90% CI]	Surgical/ Medical
Male	23	56 [29,79]	75 [50,97]	1.68 [1.55,1.77]	13/10
Female	17	55 [25,78]	65 [44,106]	1.55 [1.44,1.65]	4/13

Glucose-insulin physiology model

In this study, the clinical validated Intensive Control Insulin-Nutrition-Glucose (ICING) model (Lin *et al*., 2011) is used to identify *SI* hourly based on each patient's clinical data.

The model relates the rate of glucose decay to the concentration of insulin availability in the intersititium to assess insulin sensitivity (*SI*). The model equations are defined as:

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

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

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

$$\dot{P}_1(t) = -d_1 P_1 + D(t) \quad (4)$$

$$\dot{P}_2(t) = -\min(d_2 P_2, P_{max}) + d_1 P_1 \quad (5)$$

$$\dot{P}(t) = \min(d_2 P_2, P_{max}) + PN(t) \quad (6)$$

$$u_{en}(G) = \begin{cases} u_{min}, & u_{min} > k_1 G(t) + k_2 \\ k_1 G(t) + k_2, & u_{min} \le k_1 G(t) + k_2 \le u_{max} \\ u_{max}, & u_{max} < k_1 G(t) + k_2 \end{cases} \quad (7)$$

where the nomenclatures in the model are defined in Table-3.

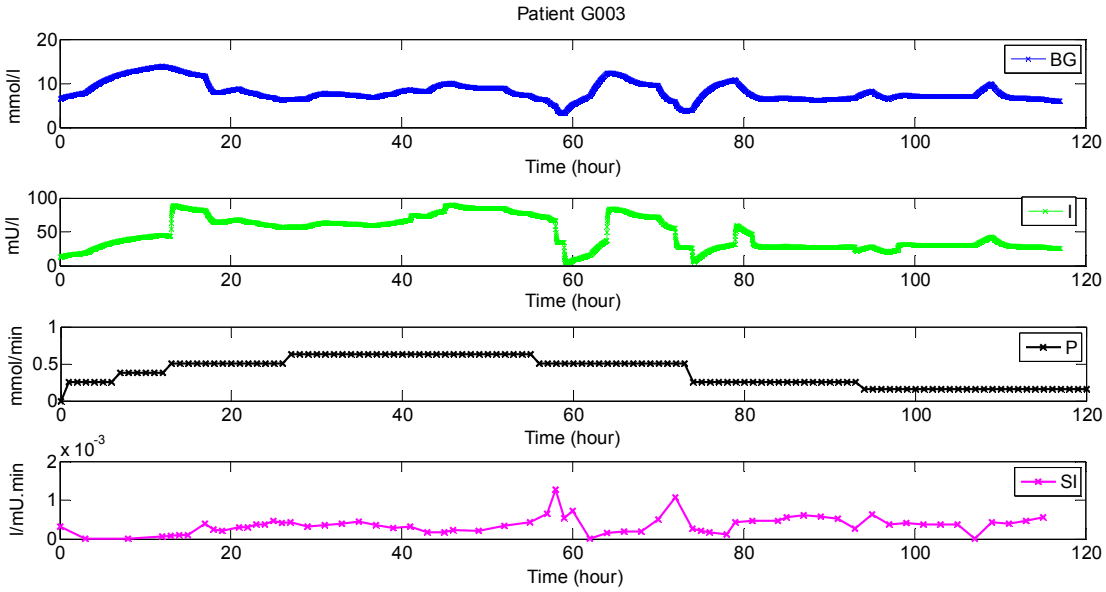

Figure-1. Patient's sample (G003) blood-glucose behaviour simulation (a) blood glucose (b) insulin (c) nutrition (d) insulin sensitivity.

Patient specific parameter identification

Model-based *SI* is identified hourly by fitting blood glucose (*BG*) measurements with estimated endogenous insulin secretion using the ICING (Intensive Control Insulin-Nutrition-Glucose) model (Lin *et al*., 2011). An integral-based method (Hann, Chase, and Shaw, 2006) and clinical data are used to identify patient-specific stepwise S rofile with 1- hour resolution.

RESULTS AND DISCUSSIONS

By fitting clinical data (i.e. blood glucose levels, insulin infusion and nutrition rates) obtained from critical unit in Hospital Tengku Ampuan Afzan, Kuantan, Pahang, patient-specific *SI* is identified hourly as shown in Figure 1(d). Although discrepancy occurred in collecting clinical data especially blood glucose levels due to the design algorithm in insulin infusion therapy protocol, with integral based-method (Hann *et al*., 2006) and ICING model, it allows prediction of the next hour blood glucose level based on the previous measurements. Thus, the glucose-insulin behaviour system can be observed hourly to understand the underlying mechanism that might contribute to *hyperglycaemia* or *hypoglycaemia* incident.

The ICING model (i.e. Equation (1) - (7)) used in this study is an integration and improvement of two clinically validated glucose-insulin physiological models (Evans *et al*., 2011; Fisk *et al*., 2012; Lin *et al*., 2011). This model explicitly relevance as the insulin kinetics is expressed with distinctive routes for insulin clearance and transport from plasma which reflects biological mechanisms. In fact, the model also comprised more realistic model for gastric glucose absorption accounting for the stomach, gut and saturable glucose appearance. Thus, it will increase the model identifiability as all

Table-3. ICING model nomenclatures.

Parameters	Description		Unit
G	Blood glucose level		$mmol.L^{-1}$
Q	Interstitial insulin level		$mU.L^{-1}$
I	Plasma insulin level		$mU.L^{-1}$
P_1	Stomach glucose content		mmol
P_2	Gut glucose content		mmol
P	Rate of glucose appearance in plasma		$mmol.min^{-1}$
u_{en}	Endogenous insulin secretion rate		$mU.min^{-1}$
Parameters and kinetic values of ICING model based on diabetic status			
EGP	Endogenous glucose production rate	1.16	$mmol.min^{-1}$
CNS	Central nervous system glucose uptake	0.3	$mmol.min^{-1}$
p_G	Patient endogenous glucose removal	0.006	min^{-1}
S_I	Insulin sensitivity		$L.mU^{-1}.min$
α_G	Saturation parameter of insulin-mediated glucose removal	0.0154	$L.mU^{-1}$
V_G	Plasma glucose distribution volume	13.3	L
n_I	Plasma-interstitium insulin diffusion rate	0.006	min^{-1}
N_C	Receptor-bound insulin degradation	0.006	min^{-1}
N_K	Renal insulin clearance	0.0542	min^{-1}
n_L	Hepatic insulin clearance	0.1578	min^{-1}
A_I	Saturation parameter for hepatic insulin clearance	0.0017	$L.mU^{-1}$
V_I	Insulin distribution volume	4.0	L
X_L	First pass hepatic clearance	0.67	
D_1	Rate of glucose transport through the enteral	0.0347	min^{-1}
D_2	route into the bloodstream	0.0069	min^{-1}
P_{max}	Maximal gut glucose flux	6.11	$mmol.min^{-1}$
U_{max}	Maximum pancreatic secretion rate	266.7	$mU.min^{-1}$
U_{min}	Minimum pancreatic secretion rate	16.7	$mU.min^{-1}$
K_1	Pancreatic insulin secretion glucose-sensitivity	*NGT 14.9 *T2DM 4.9 *T1DM 0.0	$mU.L.mmol^{-1}.min^{-1}$
K_2	Pancreatic insulin secretion offset	*NGT -49.9 *T2DM -27.4 *T1DM 16.7	$mU.min^{-1}$
Exogenous input variables of ICING model			
U_{ex}	Intravenous insulin input rate		$mU.min^{-1}$
D	Oral glucose input rate from enteral nutrition		$mmol.min^{-1}$
PN	Intravenous glucose input rate from parenteral nutrition		$mmol.min^{-1}$

*Note: NGT= Normal Glucose Tolerance, T1DM=Type 1 Diabetes Mellitus, T2DM=Type 2 Diabetes Mellitus

parameters are well defined given the limited data availablility. Despite the model parameters in this study requires many population assumptions which resulted simpler structure compared to many others (Dalla Man *et al.*, 2010; Pielmeier, Andreassen, Nielsen, Chase, and Haure, 2010), it still able to accurately capture the highly dynamic response in critical illness.

Although given limited data in a noisy and highly variable condition such as in ICU, a model basically requires the minimal number of parameters to be identified will cope successfully both mathematically and clinically. In this study, there is only one parameter that needs to be identified which is insulin sensitivity (*SI*) of each patient given all the parameters kept as population constants based on prior studies (Lin *et al.*, 2011).

Patients blood glucose level

The 90% confidence interval (CI) of 40 critically ill patient blood glucose levels were illustrated in Figure-2. Most of the median (in red line) patients' blood glucose levels are within the targeted goal range (4.4 - 8.0 mmol/l). However, 17 patients (i.e. 11 of them are male patients) were out of the targeted goal range.

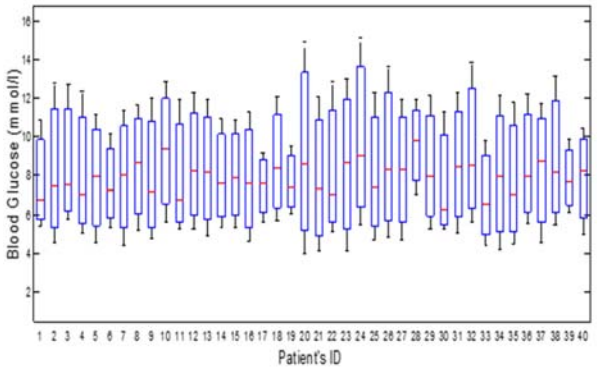

Figure-2. The 90% confidence interval of 40 patients BG.

This might be due to the admission diagnosis illnesses that the patients might experience. Overall, the blood glucose levels variability is still acceptable and requires tight glycaemic control (TGC) protocol (Chase, Le Compte, Suhaimi, *et al.*, 2011) to control and reduce the large range of 90% CI of patients' blood glucose level.

Patients specific insulin sensitivity (*SI*)

The 90% CI of patient-specific insulin sensitivity (*SI*) were identified and plotted as in Figure-3. It can be concluded that patient with ID "1" has the highest median (in red line) *SI* compared to the rest. Referring to patient's ID "1" 90% CI blood glucose levels, this patients has successfully attained stable blood glucose with median blood glucose level of 6.8 mmol/l (as shown in Figure-2). Thus, it can be concluded that this patient is highly responsed to the changes in blood glucose levels and insulin production.

For the other nine patients, the insulin sensitivity (*SI*) is considerably low although their blood glucose levels attained in Figure-2 is within the targeted goal range. This incident might be due to the unknown diagnostic illnesses or dysfunctions that occurred in the patient's body that cannot be capture by the mathematical model.

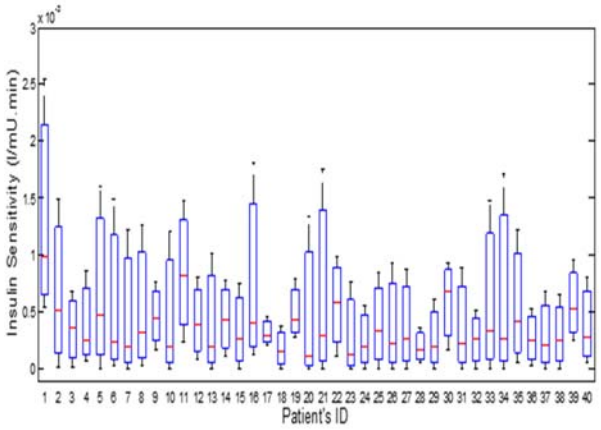

Figure-3. The 90% confidence interval of 40 patients SI.

Table-4 shows that Kurtosis value for median and 90% CI for all 40 patients based on their blood glucose levels and patient-specific *SI*. Kurtosis is defined as a measure of how outlier-prone a distribution. The normal distribution is indicated by kurtosis of 3 while distribution that are more outlier-prone than the normal distribution have kurtosis greater than 3. Distribution that are less outlier-prone have kurtosis of less than 3.

Table-4. Kurtosis value of 40 patients' BG and SI.

Parameter	Median	90% CI
BG	2.72	[2.00,4.56]
SI	3.96	[2.31,18.20]

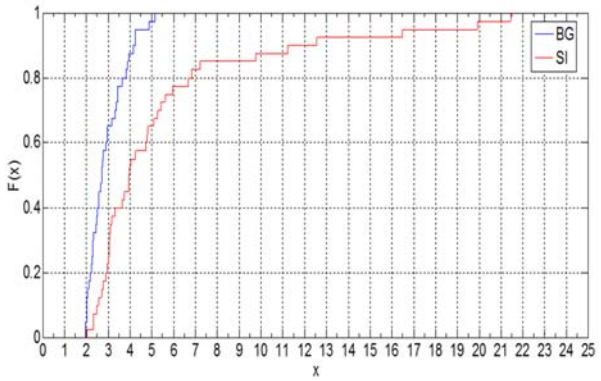

Figure-4. The BG and *SI* empirical cumulative distribution functions of kurtosis value for 40 patients.

Figure-4 represents the BG and *SI* empirical cumulative distribution function of kurtosis value for all 40 critically ill patients. The tight BG function indicates that a normal distribution (as shown in Table-4, BG

median kurtosis value is <3) is preserved within the cohort. However *SI* distribution function is significantly wide spread (i.e. outlier-prone) which presented the erratic changes in *SI* highly due to their diagnostic illnesses.

Wide spread of kurtosis for patient-specific *SI* with median of 3.96 and 90%CI: [2.31, 18.20] represents that *SI* is more outlier-prone than normal distribution. This explained that this parameter is highly dynamic to the changes in blood glucose levels. Thus, a specific study is needed in order to investigate the various metabolic dysfunction and illnesses that caused the dynamic changes in blood glucose which lead to abnormal distribution of *SI*.

CONCLUSIONS

In conclusion, a comprehensive glucose-insulin model is presented and validated using clinical data from 40 critically ill patients in Hosptal Tengku Ampuan Afzan, Kuantan. The model is capable to capture long term dynamics of a critically ill patient's glucose-insulin interaction. Insulin sensitivity *SI* is the only parameter that is identified hourly for each patient. The mathematical glucose-insulin model illustrates the physiological mechanisms that realistically explained the insulin kinetics and glucose-insulin interaction system in critically ill patients. In fact, this model offers a platform to develop robust insulin therapies for tight glycemic control to prevent hyperglycaemia incidence in the ICU. However, further investigation on the behavior of erratic changes in patient-specific *SI* which caused the outliers to the overall distribution need to be considered in the future work. Thus, a larger patient cohort with varied metabolic dsyfunctions should be deliberated to literally understand the "unknown" behavior or effects that caused this abnormality of patient-specific *SI* distribution.

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