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A 3D insulin sensitivity prediction model enables more patient-specific prediction and model-based glycaemic control

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ABSTRACT

Background: Insulin therapy for glycaemic control (GC) in critically ill patients may improve outcomes by reducing hyperglycaemia and glycaemic variability, which are both associated with increased morbidity and mortality. However, initial positive results have proven difficult to repeat or achieve safely. STAR (Stochastic TARgeted) is a model-based glycaemic control protocol using a risk-based dosing approach. STAR uses a 2D stochastic model to predict distributions of likely future changes in model-based insulin sensitivity (*SI*) based on its current value, and determines the optimal intervention.
Objectives: This study investigates the impact of a new 3D stochastic model on the ability to predict more accurate future *SI* distributions, which would allow more aggressive insulin dosing and improved glycaemic control.
Methods: The new 3D stochastic model is built using both current *SI* and its prior variation to predict future SI distribution from 68,629 h of clinical data (819 GC episodes). The 5^{th}–95^{th} percentile range of predicted *SI* distribution are calculated and compared with the 2D model.
Results: Results show the 2D model is over-conservative compared to the 3D case for more than 77% of the data, predominantly where *SI* is stable ($|\%\Delta SI| \leq 25\%$). These formerly conservative prediction ranges are now ~30% narrower with the 3D model, which safely enables more aggressive insulin dosing for these patient hours. In addition, distributions of predicted *SI* within the 5^{th}–95^{th} percentile range are much closer to the ideal value of 90% for more patients with the 3D model.
Conclusions: The new 3D model better characterises patient specific metabolic variability and patient specific response to insulin, allowing more optimal insulin dosing to increase performance and safety.

1. Introduction

Critically ill patients in intensive care units (ICUs) often experience abnormally elevated blood glucose (BG) concentrations (hyperglycaemia), as a stress response to illness and injury [1–3]. Hyperglycaemia, glycaemic variability, and hypoglycaemia are all independently associated with increased morbidity and mortality [3–10]. Glycaemic control (GC) using insulin therapy has shown beneficial outcomes, reducing organ failure and costs [11–18]. However, other studies failed to reproduce these results [19–24], and all but two studies [25] had increased risk of hypoglycaemia with tight control. GC has been hard to achieve both safely and effectively (e.g [26].). Fixed or ad hoc protocols are still typically used in hospitals, but fail to capture and fully account for patient

Abbreviations: %ΔSI, hour-to-hour percentage change in SI; APACHE, acute physiology and chronic health evaluation; BG, blood glucose; GC, glycaemic control; ICING, intensive control insulin-nutrition-glucose; ICU, intensive care unit; LOS, length of stay; SI, insulin sensitivity; SPRINT, specialised relative insulin nutrition tables; STAR, STochastic-TARgeted.

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variability impacting performance and safety [27]. This issue has led to the emergence of more complex, model-based GC protocols [28–30].

STAR (Stochastic Targeted) is a clinically-validated model-based GC framework, capable of adapting treatment to patient-specific insulin requirements while managing the risk of hypo glycaemia [25,31–33]. STAR uses a patient-specific time-varying model-based insulin sensitivity (*SI*) to estimate patient metabolic condition. Likely future changes in *SI* are assessed using population-based stochastic models [34]. The 5th-95th percentile interval of BG outcomes is calculated from the 5th–95th percentile interval in *SI* outcomes, allowing forward prediction of likely BG outcomes for any given insulin-nutrition intervention. STAR thus selects an insulin-nutrition treatment to best overlap the clinically specified target BG range, while also managing and mitigating hypoglycaemic risk [32,35], a unique risk-based dosing approach.

The stochastic model currently used by STAR forecasts future *SI* (SI_{n+1}) distributions based on the identified current *SI* value (SI_n). A Markov process is used, where outcome SI_{n+1} only depends on input SI_n [34]. This study expands this existing 2D stochastic approach by adding the most recent change in SI_n as an input parameter for forward prediction of outcome SI_{n+1}. The new 3D model will now predict future SI_{n+1} based on current SI_n and the percentage change in SI from SI_{n-1} to SI_n. The old 2D model and the new 3D model are compared to assess the new model's ability to tighten *SI* prediction ranges for tighter forward prediction of future BG. Better forward prediction of *SI* allows better characterisation of future metabolic variability, thus improving patient-specific glycaemic control without compromising safety. Narrower future *SI* prediction ranges enable more targeted insulin dosing for these patients who are more stable. This study also assesses whether more stable patients have less future metabolic variability.

2. Material and methods

2.1. Glucose-insulin model and insulin sensitivity

The ICING (Intensive Control Insulin-Nutrition-Glucose) physiological model describing glucose-insulin dynamics is defined [25,36,37]:

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

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

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

Where G(t) is the blood glucose level (mmol/L), I(t) is the plasma insulin concentration (mU/L), Q(t) is the interstitial insulin concentration (mU/L), P(t) is the glucose appearance in plasma from enteral and parenteral dextrose intake (mmol/min), and SI is insulin sensitivity (L/mU/min). Other parameters, rates and constants are given in [25,36,37] and can be found in the Appendix A.

Model-based insulin sensitivity (*SI*) is patient-specific and time varying, characterising patient-specific glycaemic system response to glucose and insulin administration. *SI* is identified hourly from clinical BG, and insulin and nutrition input data, using an integral-based fitting method [38,39]. This approach is robustly identifiable [40].

STAR currently uses a cohort-based 2D stochastic model to forecast future *SI*. As shown in Fig. 1, for any current *SI* (SI_n), the probability of *SI* (SI_{n+1}) at 1–3 hours in future is determined based on a clinical data model using kernel density methods [34]. Future *SI* distributions used in conjunction with Eqs. (1)–(3) can be used to derive likely future BG distributions for a specific insulin and nutrition intervention. The 5th percentile BG prediction is used to ensure safety, limiting the maximum risk of BG < 4.4 mmol/L to 5% and enabling risk-based, rather than target-value-based, dosing [32].

Table 1
Summary of patient demographics for the three cohorts. Results are given as median [IQR] where relevant.

	SPRINT Christchurch	STAR Christchurch	STAR Gyula
# episodes	442	330	47
# patients	292	267	47
# hours	39838	22523	6268
% male	62.7	65.5	61.7
Age (years)	63 [48, 73]	65 [55, 72]	66 [58, 71]
APACHE II	19.0 [15.0:24.5]	21.0 [16.0:25.0]	32.0 [28.0:36.0]
LOS - ICU (days)	6.2 [2.7,13.0]	5.7 [2.5,13.4]	14.0 [8.0,20.5]

2.2. Patients and cohorts

This study uses data from 3 clinical ICU data cohorts totalling 819 GC episodes (606 patients) and 68,629 h of treatment [13,25]:

1 Patients treated using STAR in Christchurch Hospital ICU, New Zealand, from June 2011 to May 2015.
2 Patients treated using SPRINT in Christchurch Hospital ICU, New Zealand, from July 2005 to May 2007
3 Patients treated using STAR in Kalman Pandy Hospital ICU, Hungary, from December 2011 to May 2015.

Demographics are summarised in Table 1.

2.3. Analysis

SI level is fit on an hour-to-hour basis for each patient [38], and the forward *SI* variability (%Δ*SI*) is defined as the hour-to-hour percentage change in *SI*:

$$\%\Delta SI_n = 100 \times \frac{SI_n - SI_{n-1}}{SI_{n-1}}$$

The existing 2D stochastic model uses the input SI_n to determine the outcome distribution of SI_{n+1}. This study builds a new 3D model to determine the outcome distribution of SI_{n+1} based on input of patient-specific current metabolic state, SI_n, and *SI* variability to current time, $\%\Delta SI_n$.

A total of 66,991 data triplets ($\%\Delta SI_n$, SI_n, SI_{n+1}) are created from the original 68,629 h of treatment, where the number of triplets is lower because no triplets are created for the first and last hour of data. The data triplets were binned with bin sizes of $\%\Delta SI$ = 10% and SI_n = 0.5e-4. These bins are limited to a range of $\%\Delta SI$ = [-100%, 200%] and the 1st–99th percentile range in identified *SI* ([1.0e-7, 2.1e-3] L/mU/min) values, bringing the total number of triplets considered to 65,051, as those few outside these ranges are excluded, corresponding to 97.1% of the original 66,991 triplets.

The minimum number of data points required for adequate data density in each bin was arbitrarily defined to be 100 data triplets to ensure any distributions were not influenced by outliers. To improve data density and smooth model extremes, bins not meeting this criterion are summed together along the $\%\Delta SI$ axis at the same SI_n level, allowing data triplets to influence neighbouring bins where there is insufficient data density. The summation process is described below, and an example is shown in Table 2.

Starting from the bin centred at 0% and going down, and at the bin centred at 10% and going up:

1 Check data density.