3D Stochastic Modelling of Insulin Sensitivity in STAR: Virtual trials analysis

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Abstract: Glycaemic control has shown beneficial outcomes for critically ill patients, but has been proven hard to achieve safely, increasing risk of hypoglycaemia. Patient metabolic variability is one of the main factor influencing glycaemic control safety and efficacy. STAR is a model-based glycaemic controller using a unique patient-specific risk-based dosing approach. STAR uses a 2D stochastic model, built from population data using kernel density methods, to determine potential forward future evolution in patient-specific insulin sensitivity (SI_{n+1}), based on its current value (SI_n).

This study uses virtual trial to compare the current 2D stochastic model used in STAR, with a new 3D stochastic model. The new 3D model also uses prior insulin sensitivity value (SI_{n-1}) to determine distribution of likely future SI_{n+1}. A total of 587 virtual patient glycaemic control episodes longer than 24 hours from three different studies are used here. Safety (% blood glucose (BG) measurements < 4.0 and < 2.2 mmol/L), performance (% time in the target 4.4-8.0 mmol/L band), insulin administration and nutrition delivery (% goal feed) are compared.

Results show similar performance (90% BG in 4.4-8.0 mmol/L), and similar safety, with slightly higher % BG < 4.0 mmol/L (0.9 vs. 1.4%) and % BG < 2.2 mmol/L (0.02 vs. 0.03%) for the 3D model, was achieved for similar workload. The slightly lower median BG level (6.3 vs. 6.0 mmol/L) for the 3D stochastic model is explained by the higher median insulin rate administered (2.5 vs. 3.0 U/hr). More importantly, simulation results showed higher nutrition delivery using the 3D stochastic model (92 vs. 99 % goal feed).

The new 3D stochastic model achieved similar safety and performance than the 2D stochastic model in these virtual simulations, while increasing the total calorific intake. This higher nutritional intake is potentially associated with improved outcome in intensive care units. The 3D stochastic model thus better characterises patient-specific metabolic variability, allowing more optimal insulin and nutritional dosing. Therefore, a pilot clinical trial using the new 3D stochastic model could be realised to assess and compared clinical outcomes using the new stochastic model.

Keywords: Glycaemic control, Hyperglycaemia, Insulin, Clinical trial, Virtual Trial, Stochastic Modelling

1. INTRODUCTION

Hyperglycaemia, hypoglycaemia and highly variable blood glucose (BG) concentrations are associated with higher mortality, morbidity and length of stay in intensive care units (ICU) (Bagshaw *et al.*, 2009; Capes *et al.*, 2000; Egi *et al.*, 2006; Egi *et al.*, 2010; Krinsley, 2008). Hyperglycaemia is a common complication for critically ill patients, suggesting glycaemic control (GC) to lower BG levels (McCowen *et al.*, 2001). GC using insulin therapy has shown positive outcomes, but has been proven difficult to achieve safely and effectively, significantly increasing risk of hypoglycaemia (Brunkhorst *et al.*, 2008; Chase *et al.*, 2010a; Finfer *et al.*, 2009; Finfer *et al.*, 2012; Krinsley, 2004, 2005; Preiser *et al.*, 2009; Reed *et al.*, 2007; Van den Berghe *et al.*, 2001; Van den Berghe *et al.*, 2003).

Safe and effective GC is required for all patient, and is a function of protocol design, not patient metabolic state (Uyttendaele *et al.*, 2017). Patients metabolic variability is one of the most important factors making GC hard to achieve safely. Fixed table-based GC protocols thus often fail to provide safe control, completely lacking patient variability. Model-based GC protocols are thus used to assess intra- and inter- patient variability and offer patient-specific insulin therapy, directly managing risk (Chase *et al.*, 2011).

STAR is a model-based GC framework, which has shown promising results across different ICU settings (Evans *et al.*, 2012; Fisk *et al.*, 2012; Stewart *et al.*, 2016). STAR uses a unique patient-specific risk-based approach to titrate insulin and nutrition safely. Patient-specific insulin sensitivity (SI) is calculated using a clinically validated physiological model (Lin *et al.*, 2011), and distribution of likely future SI variability is determined using a stochastic model (Lin *et al.*, 2008). This

distribution of likely future SI allows to calculate potential future BG outcomes for a given intervention. STAR thus determines which intervention best overlaps a clinically chosen BG target band.

Virtual trials (Chase *et al.*, 2010b), using virtual patients, are used in this study to assess the impact of a new 3D stochastic model implemented in STAR. Such trials allow safety and performance assessment of GC outcomes for protocols tested on virtual cohorts, prior to clinical implementation. The 2D stochastic model uses current identified patient-specific SI value to compute distribution of likely future SI changes. Compared to its predecessor, the new 3D stochastic model is constructed using both previous and current SI values to forecast future SI variability. It thus uses the prior variability in SI to enhance prediction. BG outcomes are compared with the 2D stochastic model, to determine whether this new 3D model significantly improves safety and performance of STAR, by better characterizing inter-patient variability.

2. METHODS

2.1 STAR protocol and model-based insulin sensitivity

The physiological model describing the glucose-insulin pharmacokinetics is schematically represented in Figure 1, and is defined (Lin, *et al.*, 2011):

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

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

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

Where *G(t)* is blood glucose (mmol/L), *I(t)* is plasma insulin (mU/L), *Q(t)* is interstitial insulin (mU/L), *P(t)* is glucose from dextrose intake (mmol/min), and SI is insulin sensitivity (L/mU/min). Main clearance rates and parameters are defined in (Lin, *et al.*, 2011; Pretty *et al.*, 2014).

The time-varying SI parameter describes the patient-specific metabolic response to insulin. SI is determined hourly from clinical data using integral-based fitting methods (Docherty *et al.*, 2012; Hann *et al.*, 2005), accounting for intra-patient variability.

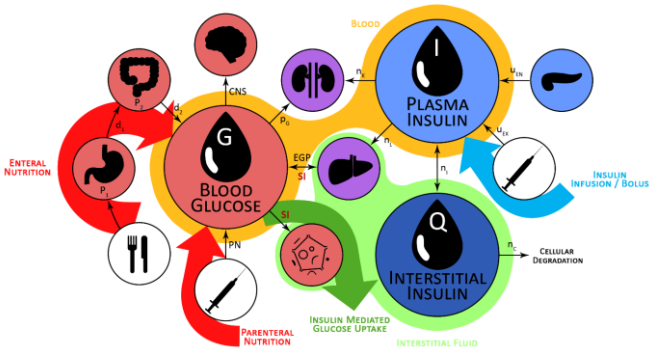

Figure 1 – Schematic representation of the glucose-insulin physiological model defined in Equations (1) – (3).

2.2 2D vs. 3D stochastic model

STAR uses a stochastic model, built on population data using kernel density estimations, to predict likely 1-3 hourly future changes in SI (Lin, *et al.*, 2008). Based on the predicted distribution of future SI, the distribution of likely corresponding predicted future BG concentrations can be determined for a given intervention (Figure 2). STAR seeks the best intervention ensuring the 5th percentile of predicted BG $\geq$ 4.4 mmol/L, while maximizing the overlapping with the clinically specified target band (4.4-8.0 mmol/L). This unique risk-based dosing approach, significantly decreases risk of hypoglycaemia, while improving GC performance. STAR is the standard of care of two different ICUs, in Christchurch Hospital, New Zealand, and Gyula, Hungary.

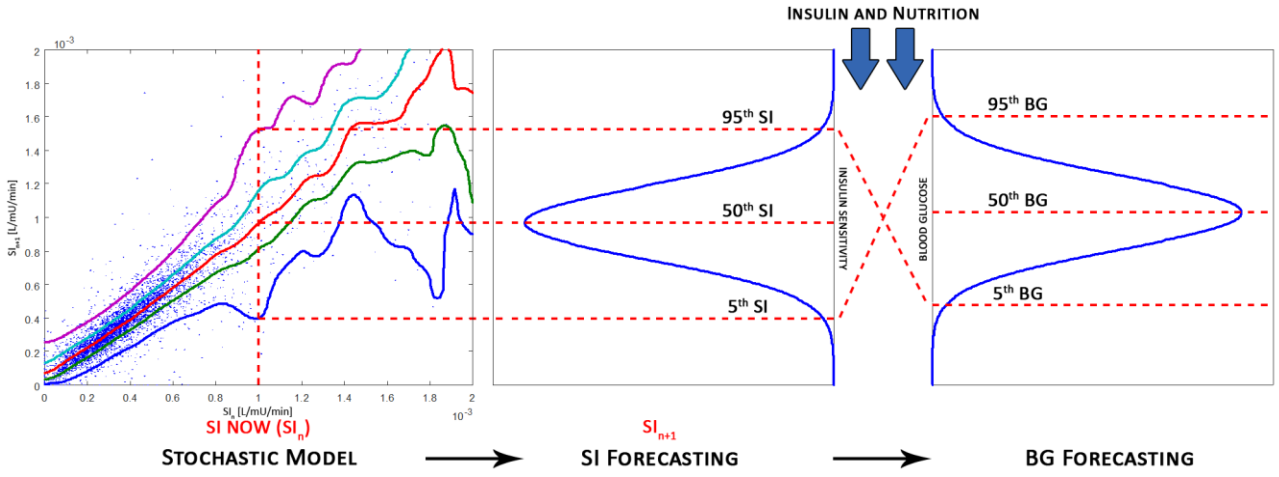

Figure 2 – STAR uses stochastic models to forecast change in SI based on current SI value, and determines BG outcomes for given insulin and nutrition intervention.

One important feature of STAR is its ability to modulates both insulin and nutrition inputs. Enteral nutrition can be lowered if insulin only intervention is not sufficient decrease BG levels, but STAR will always try to reach back 100% goal feed (GF) to maximise carbohydrates intake. Insulin is administered as intravenous boluses, with an equivalent maximum of 6U/hr, and authorizing up to 3U/hr in continuous infusion for consistent resistant patients. Enteral nutrition administration can be modulated between 30-100% of the total calorific GF if needed. As patient weight is not always known, 100% GF is estimated based on body frame size, age, and sex of the patient. More details can be found elsewhere (Stewart et al., 2018).

The 2D stochastic model uses only current SI (SI_n) as input to determine the distribution of likely future SI (SI_{n+1}). The new 3D stochastic model uses both previous (SI_{n-1}) and current SI_n values to determine the distribution of future SI_{n+1} (Uyttendaele *et al.*, 2018a). These stochastic models are made using local data density weighted Gaussian kernel estimation (Lin*, et al.*, 2008). The resulting 5th-95th percentile prediction ranges are shown in Figure 3, where the 2D stochastic model is constant across all SI_{n-1}, while the 3D model is variable across both SI_n and SI_{n-1}, yielding narrower and wider prediction ranges.

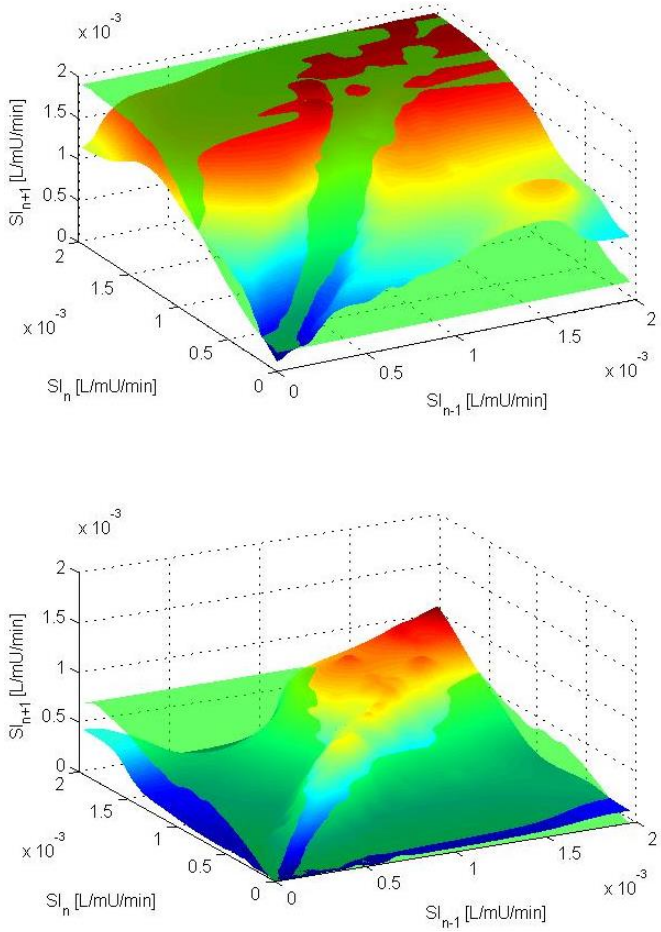

Figure 3 – Comparison between 2D (green) and 3D (colour) stochastic model surfaces of the 5th (bottom) and 95th (top) percentile predictions of future SI_{n+1}. The 2D model is constant across SI_{n-1}, where the 3D model is different for every (SI_{n-1}, SI_n) pair, both narrower and wider across the range.

Previous studies have shown the 3D model better captures SI variability, with tighter prediction bands for over 70% of the time, and showed stable patients tend to remain stable where variable patients are more likely to remain variable and are more variable than the 2D model represents (Uyttendaele*, et al.*, 2018a; Uyttendaele *et al.*, 2018b). This outcome suggests more aggressive dosing can be used for these more stable time periods, improving BG outcomes without compromising safety.

2.3 Virtual trials and virtual patients

Virtual trials are used to simulate GC protocols on virtual cohort, allowing to assess and compare BG outcomes for these protocols (Chase *et al.*, 2018; Chase*, et al.*, 2010b). Virtual patients are created from real patient clinical data, and are characterised by their SI profile over time. SI is considered treatment independent and hourly constant. Two different protocols can thus be simulated on a same virtual patient, resulting in different BG outcomes. Virtual trial simulations are a powerful tool allowing to avoid any undesired behaviour prior to clinical implementation. Virtual trials have been previously validated and shown generalisable across different ICUs practices (Dickson *et al.*, 2017).

A total of 587 virtual patient episodes longer than 24 hours are used in this study, totalling 65260 hours of GC. These virtual patient episodes were created using clinical data from 3 different studies in 2 different countries (STAR protocol, Christchurch, New Zealand (Evans*, et al.*, 2012); SPRINT protocol, Christchurch, New Zealand (Chase *et al.*, 2008); STAR protocol, Gyula, Hungary (Benyo *et al.*, 2012)). Patient demographic details are in (Stewart*, et al.*, 2016).

2.4 Analyses

New 2D and 3D stochastic models are created using SI from 411 (70%) random patient episodes out of the total 587. Virtual trial of STAR using the 2D and 3D stochastic models are simulated on the other 176 (30%) patient episodes, allowing fair GC outcome comparison. This overall process is realised three times, where patient episodes are each time randomly chosen for the training (70%) and testing (30%) sets, resulting thus in 528 simulated GC episodes. Thus, one virtual patient episode is possibly simulated three times if not used to build the stochastic models, but results will be different time to time according to the specific 2D and 3D stochastic models built.

Safety and performance from GC simulation results are thus compared between both stochastic models. In this analysis, BG data is resampled hourly to allow fair comparison across different measurement intervals. Safety is evaluated by the %BG $\leq$ 4.4 mmol/L, %BG $\leq$ 4.0 mmol/L (mild hypoglycaemia) and %BG $\leq$ 2.2 mmol/L (severe hypoglycaemia). Performance is assessed by the percentage time in band (%BG with 4.4-8.0 mmol/L), and the median [IQR] per-patient BG. Insulin and nutrition %GF rates are also compared. Finally, workload is assessed by numbers of BG measurements per day, where a higher value would indicate more work for the change in stochastic models.

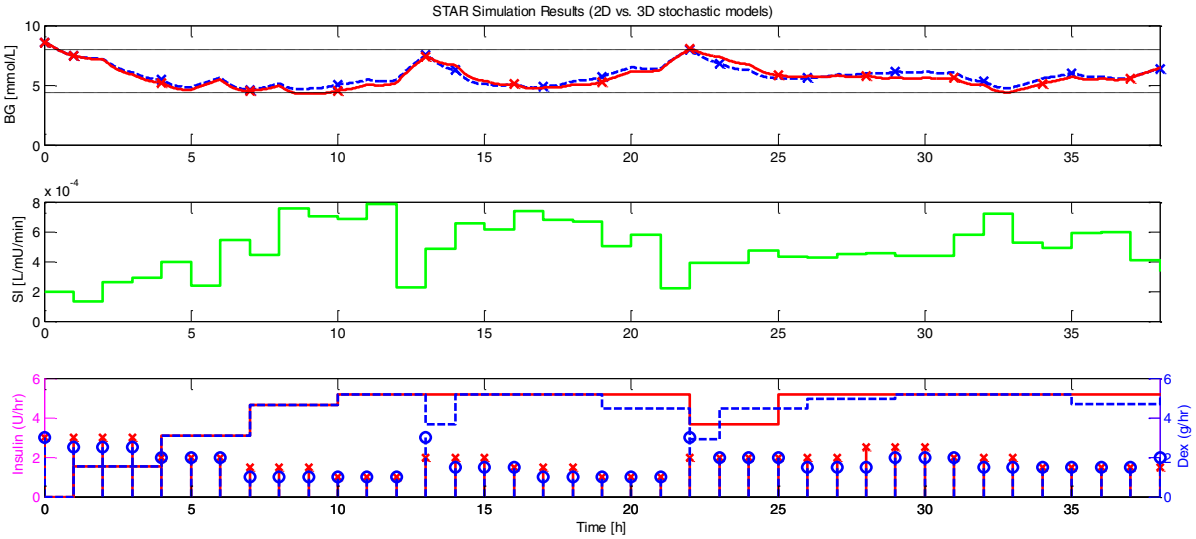

Figure 4 – Simulation results comparison using the 2D (blue) and 3D (red) stochastic models for the same patient. Top panel shows the evolution of simulated BG, crosses represent BG measurements. Middle panel show this patient-specific SI profile. Bottom panel shows insulin boluses and nutrition rates over time.

3. RESULTS

Clinical and simulation results are summarised in Table 1 for each protocol. An example of the GC outcome results for each protocol is shown for one patient in Figure 4. Resampled BG, insulin rate, and percentage goal feed rate cumulative distribution functions (CDFs) are shown in Figure 5.

Regarding performances, simulations results in Table 1 show both models achieved similar 90% time in the 4.4-8.0 mmol/L band for similar workload (11.6 vs. 11.7 measurements per day). The median [IQR] BG level achieved is slightly lower for the 3D stochastic model (6.3 [5.7, 6.9] vs. 6.0 [5.5, 6.7] mmol/L), reflected in Figure 5 (top). Additionally, both median [IQR] insulin and nutrition rates are higher for the 3D stochastic model (3.0 [1.5, 5.0] vs. 2.5 [1.5, 4.0] U/hr, and 92 [70, 100] vs. 99 [66 100] %), also reflected in Figure 5 (middle and bottom).

Concerning safety, the 3D stochastic model achieved lower % BG > 8.0 mmol/L (8 vs 7%), but higher % BG < 4.4 mmol/L (2 vs. 3%). More specifically, 0.5% higher BG < 4.0 mmol/L (mild hypoglycaemia) is observed for the 3D stochastic model, while very low % BG < 2.2 mmol/L (severe hypoglycaemia) for both models (0.02 vs. 0.03%) occurred. However, 12 patients experienced severe hypoglycaemia with the 3D stochastic model, compared to 9 patients with the 2D stochastic model.

These overall result trends can be seen in Figure 4, showing simulation results for one patient. BG (top) is similar, but slightly lower for the 3D stochastic model simulation (red). Insulin bolus sizes are often ~0.5 U/hr higher (bottom), as well as nutrition rates for the 3D stochastic model. The protocol simulations are based on identical SI profiles (middle), characterising this patient-specific metabolic evolution over time, thus really reflecting GC outcomes behaviour difference of these two protocols on the same underlying patient.

Table 1 – Simulation results summary for safety and performance comparison. BG stats are calculated from hourly resampled BG as measurement intervals can differ treatment to treatment. Data is presented as median [IQR] where appropriate.

	2D model	**3D model**
# Patients	528	528
Total hours	60246	60267
Mean measurements per day	11.6	11.7
BG level (mmol/L)	6.3 [5.7, 6.9]	6.0 [5.5, 6.7]
Insulin rate (U/hr)	2.5 [1.5, 4.0]	3.0 [1.5, 5.0]
Nutrition rate (%GF)	92 [70 100]	99 [66 100]
% BG in 4.4-8.0 mmol/L	90	90
% BG in 8.0-10.0 mmol/L	6	5
% BG > 10.0 mmol/L	2	2
% BG < 4.4 mmol/L	2	3
% BG < 4.0 mmol/L	0.9	1.4
% BG < 2.2 mmol/L	0.02	0.03
# patients (%) < 2.2 mmol/L	9 (1.7)	12 (2.3)

4. DISCUSSION

Overall, these simulations show both protocols using the 2D or 3D stochastic model achieved safe and effective GC, with very low % BG < 4.4 mmol/L and high 90% time in the 4.4-8.0 mmol/L target band. The main difference between the two approach remains in the insulin and nutrition rates administered. As expected, the higher insulin rate administered allowed higher per-patient median nutritional deliver rates as a function of goal feed rate, improving a delivery rate that is near the best in the world (Stewart, *et al.*, 2018). Therefore, the similar safety and performance, achieved with similar workload, were realised with overall greater carbohydrates delivery.

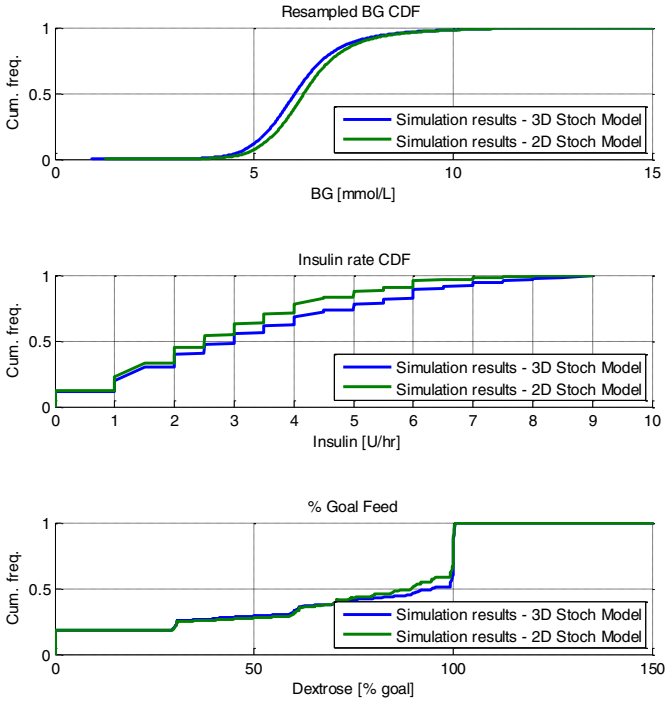

Figure 5 – Cohort resampled BG, insulin rate, and %GF CDFs comparison between simulations.

A recent study showed STAR capacity to deliver nutrition rates better than 158 ICUs in 20 different countries (Stewart, *et al.*, 2018), which may be associated with improved clinical outcomes in ICU (Heyland *et al.*, 2011). In this study, the new 3D stochastic model provided even better carbohydrate delivery compared to the previous 2D stochastic model.

As explained, previous analysis on the new 3D stochastic model has shown the 3D stochastic model has consistently tighter prediction bands more than 70% of the time, particularly when SI is stable. These virtual trials confirm the accuracy on the forward prediction of SI variability of the new 3D stochastic model, allowing more aggressive dosing, while increasing calories intake and ensuring both safety and performance. The 3D stochastic model thus improves the patient-specific GC approach in STAR.

Based on these results, a pilot clinical trial can be realised to assess and compare safety, performance, nutrition delivery and workload of STAR using this new 3D stochastic model.

5. CONCLUSIONS

This study compared virtual trial results of STAR GC protocol using a 2D stochastic model, using only current SI to predict future SI, and a new 3D stochastic model using both current and previous SI to predict future SI changes. Simulations results showed similar safety and performance, while the 3D stochastic model version uses more aggressive insulin dosing. The main difference relies in the greater delivered % GF calorific content, for similar clinical workload.

The 3D stochastic model implementation within the STAR framework can thus potentially lead to beneficial outcome in critically ill patients, as increased nutrition rate delivery is associated with improved clinical outcomes. A pilot clinical trial could thus assess and confirm these results.

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