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Changes in Identified, Model-based Insulin Sensitivity can be used to Improve Risk and Variability Forecasting in Glycaemic Control

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Abstract: Hyperglycaemia, hypoglycaemia and glycaemic variability in critically ill patients are associated with increased mortality and adverse outcomes. Some studies have shown insulin therapy to control glycaemia has improved outcomes, but have proven difficult to repeat or achieve safely. STAR (Stochastic Targeted) is a model-based glycaemic control protocol using a stochastic model to forecast future distributions of insulin sensitivity (SI) based on its current value, to predict the range of future blood glucose outcomes for a given intervention. This study presents an improved 3D stochastic model, forecasting future distributions of SI based on its current value and prior variation. The percentage difference in the 5th, 50th, and 95th percentiles between the current 2D and new 3D models are compared. Results show the original 2D stochastic model is over-conservative for around 77% of the data, predominantly where prior variability was low. For higher prior variation (more than ±25% change in SI), the 3D stochastic model prediction range of future SI is wider. The new 3D model was found to have overall narrower 5th – 95th prediction ranges in SI, but to retain a similar per-patient (60 – 100%) and overall (92%) percentage of SI outcomes correctly predicted within these ranges. These results suggest the new 3D model is more patient-specific and will enable more optimal dosing, to increase both safety and performance. This improvement in forecasting may result in tighter and safer glycaemic control, improving performance within the STAR framework.

Keywords: Glucose, Hyperglycaemia, Glycaemic Control, Insulin sensitivity, Insulin

1. INTRODUCTION

Hyperglycaemia, elevated blood glucose (BG) concentration, is common in adult intensive care units (ICUs) (Capes et al., 2000, Finney et al., 2003, McCowen et al., 2001). It is associated with worsened outcomes (Capes et al., 2000, Krinsley, 2003, Krinsley and Grover, 2007). Hypoglycaemia, abnormally low BG concentrations, and glycaemic variability have also been associated with adverse outcomes and mortality (Ali et al., 2008, Bagshaw et al., 2009, Egi et al., 2006, Egi et al., 2010, Krinsley, 2009).

Glycaemic control (GC) using insulin therapy to lower BG level has shown beneficial outcomes, but also shown increased risk of hypoglycaemia (Chase et al., 2008a, Krinsley, 2004, Reed et al., 2007, Van den Berghe et al., 2006, van den Berghe et al., 2001). Fixed or ad hoc protocols are typical, but fail to capture the inter- and intra- patient variability hindering control performance and safety (Chase et al., 2011). It is thus important to have a safe and effective glycaemic control protocol capable of adapting to patient-specific insulin requirements, and able to directly manage risk.

STAR (Stochastic TARgeted) is a clinically-validated model-based GC framework with promising clinical results (Evans et al., 2012, Fisk et al., 2012b, Stewart et al., 2016a). STAR captures patient-specific metabolic state using model-based insulin sensitivity (SI), and is able to quantitatively forward predict a distribution of future SI and thus its variability. Insulin-nutrition treatments are thus selected based on likely future BG outcomes for a given intervention, directly managing and minimizing hypoglycaemic risk and actively targeting a clinically determined glycaemic range (Fisk et al., 2012a).

In particular, STAR uses a stochastic model to predict future SI (SI_{n+1}) distributions based on a Markov Process dependant only on identified current SI (SI_n) value (Lin et al., 2008). This study investigates the impact of identified prior changes in SI on the distribution of future SI values. Identifying trends based on the previous change in SI could improve forecasting precision, add further patient-specificity, and thus help to achieve safer and tighter control by adapting treatment according to a new updated stochastic model that further segregates patients based on patient-specific response to care.

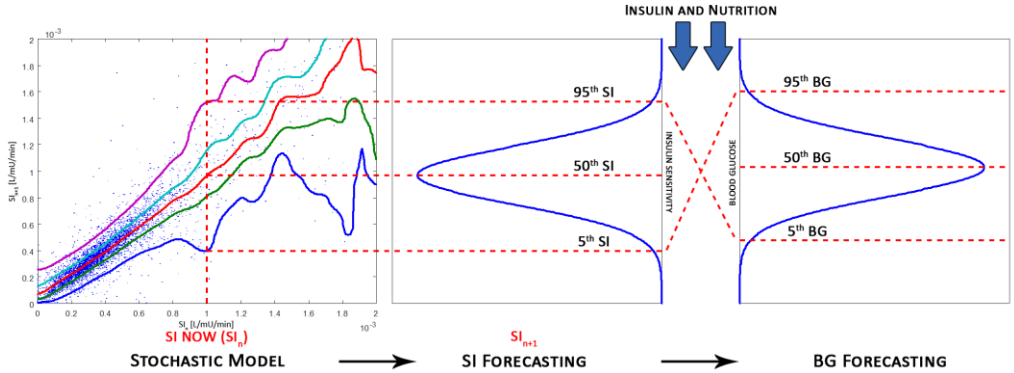

Figure 1 – STAR uses stochastic models to forecast change in SI based on current SI value, and determines BG outcomes for given insulin and nutrition intervention.

2. METHODS

2.1 Patients

This study uses data from 3 cohorts and 2 GC protocols, totalling 819 episodes and 68629 hours of treatment. SPRINT (Chase et al., 2008b) and STAR (Stewart et al., 2016a) are the two protocols used in the Christchurch Hospital ICU and Kalman Pandy Hospital ICU. Demographics are summarised in Table 1.

2.2 Model-Based Insulin Sensitivity

The physiological model is defined (Lin et al., 2011):

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

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

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

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 S_I is insulin sensitivity (L/mU/min). All other variables and parameters are defined in (Stewart et al., 2016b).

SI is patient-specific and time-varying. It captures patient-specific response to glucose and insulin administration. It is identified hourly on a patient-specific basis from measured clinical data, using an integral-based fitting method (Hann et al., 2005).

STAR forecasts SI using a cohort-based stochastic model (Figure 1). For any given current SI_n, a distribution of future SI_{n+1} at 1-3 hours in future is determined based on a clinical data model derived using kernel density methods (Lin et al., 2008). STAR then determines BG outcome distributions for a given intervention, as shown in Figure 1. The 95th percentile in SI is used to target a minimum BG for a given intervention to ensure safety, as it quantifies to likelihood of hypoglycaemia (Fisk et al., 2012a), a risk based dosing approach.

2.3 Analysis

Forward SI variability (%ΔSI) is defined as the hour-to-hour percentage change in SI:

$$\%\Delta SI_i = 100 \times \frac{SI_i - SI_{i-1}}{SI_{i-1}}$$

In contrast to previous work, which constructed a 2D stochastic model with one input (SI_n) and one output (distribution of SI_{n+1} values), this analysis constructs a 3D model, where a future SI (SI_{n+1}) distribution is predicted given the current patient metabolic state (SI_n) and the previous change in SI ($\%\Delta SI_n$), corresponding to 2 inputs for 1 output.

To avoid the effect of data outliers skewing distributions with small numbers of data points, only the middle 98% of the data (SI = [1.0e-7, 2.1e-3] L/mU/min) is used. Data triplets ($\%\Delta SI_{n-1}$, SI_n, SI_{n+1}) with SI_n outside this range are excluded, leaving 65492 data triplets, representing 97.7% of the original 66991 possible data triplets.

Bins sizes of %ΔSI = 10% and 1e-4 in SI_n are used. These bins are limited to a range of %ΔSI = ±100% and the observed range in SI, bringing the included number of data triplets to 63209 (94.4% of 66991 triplets). Bins are considered to have sufficient data density if at least 100 data triplets are present.

Boundary bins with less than 100 data triplets are summed to improve data density and smooth model extremes by transferring data triplets of from extreme bins to the adjacent bin along the %ΔSI axis, for a given SI_n level, if the number of data point in each is lower than 100. If the new total of data triplets is still less than 100 in this bin and the next adjacent bin, the triplets are transferred to it and so on, starting from both extreme edges and moving towards increased data density. Bin sizes remain unchanged thus representing conservative potential future SI behaviour.

Finally, the 5th, 50th, and 95th percentile of SI_{n+1} is computed for each bin, quantifying the SI_{n+1} distribution of future SI values given a specific $\%\Delta SI_n$ and a current SI_n level. These values are compared to the original 2D stochastic model (SI_{n+1} as a function of SI_n), by computing the difference between the previous and new 5th, 50th, and 95th percentiles, as well as the change in 90% confidence interval width. This analysis thus

constructs a new model and compares it to the previous model to assess where it was conservative and where it added risk.

Table 1 - Patient demographics for the 3 study cohorts. Results are given as median [IQR] where relevant.

	SPRINT Christchurch	STAR Christchurch	STAR Gyula
# episodes	442	330	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]

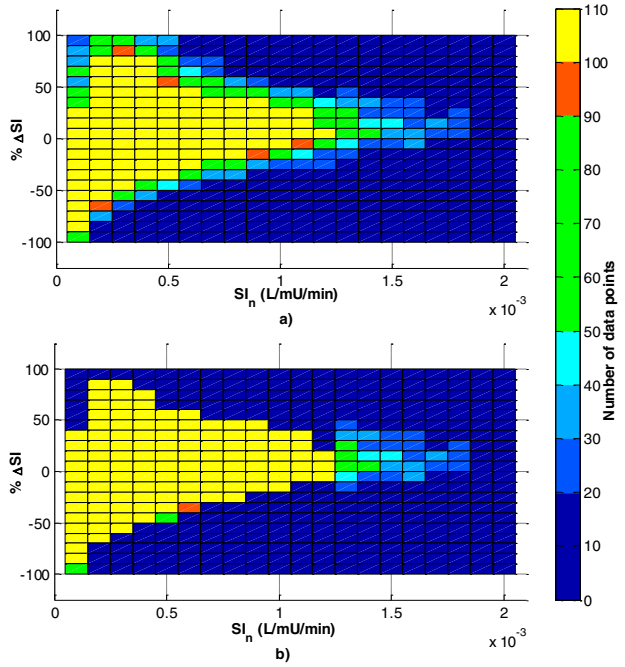

Figure 2- Number of (%ΔSIn-1, SIn, SIn+1) triplets per bin. Before (a) and after (b) merging side bins (along y-axis).

Importantly, a narrower 90% width denotes less future variability allowing more aggressive dosing where the original model was too wide and thus too conservative. A wider band indicates where the current 2D model is not conservative, and less dosing is required to reduce risk. A shift in the 50th percentile indicates where the original model was biased.

The predictive power of the new model is compared to the original stochastic model by computing the per-patient and overall percentage of SI values that fall within the 5th – 95th and 25 – 75th percentile ranges of model predictions. In the case of the new model, data points that now fall outside the new model range are not yet able to be predicted off, so are discarded. Future work will look at establishing methods for dealing with unusual and uncommon data extremes.

In this analysis, forward prediction accuracy of both models is compared using all available data triplets. Self-validation is carried out by evaluating the per-patient percentage of SI outcomes falling into model 25th-75th and 5th-95th percentiles prediction ranges. If the ideal 50% and 90% of forward prediction within those range for each patient is achieved, it indicates a cohort derived model also perfect at per-patient level.

3. RESULTS

Figure 2 shows the number of triplets (%ΔSI_{n-1}, SI_n, SI_{n+1}) per bin, before and after merging. It can be clearly seen that changes in SI are proportionally greater at lower SI level (triangular shape). The yellow areas in Figure 2 (a) and (b) contain 91% and 97% of 63209 total triplets respectively. A new stochastic model is made from all the triplets falling in the yellow bins in Figure 2 (b).

Figure 3 shows percentage changes in the 5th, 50th, and 95th percentiles for SI_{n+1}. Two main regions are identified:

1. Between %ΔSI_n = ±25% the 5th percentile is often higher than the prior 2D stochastic model, and the 95th percentile lower, regardless of SI_n, suggesting the 2D stochastic model is conservative in that it over-estimated the width of the 90% range of future SI_{n+1} outcomes. This region contains 77% of the data triplets.
2. Outside %ΔSI_n = ±25% for low SI_n > 2.3e-4 the 5th percentile is lower and the 95th higher, indicating a non-conservative region with higher risks of hypo- and hyper-glycaemia than predicted by the 2D model.

The percentage change in 50th percentile values in Figure 3 (b), are all within ± 20%. However, at the bottom left corner, larger increases can be observed due to the shift described in Region 2.

Figure 4 shows percentage change in 90% confidence interval widths. For conservative regions (Regions 1), a significant decrease of ~30-40% is observed, suggesting the new model improves predictive power in the middle region of the model containing ~ 77% of all binned data. For other regions, increases are observed up to 80% or more, allowing the new model to more safely deal with large changes in SI.

For relatively stable SI (±25 %ΔSI), it is more likely for SI to remain stable, as reflected in the tighter 90% CI. For current SI level > 2.3e-4 L/mU/min following an increase, the extreme of possible behaviour, defined by the 5th and 95th percentile, are wider.

Figure 5 shows the interpolated new stochastic model (colour) and the original stochastic model (red) for the 5th (a) and 95th (b) percentiles. Unlike the original stochastic model, this new version clearly changes based on the prior change in SI, with an obvious middle conservative region.

When the predictive power of the new model was tested, it was found that 84% of patient SI fell within the bounds of the new model. The 16% of SI that did not was either included in the initial exclusion definition (2%), or fell within bins later collapsed (14%, Figure 2). Of the SI within the model range, 91.9% of SI predictions (SI_{n+1}) fell within the 5th – 95th prediction range, which is close to the expected 90%.

However, 59.7% fell within the 25th – 75th range, which is higher than the expected 50%, perhaps as a result of combining data bins. Per-patient percent time in range is similar for both the new and previous model (Figure 6), despite the new model prediction ranges being generally significantly narrower (e.g. Figure 7). These results suggest the new model has improved predictive power over the old model, and that the percent change in SI is useful for forward prediction in SI.

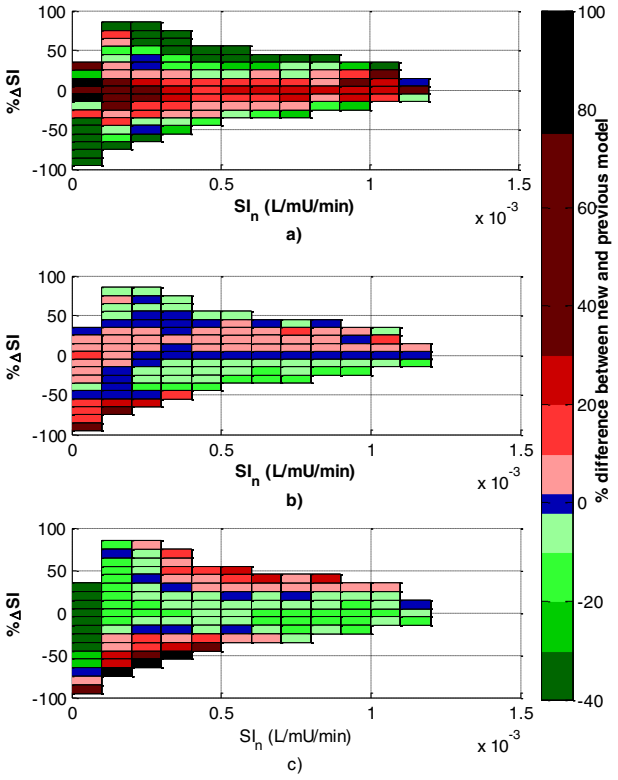

Figure 3 - Percentage change in 5th (a), 50th (b) and 95th (c) percentiles between the original 2D and new 3D models.

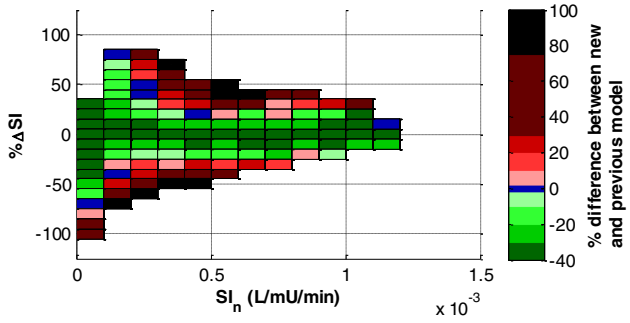

Figure 4 - Percentage change in the 90% CI width between original stochastic model and triplets within the bins

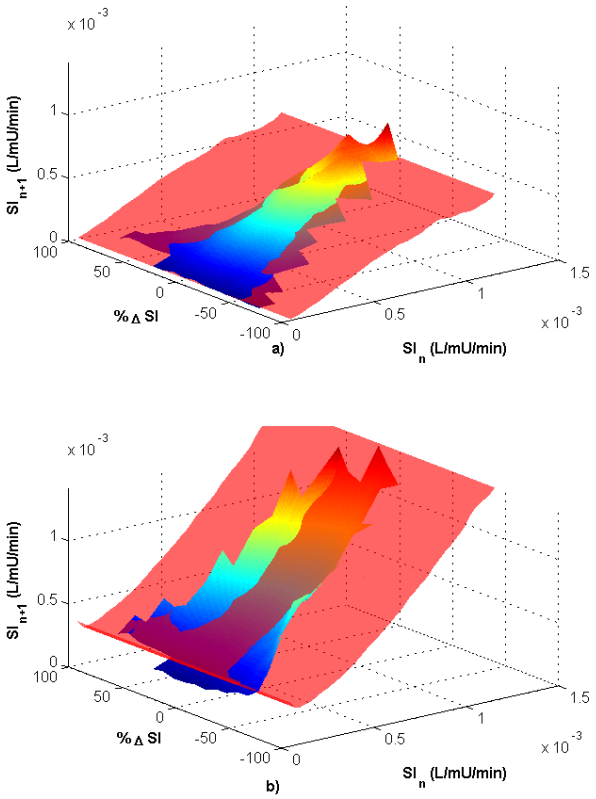

Figure 5 - Comparison between new 3D stochastic model (colour) and original 2D model (red) for 5th (a) and 95th (b) percentiles.

4. DISCUSSION

The management of SI variability has been previously shown to improve predictive power based on patient characteristics and observed trends in SI (Penning et al., 2012, Pretty et al., 2012, Thomas et al., 2014). However, these stochastic models consider the patient's current state only (Lin et al., 2008). Adding a new dimension to the model by considering the prior change in SI allows the stochastic model to better respond to identified SI variability, and, in this case, suggests future SI depends on both the prior and current metabolic states.

The results show that for the 77% of the data within %ΔSI = ±25%, the prior 2D model is conservative, and the new model is thus more patient (response) specific and will allow more aggressive dosing. The likelihood of any resulting BG changes will also be better predicted. While 2D model conservatism reduces hypoglycaemic risk, it also affects performance in treating hyperglycaemia. The new 3D model could lead to tighter, less variable control, and thus improved outcomes (Penning et al., 2015, Signal et al., 2012) with no compromise in safety.

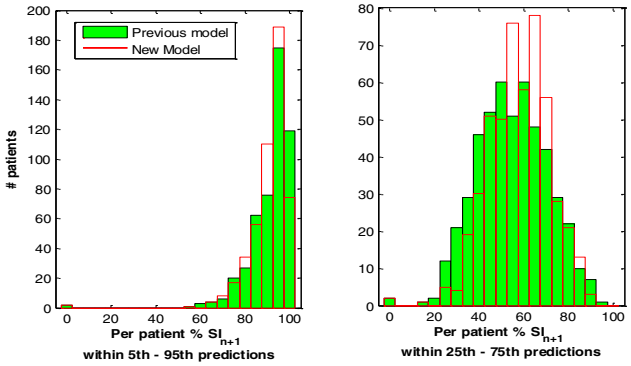

Figure 6 – Per-patient predictive power of new (red) and old (green) stochastic models.

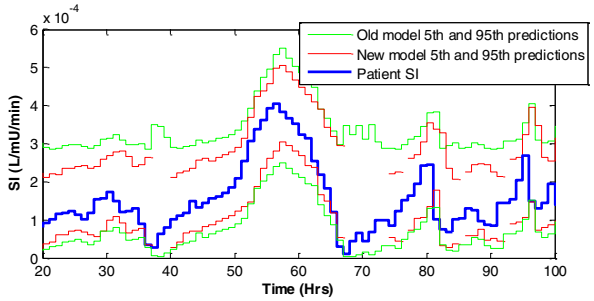

Figure 7 – Excerpt from a patient showing fitted SI, as well as 5th and 95th predictions of future SI_{n+1} for both new and old models.

Testing the predictive power of the new model showed that approximately 92% of the SI forward predicted from SI within the model bounds fell in the 5th – 95th percentile prediction range, which is close to the expected 90%. Per patient percentage time within this 5th – 95th range varied between patients, partly influenced by the number of hours of SI and GC for each patient. In comparison, the previous model has more consistent ability to forward predict changes in SI, with fewer patients treated in an over-conservative manner (>90% of predicted SI in the 5th – 95th range).

Across all patients, the new models predictive ranges are typically significantly narrower (e.g. Figure 7), which suggests that the new model has improved predictive power over the previous, as it is able to capture changes in SI with comparable performance (Figure 6) and narrower predictive ranges where appropriate. This should translate in simulation to improved GC performance, as narrower predictive ranges in SI correspond to narrower predictive ranges in BG, and therefore greater certainty in GC outcomes when selecting insulin dosing.

The percentage changes in the 95th and 5th percentiles in the non-conservative region suggest two possible behaviours. The first says that after a big increase in SI, the metabolic system may continue this increase (20-30%). Conversely, the second says that after this big increase, SI could also decrease drastically (30-40%). These two extremes show how variable the metabolic system can be when it has already displayed variability the prior hour(s). However, extreme changes may also be the result of errors in SI due to BG measurement errors or data recoding errors or insulin-nutrition delivery errors. Future work should examine the potential effects of these errors on stochastic model construction, but in any of the cases, the ability to see potential future variability in identified behaviour is improved and safety is better assured.

This analysis used bins of size 10 %ΔSI and 1e-4 SI level. The choice of this bin size is motivated by the typical ±10% percentage change in SI induced by a BG measurement error of 7%, reported for the device used in highly controlled tests (SKUP, 2006). Hence, these bin sizes reflect resolution in model-based SI, where data with better measurement devices could use smaller bins given enough data triplets.

A limitation of the current model is that it is not yet adapted to cope with SI that fall outside of the current model ranges. The current model was built off areas of high data density, so these SI outliers are generally unusually large changes in SI, or unusually high SI, which in reality may reflect inaccuracies in data recording or patient-specific deviations from model-dynamics. Cross-validation is needed to further validate the new model. Future work will examine how to manage these extreme changes in a conservative manner, and their origins and effect on control.

5. CONCLUSION

In summary, a new stochastic model based on both the previous change in SI and current SI suggests possible improvement in performance and safety of the glycaemic control STAR protocol. For more than 81% of the data triplets used to build the new model, the original stochastic model has been shown over-conservative. Outside this range, more likely extreme variations were identified. Therefore, it is possible to more accurately forecast SI and its variability, and adapt control in a manner more specific to patient response. Thus, the new model presented has the potential to significantly improve predictive power in SI forecasting. This improvement in forecasting may improve safety and performance within the STAR framework. Future work will effectively analyse the impact of this new stochastic model using *in silico* trials.

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