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Clinical application scenarios to handle insulin resistance and high endogenous glucose production for intensive care patients

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Abstract: Intensive care patients often experience hyperglycemia, insulin resistance (low insulin sensitivity), and high endogenous glucose production due to their critical situation. STAR is a model-based glycemic control protocol that uses insulin sensitivity (SI) identified on hourly bases to define patient variability. The numerical calculation during the identification phase of SI may result in negative SI value, which is an indication of high insulin resistance or another pathological patient state. Negative values of SI are physiologically not possible and are prevented in the parameter identification phase by a non-negative constraint. These cases, when SI is forced to take a non-negative value, potentially result in poor blood glucose (BG) fitting and signaling some model limitations like an estimated low EGP.

Using clinical data of 717 patients from three independent ICUs (Malaysia, New Zealand, and Hungary), the time occurrence and durations of constrained SI situations are analyzed, and different practical scenarios were suggested to estimate and handle patient's EGP levels in clinical application. An EGP estimation method is used to estimate the most suitable EGP value based on model fitting. By setting different EGP higher limit values, the fitting error and remaining constrained SI values are also analyzed and assessed.

Results show that 96% of these constrained SI situations happen within the first 96H, and 95% of it lasts for 3h. Results also confirm that using an EGP limit higher than 3.5 s shows no further improvement in terms of modeling accuracy.

Based on results, the most practical scenario to handle these situations is to keep the increased EGP until four days of treatment passed; after that, if it happens again, we may set back EGP to the initial value after 3h each time we increase it.

Keywords: Blood glucose; Glycemic control; Intensive Control Insulin-Nutrition-Glucose; Insulin resistance; Insulin sensitivity; Endogenous glucose production.

1. INTRODUCTION

Critically ill Intensive care unit (ICU) Patients can develop acute insulin resistance manifesting as hyperglycemia which can be induced primarily by stress and linked to raising the rate of morbidity and mortality (Krinsley 2003). Safe, effective and consistent glycaemic control results have proven difficult (Bagshaw, Bellomo et al. 2009, Signal, Le Compte et al. 2012), often caused the lack of patient-specificity and consideration of patient variability. This outcome illustrates the need for model-based patient-specific glycaemic control solutions.

The Stochastic TARgeted (STAR) protocol is a model-based Glycemic control (GC) protocol (Evans, Shaw et al. 2011, Evans, Le Compte et al. 2012), directly capturing and modeling patient-specific intra and inter potential variability. STAR is driven by a model-based insulin sensitivity (SI), a key parameter to assess patient state variability (Docherty, Chase et al. 2011, Docherty, Chase et al. 2012). SI identification constraints negative values to a low minimum value as negative values are non-physiological. In this case, the model prediction will be biased and the fitting error becomes significant, signaling some model limitations (Pretty 2012). This situation may happen because of the complexity and severity of critical illness, such as severe sepsis (McCowen, Malhotra et al. 2001, Pretty 2012).

In prior work (Anane, Benyo et al. 2019) we assessed the assumption that one of the model key parameters, endogenous glucose production (EGP), which is set to a fixed cohort-based value, is too low to represent the real physiological value of certain patients. A constrained SI value is thus an indication that EGP needs to be raised to a higher value. Increasing EGP enabled the model to follow the observed BG dynamics and surpass this limitation, also showed impressive results in error reduction and change in the insulin sensitivity distribution.

In this study, practical scenarios were suggested for the clinical implementation of an EGP estimation method by analyzing the

time occurrence and duration of these episodes, using clinical data of 717 patients from 3 different ICUs.

2. METHODS

2.1 ICING model

STAR utilizes the Intensive Care Insulin-Nutrition-Glucose (ICING) model to simulate the fundamental metabolic dynamics of the glucose/insulin system of the human body. The main 3 of 7 total equations are defined:

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

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

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

Table 1. MAIN PARAMETERS, INPUTS AND VARIABLES OF THE ICING MODEL

Main Variable	Description	Values
G	Blood glucose	(mmol/liter)
Q	Interstitial insulin concentration	(mU/liter)
I	Plasma insulin concentration	(mU/liter)
Key Parameter	Description	Values
PG	Insulin independent glucose removal	0.006 (min−1)
SI	Insulin-mediated glucose removal	(liter/mU/min)
EGP	Endogenous glucose production	1.16 (mmol/min)

All equations, parameters, inputs, and variables are defined in (Stewart, Pretty et al. 2016).

2.2 Patient data /cohorts

Clinical data that contains a patient's personal information, blood glucose measurements, and insulin/nutrition treatment was collected from 3 different cohorts of 717 ICU patients.

216 from the International Islamic University Malaysia Medical Centre, Malaysia, 408 from Christchurch Hospital, New Zeeland, 93 patients from Kalman Pandy Hospital, Gyula, Hungary.

Patients with glycemic control of less than 10 hours were excluded. The 3 cohorts were treated with STAR. Malaysian patients were using a target range of 6.0-10.0 mmol/L with continuous insulin infusions. New Zealand patients had a lower BG target range 4.4-8.0 mmol/L and insulin delivered via bolus. Hungarian patients were treated with continuous insulin infusion to the lower range (Lin, Razak et al. 2011).

2.3 Insulin sensitivity identification

SI, as a single parameter, is used to represent the 'whole body' metabolic state condition, and it captures patient-specific deviation from model population parameters.

Clinical data including two last BG measurements, insulin/nutrition inputs, and ICING model Equations (1)-(7) is utilized to identify SI in hourly bases using the integral-based method (Lin, Razak et al. 2011).

The Identified SI is used for the prediction of the blood glucose outcomes based on current treatment suggestions.

In the identification phase, Negative SI values are prevented and constrained to a minimum value = 1e-7. Negative values of SI are also an indication of insulin resistance but are physiologically not possible.

2.4 Insulin resistance, constrained SI and low EGP

Insulin sensitivity (SI), is uniquely identified from clinical data on an hourly basis. Patient variability is assessed by the hour-to-hour change in SI levels. Low values of SI indicate insulin resistance and the need to either add insulin or reduce nutrition to achieve lower glycemic levels (Lin, Razak et al. 2011).

Another key parameter is the endogenous glucose production (EGP) representing the net glucose produced by the body and released into the blood. It directly impacts SI by contributing to the net glucose flux to be balanced by insulin-mediated glucose uptake in equation (1) (McCowen, Malhotra et al. 2001, Thorell, Rooyackers et al. 2004). In the STAR Treatment protocol, EGP is set to a cohort-based value of 1.16 mmol/min.

Cases, where SI is constrained to a non-negative value, are often preceded by an unexpected rise in blood glucose levels, potentially resulting in a poor BG fitting. One main cause is the assumed EGP value is too low to represent the real physiological value at that specific situation. These situations affect 22-62% of ICU patients from the 3 different cohorts.

2.5 EGP estimation approach

The model-based EGP estimation method developed in (Anane, Benyo et al. 2019) is used to adjust EGP levels based on patient-specific SI levels and runs only when the identified SI value hits the lower constraint limit (see fig. 1). The EGP parameter value range in this paper is 1.25<EGP<3.5 mmol/min with a step of 0.25 selected experimentally which gives a vector of N=10 after the initial fixed value of EGP = 1.16. The upper range limit value (3.5) selected based on results to be shown in the result section.

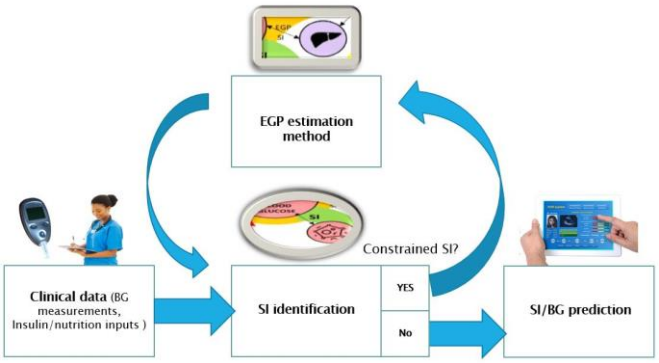


Fig. 1. Illustration of the implementation of the new EGP estimation method in the SI identification phase.

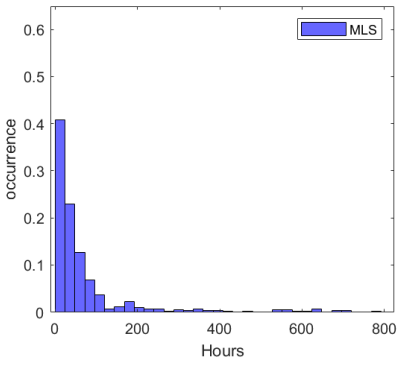
2.6 Analysis

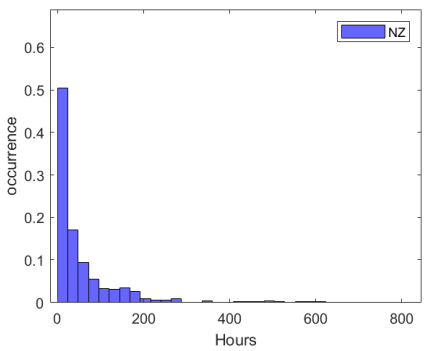
In this paper, in order to provide practical scenarios of how we can handle these constrained SI situations, we analyzed the time occurrence and duration of these episodes for the three different ICUs. We analyzed and compared different EGP upper limit values and the number of remaining constrained SI values using a cohort of 22 most affected Malaysian patients.

3. RESULTS

3.1 Insulin resistance, constrained SI and low EGP

Fig. 2 shows the distribution in time per day of constrained SI for the 3 different cohorts. The overall trends for the New Zealand and Malaysian cohorts are exponential with most episodes arising in the first 3-4 days, as expected given stress response physiology. The Hungarian cohort has quite a similar pattern except on the third day where there was a rise in the rate of occurrence compared to the first 2 days.





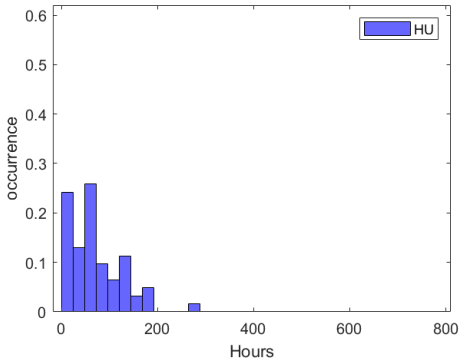


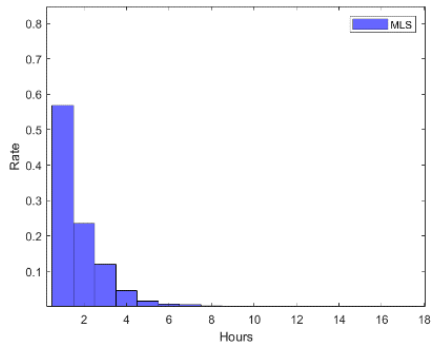
Fig. 2. Constrained SI probability of occurrence per day (1bin= 24h) for MLS (top), NZ (middle) and HU (bottom).

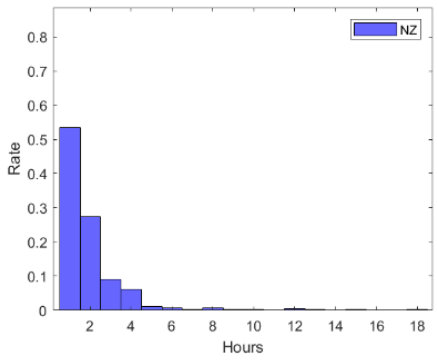
Overall results show ~30-60% of the occurrence situations happen in the first 24H (first day), ~46-80% of the occurrence situations happen in the first 48H, ~78-90% of the occurrence situations happen in the first 72H and ~90-96% of the occurrence situations happen in the first 96H across all cohorts. Less than 10% of constrained SI occurrence occurs after the 4th day.

3.2 Duration of episodes

Fig. 3 shows the time duration in hours of constrained SI for the 3 different cohorts. All 3 cohorts have similar exponential trends with most episodes lasting up to 4 hours.

A small minority of New Zeeland patients have constrained SI duration up to 18 hours, where in Hungarian and Malaysian patients, the maximum is 7-8 hours.





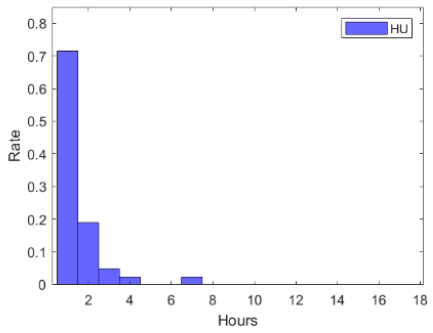


Fig. 3. Duration of constrained SI episodes when it occurs (1bin= 1hour) for MLS (top), NZ (middle) and HU (bottom).

Overall results show ~53-71% of the insulin resistance situations last for 1 hour, ~19-27% of the insulin resistance situations last for 2 hours and ~5-11% of the insulin resistance situations last for 3 hours. Thus ~89-95% of the insulin resistance situations last between 1-3 hours across all the cohorts.

3.3 EGP parameter value limits, fitting error and remaining constrained SI values

Out of 216 Malaysian patients (the most affected cohort), we selected patients with the poorest BG fitting (BG error > 20%) to analyze the effect of applying different EGP upper limits mainly on modeling error (the result of the selecting is 22 patients). Table 2 shows Mean/Max fitting error and remaining constrained SI hours after increasing EGP with different limits compared to using a fixed EGP (1.16 mmol/min).

Table 2. MEDIAN IQR OF ERROR PER COHORT AND MEDIAN IQR OF MAXIMUM ERROR PER PATIENT.

EGP(mmol/min)	1.16		2.5	
Mean/Max	Mean	Max	Mean	Max
Fitting Error (%)	18	48	2.03	16.89
N° of remaining constrained SI	468		18	

3		3.5		6	
Mean	Max	Mean	Max	Mean	Max
1.04	6.38	0.77	2.33	0.63	2.23
9		6		3	

Using fixed EGP values comes with significant fitting error and a large number of constrained SI hours. Increasing the limit of EGP to 2.5 mmol/min shows a reduction of 96% in the constrained SI value, but still, have a slightly large maximum fitting error. In contrast, setting the limit of EGP up to 3.5 mmol/min shows a large reduction in BG fitting error to a very low value (2.33%) and reduction of constrained SI values by 98%. Using EGP values higher than 3.5 mmol/min did not show any further improvement and using 6 mmol/min as a limit has similar results to using 3.5 mmol/min.

Forcing SI to take a non-negative value is a model limitation, and the identified constrained SI will result in a poor SI prediction in the real clinical application, which also will result in a poor BG prediction.

In the method presented in the paper, there is a situation where the EGP values minimizing the BG fitting error results in also a constrained SI value (see Table 3). This leads to the idea of modifying the estimation method to prioritize the positive SI values over a constrained value with the acceptance of a small BG fitting error.

Table 3. THE NUMBER OF REMAINING CONSTRAINED SI IN ALL THE COHORTS USING FIX EGP VS. ESTIMATED EGP (EST EGP)

Cohorts	MLS		NZ		HU	
EGP value	Fix EGP	Est EGP	Fix EGP	Est EGP	Fix EGP	Est EGP
N°of constrained SI	1002	20	1117	11	63	1

Results show over 98% of the constrained SI disappears when estimating EGP up to 3.5 mmol/min. This means no need for any further modifications of the current estimation method.

4. DISCUSSION

4.1 Insulin resistance and patient's condition relationship

For those hours where SI was hitting the lower limit, 90-96% of them occurred in the first 96 hours of stay for the Malaysian, New Zealand and Hungarian patients, as shown in Fig. 2. This early occurrence is likely due to the surge in EGP seen particularly in severe sepsis and septic shock patients in the first 12-24 hours of the stay (Shaw, G.M. 2012, Chase, J.G. 2012). Thus, the location of these hours qualitatively matches broad clinical expectations, where severe sepsis is one of the leading causes of ICU admission (McCowen, Malhotra et al. 2001, Pretty 2012).

Around 50% of the constrained SI situation happens in the first 24H for Malaysian and New Zealand patients where only 30% for the Hungarian cohort with the highest rate was on the third day of the ICU stay. These differences may also reflect cohort differences in the incidence of greater complexity and level of critical illness, such as incidence of severe sepsis, in some cohorts, which can occur from the areas and types of patients treated, as well as from treatment selection or failure bias.

4.2 Handling EGP and constrained SI

Using a limit higher than 3.5 mmol/min shows no further improvement and for that, there will be no reason to go above that. The 3.5 mmol/min limit of EGP still an acceptable physiological value for a patient with a very high EGP.

The question now is, what should we do after we increase EGP? And For how long should we keep it high?

Based on the results achieved, we suggest different practical scenarios to handle EGP and the identified constrained SI in the clinical application:

1) Set back EGP to the initial value after 72H-96 of treatment: As ~78-96% of the occurrence situations happen in the first 72-96H, this scenario tends to be the most preferable, because once we identify a patient with an insulin resistance (constrained SI) it is more likely to happen more frequently and it will continue until the 4th day where up to 96% of the situations happens within.

2) Set back EGP to the initial value after 3-4H from increasing it: As ~90-95% of the cases last between 1 and 3 hours, it is possible to set back the estimated EGP to the initial value, which is 1.16 once 3 hours passed. However, the downside of this scenario that random frequent occurrence of the constrained SI may lead to an 'increase–set_back–increase_again' loop, also we will be always missing the first occurrence as the identification stats right after having the new BG measurements.

3) Keep EGP high for the entire treatment period: We assume once we identify a patient with a constrained SI it is more likely that it will happen again, and this patient will have a high EGP level during the entire stay in the ICU, the downside of this choice is we may overestimate the EGP level especially after patient state stabilize.

The more practical way to handle EGP estimation is to use a mix of approaches 1 and 2:

If the constrained SI happens in the first days of treatment, we keep the increased EGP value until the 4th day of stay. If it happens after the 4th day, we set back the initial EGP values after 3 hours of each time we increase it.

The first reason behind this choice is that we know patients have a higher EGP in their first days after ICU admission, so we want to increase our estimation only for those four first days. After that period, if we keep our high estimated value, we may end up overestimating the EGP level. The second reason is that after the first four days, a patient may have some spikes in EGP as we saw in Fig. 2, so increasing and keeping it four 3 to 4 hours before setting back to initial value seems to be also a good solution.

7. CONCLUSIONS

Understanding the relationship between hyperglycemia, insulin resistance, and high endogenous glucose production has a huge impact on model-based control and treatment in intensive care units. Underestimating the EGP in situations where patients are experiencing insulin resistance showed poor modelling results. By the estimation of the right EGP level, it significantly improves the outcomes and surpasses the model limitation. The next step is to design a practical way of implementing the new EGP estimation method on the STAR clinical application. Based on results, 96% of these constrained SI episodes happen within the first 96H and 95% of it lasts for 3h, for this the most practical scenario to handle these situations is to keep the increased EGP until 4 days of treatment passed, after that if it happens again we may set back EGP to the initial value after 3h each time we increase it. In summary, the clinical implementation of the EGP estimation method presented can effectively capture and handle patients' EGP variability, improve the model outcomes, enhance glycemic control and create a space for further development.

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