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Estimating (unidentifiable) enhanced EGP in glycaemic control modelling: Dancing with minions of the Dark Lord

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Abstract: Critically ill patients frequently experience stress-induced hyperglycaemia. Glycaemic control (GC) with insulin therapy can improve patient outcomes, but effective GC is not currently well achieved in most critical care units. STAR is a model-based decision support system, utilizing the ICING model, for glycaemic control in intensive care. Understanding model-based parameters and assumptions within their clinical context is important. The ICING model uses a population constant for endogenous glucose production (EGP), but EGP can vary considerably in patients during extreme stress and trauma. This study uses data from 145 patients on the SPRINT protocol to explore the assumptions around the EGP parameter and estimate minimum EGP values when the model is constrained to a minimum insulin sensitivity (SI) value. The model is frequently constrained when there is no nutritional input, highlighting the importance of the EGP parameter for glucose flux in the model equation. Minimum EGP values were calculated when SI was less than or equal to $1e^{-5}$ L/mU/min and ranged from 1.16 mmol/min to 2.72 mmol/min, where the median value is a 12% increase from the population value of 1.16 mmol/min. This analysis provides a relative indication of EGP changes in patients and supports the use of the EGP population value as only 2.3% of hours require EGP modification.

Keywords: Physiological model, critical care, decision support and control, clinical validation, kinetic modelling and control of biological systems, EGP, glycaemic control

1. INTRODUCTION

Critically ill patients, regardless of diabetic status, frequently experience stress-induced hyperglycaemia (McCowen et al., 2001; Mizock, 2001) that results in a positive feedback loop of metabolic stress and inflammation. High and low blood glucose levels, hyperglycaemia and hypoglycaemia, as well as glycaemic variability regardless of blood glucose level, have all been shown to be independent risk factors for increased mortality in critically ill patients (Bagshaw et al., 2009; Krinsley, 2015, 2003). Regulating glycaemic state through glycaemic control (GC) in the critically ill has been shown to improve patient outcomes (Chase et al., 2008b; Krinsley, 2004; Van den Berghe et al., 2006, 2001) and reduce costs (Krinsley and Jones, 2006).

Safe, effective control is required to reduced glycaemic variability and mitigate the risk of hypoglycaemia, in particular, as one episode can significantly increase risk of death (Penning et al., 2015). It is also critical to obtain this level of control for virtually all patients to ensure the potential benefit is obtained (Chase et al., 2010). However, safe, effective GC can be difficult to achieve for many patients due to clinical limitations and, in particular, inter- and intra- patient variability (Chase et al., 2011; Dickson et al., 2014) and may be the reason other studies have not been able to show benefit (Arabi et al., 2008; Griesdale et al., 2009; Preiser et al., 2009; The NICE-SUGAR Study Investigators, 2009; Wiener et al., 2008).

Physiological models such as the Intensive Control Insulin-Nutrition-Glucose (ICING) model (Lin et al., 2011) used in the STAR glycaemic control protocol (Evans et al., 2012; Fisk et al., 2012; Stewart et al., 2016) have demonstrated repeatable, replicable, safe and effective GC. Such model-based methods can directly account for and use the inter- and intra- patient variability to guide control (Lin et al., 2006). The ICING model captures basic metabolic physiology well, and has been used in the design and implementation of glycaemic control protocols such as STAR and SPRINT, to provide effective GC for virtually all patients (Chase et al., 2010, 2008a; Stewart et al., 2016; Uyttendaele et al., 2017). However, there are limitations to the models, particularly the assumptions used around dynamics which are not easily measured at the bedside or are difficult to separate from other related dynamics. Endogenous glucose production (EGP) is one such important dynamic, particularly in the critically ill.

EGP is very difficult and extremely invasive to measure directly, requiring arterial-venous balance or tracer methods (Rizza et al., 2016) for durations longer than 2.5 hours (Tigas et al., 2002), thus making its measurement both highly intensive and time consuming. EGP can be highly variable (Black et al., 1982; Chiolero et al., 2000; Shaw and Wolfe, 1989; Tappy et al., 1997) and elevated due to stress-response (McCowen et al., 2001). Significant inter-patient variability in EGP measurements may reflect physiological responses or it may also reflect issues in clinical assessment of EGP.

Different attempts have been made to model EGP in critically ill patients, including as a function of plasma insulin (Hovorka et al., 2008), BG and insulin (Pielmeier et al., 2010), and BG, insulin, and glucagon (Wendt et al., 2017). Many of these models fail to capture the complexity of EGP stimulus and suppression in stress hyperglycaemia and/or rely on additional blood measures, assays and/or procedures that are not available or clinically feasible to perform at the bedside. Hence, there is no accepted, proven, or ready way to model or assume a value of EGP in this cohort.

Previous attempts at varying EGP dynamics resulted in unstable BG control dynamics (Dickson et al., 2013; Pretty, 2012) using the ICING model. Currently, EGP is a population constant and error in this value is adsorbed as an offset on patient-specific, identified insulin sensitivity (SI). The stochastic modelling approach captures this variability and helps guide care (Le Compte et al., 2011; Lin et al., 2008). In extreme cases, when physiological EGP is much higher than the model population constant, negative SI values can be identified that are not physiologically possible, and this can skew care.

This study uses the validated ICING model (Lin et al., 2011; Stewart et al., 2016) to assess model parameter values during low, identified SI events in critically ill patients. The aim is to quantify the frequency of these events and quantify a lower bound, by enhanced or higher EGP value during the events. The results can then be used to determine whether the impact influences care choices.

2. METHODS

2.1 Patient Demographics

Study data comprises 145 patients on SPRINT GC (Chase et al., 2008a; Lonergan et al., 2006) in Christchurch Hospital ICU from June 2011 to May 2015. Patients were on the protocol for a minimum of 24 hours and started GC within 12 hours of ICU admission to ensure timing was the same. The average patient length of ICU stay was 113 hours, with 83 hours on SPRINT. Up to the first 72 hours on SPRINT was analysed for each patient, making 9,304 hours of GC in the data set. Demographic data can be found in (Uyttendaele et al., 2017).

2.2 Model and SI

The metabolic system dynamics of the ICING (Intensive Control Insulin Nutrition Glucose) physiological model are defined (Lin et al., 2011):

$$\dot{G} = -p_G G(t) - SI * G(t)\frac{Q(t)}{1 + a_G Q(t)} + \frac{P(t) + EGP - CNS}{V_G} \quad (1)$$

$$\dot{I} = -n_k I(t) - n_L \frac{I(t)}{1 + a_I I(t)} - n_I\big(I(t) - Q(t)\big) + \frac{u_{ex}(t)}{V_I} + (1 - x_L)\frac{u_{en}(G)}{V_I} \quad (2)$$

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

Where $G(t)$ is blood glucose concentration (mmol/L), $I(t)$ is plasma insulin concentration (mU/L), $Q(t)$ is interstitial insulin concentration (mU/L), $P(t)$ is plasma glucose from dextrose intake (mmol/min) and SI is insulin sensitivity (L/mU/min). *EGP* is endogenous glucose production and has a constant population value of 1.16 mmol/min (Lin et al., 2011), per values in (Chambrier et al., 2000). Other rates and constants can be found in (Stewart et al., 2018). A detailed model description can be found in (Lin et al., 2011).

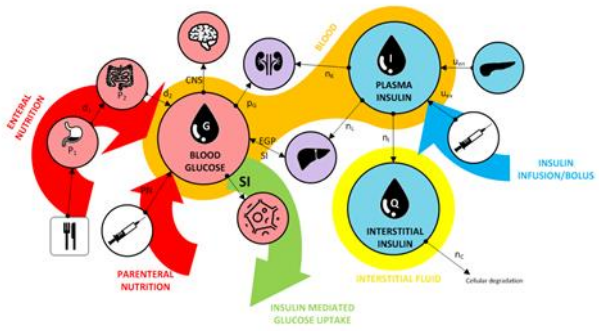

Figure 1. Schematic representation of the glucose-insulin model showing endogenous and exogenous contributions. *CNS* Central nervous system, *EGP* Endogenous glucose production, *PN* Parenteral nutrition, *SI* Insulin sensitivity, *u* insulin, *d* glucose transport rate, p_G non-insulin mediated glucose removal, *n* insulin diffusion/degradation rates.

Patient metabolic ability for insulin mediated glucose uptake is captured using hour-to-hour relative changes in a model-based insulin sensitivity (SI) value. Hourly insulin sensitivity (SI) values based on clinical inputs of measured blood glucose, and insulin and glucose administration are identified using an integral based fitting method (Docherty et al., 2012, 2011).

2.3 Calculation of lower bound enhanced EGP

An SI value of $1e^{-5}$ L/mU/min is taken to be reflective of the likely lower limit of physiological SI, and is around 100x lower than SI in individuals with diabetes (Lotz et al., 2010; McAuley et al., 2011). During periods when SI is identified at or below SI = $1e^{-5}$ L/mU/min, the model SI value can be constrained to $1e^{-5}$ L/mU/min, and a new augmented, but lower bound EGP value calculated directly. This calculation of EGP ensures model fit to clinical BG measures where non-insulin mediated glucose uptake is higher than the modelled glucose sources in the *G* compartment of Equation 1. This calculated EGP value is a minimum or lower bound estimate of what the elevated EGP value at this time could be. A higher EGP value would result in SI >$1e^{-5}$ L/mU/min, but is not identifiable without significant extra data and/or procedures. This lower bound enhanced EGP during hours with constrained SI is calculated:

$$EGP = V_g\left[\frac{G_E - G_S + p_G\int G dt + SI\int\frac{GQ}{1+a_G Q}dt - \int\frac{P+PN-CNS}{V_g}dt}{\int dt}\right] \quad (4)$$

Where G_E is end blood glucose concentration (mmol/L) and G_S is starting blood glucose concentration (mmol/L), and all other parameters are defined previously. Integrals are evaluated over the identified 1 hour period where SI is constrained at 1e^{-5} L/mU/min.

Identified SI values that are negative indicate that the EGP value may need to be augmented. Constrained values are clear limit states and resulting BG error would be due to error in the assumed EGP population value as shown in Figure 2. The approach separates clear cases where the EGP value is in error, making this value identifiable. It is thus a minimal estimate of enhanced EGP level and incidence.

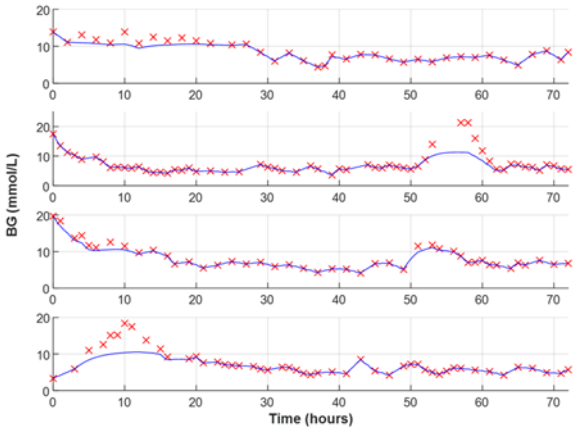

Figure 2. During stress response, EGP can be significantly elevated resulting in blood glucose (BG) model predictions (blue line) not matching actual BG level (red crosses).

2.4 Analyses

Time periods when EGP is significantly enhanced over assumed model values were identified by evaluating when SI was constrained to 1e^{-5} L/mU/min. Time and length of events are tabulated and single 1-hour events are excluded in further analysis as they were found to be primarily due to data entry or sensor errors. All events lasting 2 or more consecutive hours are further evaluated.

The rate of EGP can be significantly increased over the constant population value due to stress response, particularly in the most critically ill ICU patients, and this increase can be a large contributor to glucose flux. EGP values were calculated for those hours when the identified SI values were less than or equal to 1e^{-5} L/mU/min. The range, time, and frequency of EGP values were evaluated and compared to clinical observations and expectations.

3. RESULTS

3.1 Insulin Sensitivity (SI) and constrained events

A total of 214 low SI hours were analysed. The cumulative distribution function (CDF) of the calculated SI values, excluding 1 hour events, is shown in Figure 3 with 2.3% of values below or equal to the SI = 1e^{-5} L/mU/min minimum level. Though relatively scarce by hour (2.3% of 9,304 total hours), 45.5% of patients have at least 1 event of constrained SI lasting 2 or more hours.

3.2 Patient and care states during constrained events

Table 1 shows the percentage of constrained events occurring during particular parameter states. Less than one-third of events occurred when no insulin was being administered, but more than 80% of constrained SI events occurred when nutrition was not being administered in the current hour. In particular, with no (or low) nutritional intake, the model relies excessively on the accuracy of the assumed EGP population parameter's to capture incoming glucose flux (Chase et al., 2009). It thus supports the choice of modifying the EGP parameter value in these cases and this analysis.

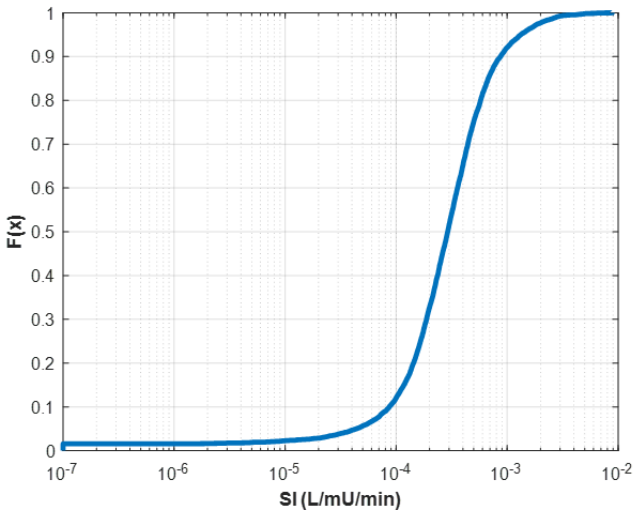

Figure 3. Cumulative distribution function of model-identified SI values. Note that the x-axis is a log scale.

Table 1. Input states when SI is less than or equal to 1e^{-5} L/mU/min.

Input condition	% constrained SI hours
No insulin in constrained hour	28.7%
No nutrition in constrained hour	82.6%
No insulin or nutrition in constrained hour	24.6%
No nutrition in previous hour	79.5%

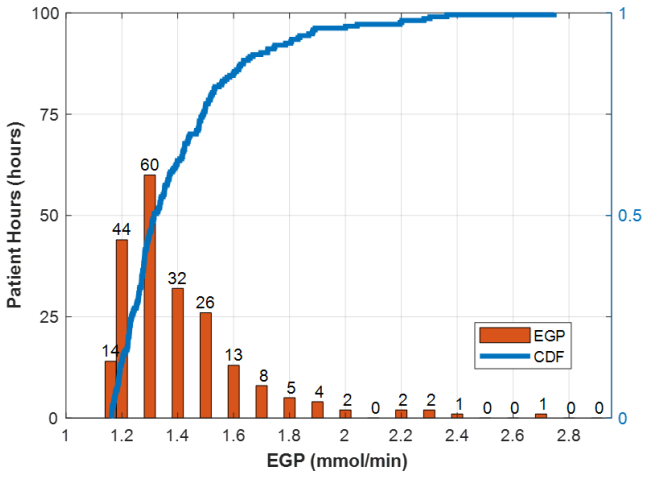

Figure 4. Minimum EGP values calculated using SI = $1e^{-5}$ L/mU/min during hours when SI is constrained. The bar chart shows hourly incidence of minimum EGP values (left y-axis) and the solid line is the cumulative distribution (right y-axis) of minimum EGP values for all constrained hours.

3.3 Calculated Minimum EGP Values

During constrained events, when SI was less than or equal to $1e^{-5}$ L/mU/min, a minimum EGP value was calculated from Equation 4 using the constrained SI value of $1e^{-5}$ L/mU/min. Minimum EGP values ranged from 1.16 to 2.72 mmol/min, with 50% of the values being above 1.31 mmol/min. The median value is a 12% increase from the assumed population value of 1.16 mmol/min used in the model. Five percent of values are greater than 1.88 mmol/min, representing a 62% increase from the assumed population value.

4. DISCUSSION

This analysis used a model-based approach to evaluate an increased lower bound enhanced EGP value in critically ill patients based on incidence, the time dependent nature and extent of lower bound, constrained SI values, and associated likely high EGP. This approach allows this lower bound EGP value to be directly identified by constraining SI to non-negative values. The range of SI values shown in Figure 3 are 100x lower than a typical type 2 diabetic individual (Lotz et al., 2010; McAuley et al., 2011), which also captures and clearly shows the significant stress response insulin resistance seen in critically ill patients.

EGP affects the glucose flux in Equation 1, but is difficult to measure directly (Rizza et al., 2016). It also increases significantly and variably during the stress response (Dickson et al., 2013; McCowen et al., 2001; Watters et al., 1997). It thus, in part, affects the increased variability of insulin sensitivity in the initial stage of critical illness (Pretty et al., 2012). EGP can be significantly elevated early in the patient stay as part of stress response and these patients may require adjustment of the EGP value used, although the constant value of EGP=1.16 mmol/min chosen (Chambrier et al., 2000; Lin et al., 2011) is suitable for the vast majority of patients at all time points.

The range of 1.16 to 2.72 mmol/min found in this study is within other published ranges of trauma patients (Chiolero et al., 2000; Tappy et al., 1997; Wolfe et al., 1979). The reported range of enhanced lower bound EGP values reflects a minimum estimate of elevated EGP production in these incidences as it is calculated based as a lower bound, constrained SI value. Thus, the incidence and level of augmented EGP reported here are lower bounds and may be higher, but the conditions used here ensure identifiability of the problem so the results are robust.

Parameter trade-off in the model can affect the incidence of low SI, and was considered in this analysis. The most likely parameter in this case is EGP because of the known physiological response, and because 80% of low SI occurrences happen when there is no exogenous nutrition being administered, as shown in Table 1. The only other source of glucose to keep BG elevated is the much greater rate of appearance from exogenous sources, which Table 1 shows are often not present in these instances, clearly highlighting the role of EGP physiologically and in the model. In this case, the results thus match clinical expectations and within the model, the error is amplified in the case of low to no exogenous nutritional input and it leaves only the EGP value as a cause of error.

When there is a difference between the actual physiological EGP value and the model assumed term, the error is usually minimized because the patient is fed at much higher rates than the EGP term, thus minimizing EGP contribution overall. This implies that patients with low, but unconstrained SI could have higher EGP and higher peripheral SI, but are not detected. Currently, there is no known way to identify these patients at the bedside (Docherty et al., 2011), making implementation of variable EGP based on bedside measures less practicable at this time, especially because it can vary significantly due to stress response and over the wide range found here.

The model used in this analysis has been proven both clinically and analytically (Chase et al., 2019; Lin et al., 2011; Stewart et al., 2016) and used in a variety of contexts. The data set comprised a mixed cohort, single centre population, and as patients are variable, a larger cohort study in multiple centres would offer more insight into EGP variation.

5. CONCLUSIONS

Model-based insulin sensitivity was constrained to a physiologically realistic lower limit in 2.3% of patient hours on model-based glycaemic control. This constrained SI most likely represents model error in the EGP parameter in these cases, as most of the constraints occurred around low or no nutritional input periods. It also reflects the stress response, as the majority of constrained SI values occurred in the first 12 hours of insulin therapy. Minimum EGP values calculated in the case of constrained SI varied from 1.16 to 2.72 mmol/min, which are within reported ranges for this cohort and thus physiologically realistic, further validating the model and analysis. Overall, the current population value of 1.16 mmol/min used in the model is justified given less than

2.5% of hours are constrained, representing a small subset of patients and hours with physiology that is not well-captured in the current model.

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