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Generalizability of a Nonlinear Model-based Glycemic Controller

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Abstract: Critically ill patients exhibit a highly complex and dynamic metabolic state, making safe, effective management of hyperglycemia difficult. Clinical practices vary significantly, thus making glycemic control (GC) protocols difficult to generalize across units. This study examines the generalizability of a nonlinear, model-based GC protocol, STAR (Stochastic TARgeted), across two different intensive care units (ICUs) with very different practices and use of GC. Patient data from the ICUs at Christchurch Hospital, New Zealand (267 Patients) and Kalman Pandy Hospital, Hungary (47 Patients) are examined. Safety and performance are examined, where complete generalizability would be indicated by similar glycemic performance distributions using non-parametric statistics as appropriate. STAR spent over 86% of time in the target BG band of 4.4-8.0 mmol/L per-episode in both Christchurch and Gyula, with the BG (blood glucose) distributions being almost identical. STAR provided safe GC with very few patients experiencing mild hypoglycemia (< 5 patients, 1.5%). The nonlinear model-based STAR GC protocol delivered equivalent high performance and safety across patient types, time, clinical practice culture, and clinical resources.

Keywords: Glycemic Control, Intensive Care, Hyperglycemia, Model-based, Personalized, Nonlinear, Stochastic, Targeted

1. INTRODUCTION

Hyperglycemia is prevalent in ICU patients (McCowen et al., 2001, Capes et al., 2000), and associated with increased mortality (Krinsley, 2003, Krinsley and Preiser, 2015). Blood glucose (BG) variability in these highly dynamic patients has also been independently related to increased mortality (Egi et al., 2006, Krinsley and Preiser, 2015). Safe, effective GC can significantly reduce the negative effects of dysglycemia (Krinsley, 2004, Van den Berghe et al., 2001, Chase et al., 2008), including the rate and severity of organ failure (Chase et al., 2010) and cost of care (Krinsley and Jones, 2006).

However, the critically ill stress response is highly complex, variable and dynamic (Pretty et al., 2012), making safe, effective GC difficult, resulting in increased hypoglycemia and failure improve clinical outcomes (Chase et al., 2011). It is thus possible that previous studies failed to achieve safe consistent GC because the GC protocols were unable to observe or identify patient-specific dynamics. Hence, a patient-specific approach is required to control the significant inter- and intra- patient variability (Chase et al., 2011). Equally, to date, no protocol has been able to successfully generalise across significant differences in clinical practice (Finfer et al., 2009, Preiser et al., 2009), ergonomics or culture. These two main issues provide the motivation to assess new approaches so that successful GC cannot be more widely disseminated in a stochastic adaptive framework that provides "one method fits all" approach to successful GC.

The tablet-computer-based Stochastic TARgeted (STAR) GC protocol provides patient-specific GC (Fisk et al., 2012). STAR uses a clinically validated model of the insulin-glucose system and a cohort model of insulin sensitivity variability (Lin et al., 2006) to compute optimal patient-specific insulin and nutrition interventions that maximize control and nutrition, while maintaining a maximum 5% risk of BG < 4.4 mmol/L. STAR has been the standard of care in Christchurch Hospital ICU, Christchurch, New Zealand and in the Kálmán Pándy Hospital ICU, Gyula, Hungary since 2011. This dual-center retrospective analysis will determine if patient-specific, safe, effective GC is possible with STAR.

2. METHODS

2.1 STAR GC Model, Method and Clinical Implementation

STAR provides adaptive, patient-specific and model-based GC using the ICING model (Lin et al., 2011):

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

$$\dot{I} = -n_K I(t) - \frac{n_L I(t)}{1+\alpha_I I(t)} - n_I(I(t)-Q(t)) + \frac{u_{ex}(t)}{V_I} + (1-X_L)\frac{u_{en}(t)}{V_I} \quad (2)$$

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

$$P(t) = \min\left(d_2 P_2, P_{\max}\right) + PN(t) \quad (4)$$

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where $G(t)$ [mmol/L] is BG, $I(t)$ [mU/L] is plasma insulin, and $Q(t)$ [mU/L] is interstitial insulin.. Also, n_I [1/min] is the transport rate for plasma to interstitial insulin and n_C [1/min] is the interstitial insulin degradation rate. Endogenous insulin is $u_{en}(t)$ [mU/min] and $u_{ex}(t)$ [mU/min] is exogenous insulin, where first-pass hepatic extraction is x_L. V_I [L] is the insulin distribution volume, V_G [L] the glucose volume, and n_K [1/min] and n_L [1/min] are renal and hepatic clearance rates. Endogenous glucose production is assumed constant as EGP [mmol/min] and CNS [mmol/min] is the constant, non-insulin mediated glucose uptake by the central nervous system. Michaelis-Menten functions capture saturation, with α_I [L/mU] for saturation of plasma insulin transport and α_G [L/mU] for saturation of insulin-dependent glucose clearance. Finally, non-insulin mediated glucose disposal rate and insulin sensitivity are p_G [1/min] and S_I [L/mU/min] or SI. Figure 1 shows a model schematic.

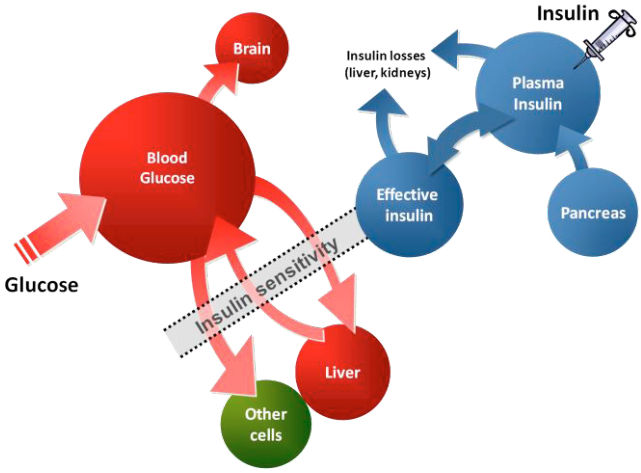

Fig. 1: ICING model schematic showing main elements.

In use, a patient-specific SI value is identified from insulin and nutrition data at each 1-3-hourly BG measurement. This identified SI value is used with a stochastic model as shown in Figure 2, to assess the potential variation over the coming 1, 2 and 3 hours (Fisk et al., 2012). A stochastic model of SI (Lin et al., 2006) provides 5th and 95th percentile SI bounds to test a range of insulin and nutrition interventions. The overall goal places the 5th percentile BG on 4.4 mmol/L, ensuring the BG distribution is centered on 4.4-8.0 mmol/L. Measurements are hourly for BG outside this range, and nurses choose a 1-3-hourly intervention when in this band.

2.2 Patient Cohorts, Protocols and Data

The study compares STAR over 2 patient cohorts:

- **Christchurch** Hospital ICU, Christchurch, New Zealand, from June 2011 – May 2015.
- Kálmán Pándy Hospital ICU, **Gyula**, Hungary, from December 2011 – May 2015.

It excludes patients who spent less than 10 hours on protocol or were fed greater than 120% of their SCCM/ACCP caloric target (Cerra et al., 1997) for clinical reasons. Thus, all patients were treated similarly within the STAR framework. Demographic data is presented in Table 1.

Table 1: Cohort demographics, where shaded areas indicate differences (P < 0.05 Mann-Whitney).

	Gyula	Christchurch
Number	47	267
Age	66 [58 : 71]	65 [55 : 72]
Percent male	61.7	65.5
Length of Stay	14 [8.0 : 20.5]	5.7 [2.5 : 13.4]
APACHE II	32.0 [28.0 : 36.0]	21.0 [16.0 : 25]
Mortality (%)	38.3	24.3

Christchurch: Starting criteria for STAR in Christchurch is two successive BG measurements over 8 mmol/L within a 4-hour period. IV insulin is delivered in hourly bolus form, with added background infusions of up to 3U/hour when insulin requirements are high and sustained [28, 29]. Blood for BG measurement was typically taken directly from an arterial line, and measured using an Arkray Super Glucocard™ II glucometer (Arkray, Minnesota, USA). They are typically fed enterally with Glucerna™ Select (Abbott Labs, Illinois, USA), a low carbohydrate formula (32%). Parenteral nutrition is used occasionally as a supplement.

Gyula: Starting criteria depends on expected length of stay and illness severity. This difference can be seen in Table 1, with the Gyula cohort having much higher Apache II scores and ICU length of stay. IV insulin is delivered via continuous infusion, and local nutrition guidelines specify aggressive early parenteral nutrition to supplement enteral nutrition to the same goal rate of 25kcal/kg/day. Patients are transitioned from parenteral to enteral nutrition as their stay progresses,

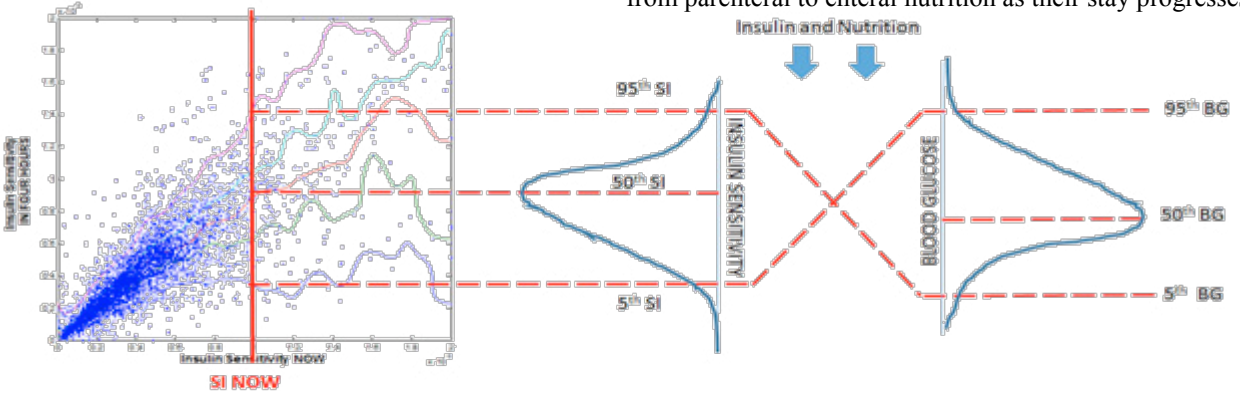

Fig. 2: Using stochastic models to forecast likely changes in insulin sensitivity (SI), given its current value, and thus blood glucose (BG) outcomes for given insulin and nutrition interventions