Improved 3D Stochastic Modelling of Insulin Sensitivity Variability for Improved Glycaemic Control

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Abstract: Glycaemic control in intensive care unit has been associated with improved outcomes. Metabolic variability is one of the main factors making glycaemic control hard to achieve safely. STAR (Stochastic Targeted) is a model-based glycaemic control protocol using a stochastic model to predict likely distributions of future insulin sensitivity based on current patient-specific insulin sensitivity, enabling unique risk-based dosing. This study aims to improve insulin sensitivity forecasting by presenting a new 3D stochastic model, using current and previous insulin sensitivity levels. The predictive power and the percentage difference in the 5^{th}-95^{th} percentile prediction width are compared between the two models. Results show the new model accurately predicts insulin sensitivity variability, while having a median 21.7% reduction of the prediction range for more than 73% of the data, which will safely enable tighter control. The new model also shows trends in insulin sensitivity variability. For previous stable or low insulin sensitivity changes, future insulin sensitivity tends to remain more stable (tighter prediction ranges), whereas for higher previous variation of insulin sensitivity, higher potential future variation of insulin sensitivity is more likely (wider prediction ranges). These results offer the opportunity to better assess and predict future evolution of insulin sensitivity, enabling more optimal risk-based dosing approach, potentially resulting in tighter and safer glycaemic control using the STAR framework.

Keywords: Insulin sensitivity, Insulin, Glucose, Glycaemic control, Hyperglycaemia, Intensive Care

1. INTRODUCTION

Critically ill patients often experience hyperglycaemia (Capes *et al.*, 2000; Finney *et al.*, 2003; McCowen *et al.*, 2001), associated with worse outcomes (Capes*, et al.*, 2000; Krinsley, 2003). Glycaemic control (GC) to lower blood glucose (BG) concentration, has shown beneficial outcomes (Chase *et al.*, 2008; Krinsley, 2004; Van den Berghe *et al.*, 2006; Van den Berghe *et al.*, 2001). But, it has also shown increased hypoglycaemia and BG variability (Brunkhorst *et al.*, 2008; Finfer *et al.*, 2009; Finfer *et al.*, 2012; Griesdale *et al.*, 2009; Preiser *et al.*, 2009), both associated with mortality (Ali *et al.*, 2008; Bagshaw *et al.*, 2009; Egi *et al.*, 2006; Egi *et al.*, 2010).

Achieving safe, effective control for nearly all patients is essential, and is a function of protocol design (Uyttendaele *et al.*, 2017). However, fixed clinical protocols have not delivered the functionality, safety or efficacy necessary (Griesdale*, et al.*, 2009), primarily due to their inability to accurately capture patient state. Therefore, model-based GC design is needed to capture inter- and intra- patient variability, and offer patient-specific solutions, while directly managing risk (Chase *et al.*, 2011).

STAR (Stochastic TARgeted) is a clinically validated model-based GC framework, capable of titrating insulin and nutrition (Evans *et al.*, 2012; Fisk *et al.*, 2012). STAR has shown promising clinical results across different countries and ICUs (Stewart *et al.*, 2016). It uses a physiological model (Lin *et al.*, 2011) to assess model-based patient-specific insulin sensitivity (SI) and predicts future metabolic variability using a stochastic model built on population data (Lin *et al.*, 2006). Given the distribution of the predicted future SI values, insulin and nutrition doses can be determined to maximise the overlapping of the resulting predicted BG outcomes with a clinically chosen target band (Lin *et al.*, 2008). This approach enables risk-based dosing, directly managing and minimizing hypoglycaemic risk (Fisk*, et al.*, 2012), as well as optimizing nutrition delivery (Stewart *et al.*, 2018).

This study aims to improve SI forward prediction by improving the stochastic model. STAR's stochastic model only considers current SI (SI_n) to predict future SI (SI_{n+1}) distributions. This analysis investigates the impact of prior changes in SI on the distribution of forward prediction of SI values, adding prior stability or instability to the model.

2. METHODS

2.1 Model-based insulin sensitivity.

The physiological model describes the glucose-insulin pharmacokinetics, 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). Other clearance rates and parameters are defined elsewhere (Lin, *et al.*, 2011; Pretty *et al.*, 2014).

SI is a patient-specific and time-varying parameter describing patient-specific response to insulin and glucose. Integral-based fitting methods are used to determined SI hourly from clinical data (Docherty et al., 2012; Hann et al., 2005).

2.2 Stochastic model and insulin sensitivity prediction.

STAR uses current identified SI (SI_n) and a population-based stochastic model to predict future potential changes in SI (SI_{n+1}). It is derived from clinical data using 2D Gaussian kernel density methods (Lin, et al., 2006) and shown in Figure 1. Given SI_n, the distribution of future SI_{n+1} is determined, from which the 95th percentile is used to calculate a combination of insulin and nutrition interventions, so the corresponding predicted 5th percentile BG outcome is above BG = 4.4 mmol/L. This approach specifically sets a 5% risk of BG < 4.4 mmol/L, which significantly limits hypoglycaemia, ensuring safety, and enabling unique risk-based dosing (Fisk, et al., 2012). SI ranges are predicted 1-3 hours in future.

2.3 Patient cohorts.

Clinical data from 606 patients, totalling 819 episodes and 68629 hours, from 3 clinical trials in 2 ICUs are considered. Demographics are summarized in Table 1. The 587 episodes over 24 hours were used for model construction and validation, representing 65260 hours of control in total.

2.4 Conditional probability and tri-variate kernel estimation.

The current stochastic model is two-dimensional, as it considers one input (SI_n) to produce one output (SI_{n+1}). This study aims to generalise the two-dimensional kernel density method previously developed, into a three-dimensional model with two inputs (SI_{n-1}, SI_n) and one output (SI_{n+1}). Future prediction of SI variability is thus now characterised by the evolution of SI over the last period of control rather than only current data.

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

	SPRINT Christchurch (Chase, *et al.*, 2008)	STAR Christchurch (Evans *et al.*, 2011)	STAR Gyula (Benyo *et al.*, 2012)
# 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]

Based on the same assumptions presented in (Lin, et al., 2006), but considering SI evolution as a Markov Chain of order 2, the probability distribution of likely future SI_{n+1} only depends on current SI_n and previous SI_{n-1} values, where the random variable SI_n is the state of the process at time n. The 3D conditional probability density function of SI_{n+1} given past states can thus be written:

$$P(SI_{n+1}|SI_n, SI_{n-1}, \dots, SI_0) = P(SI_{n+1}|SI_n, SI_{n-1}) = \frac{P(SI_{n+1}, SI_n, SI_{n-1})}{P(SI_n, SI_{n-1})},$$

where the right-hand side equation is derived from the conditional probability chain rule definition.

The tri- and bi- variate product kernel density estimated joint probabilities $P(SI_{n+1}=z, SI_n=y, SI_{n-1}=x) = \frac{1}{N}\sum_{i=1}^{N}\frac{K_{hx_i}(u_{x_i})}{p_{x_i}}\frac{K_{hy_i}(u_{y_i})}{p_{y_i}}\frac{K_{hz_i}(u_{z_i})}{p_{z_i}}$ and $P(SI_n=y, SI_{n-1}=x) = \frac{1}{N}\sum_{i=1}^{N}\frac{K_{hx_i}(u_{x_i})}{p_{x_i}}\frac{K_{hy_i}(u_{y_i})}{p_{y_i}}$ are constructed using N available data triplets (SI_{n-1}=x_i, SI_n=y_i, SI_{n+1}=z_i) identified from the original clinical data. $K_h(u)$ denotes the gaussian kernel density function $\frac{1}{\sqrt{2\pi}h}e^{-\frac{1}{2}\left(\frac{u}{h}\right)^2}$ centred in u, where the scale factor h depends on local data density (Lin, et al., 2008). An example of the resulting bi-variate and tri-variate kernel density estimation for 8 data triplets is presented in Figure 2.

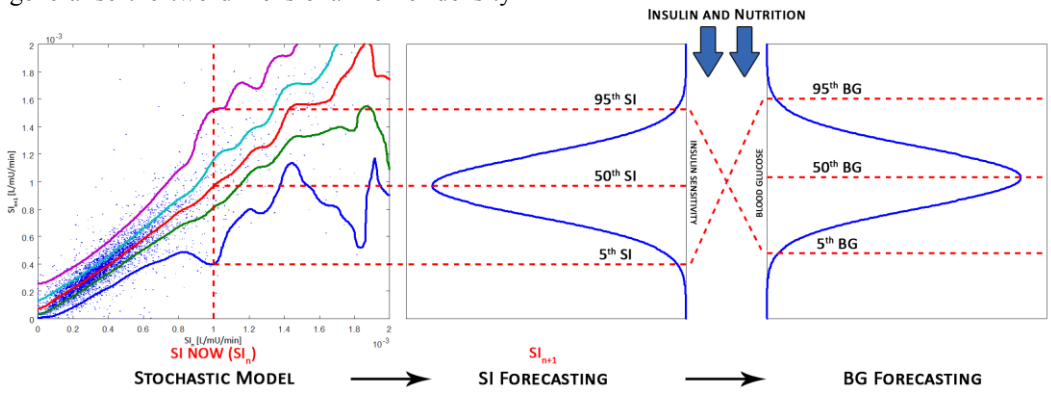

Figure 1 – STAR uses stochastic models to forecast change in SI based on current SI value, and determines BG outcomes for given insulin and nutrition intervention.

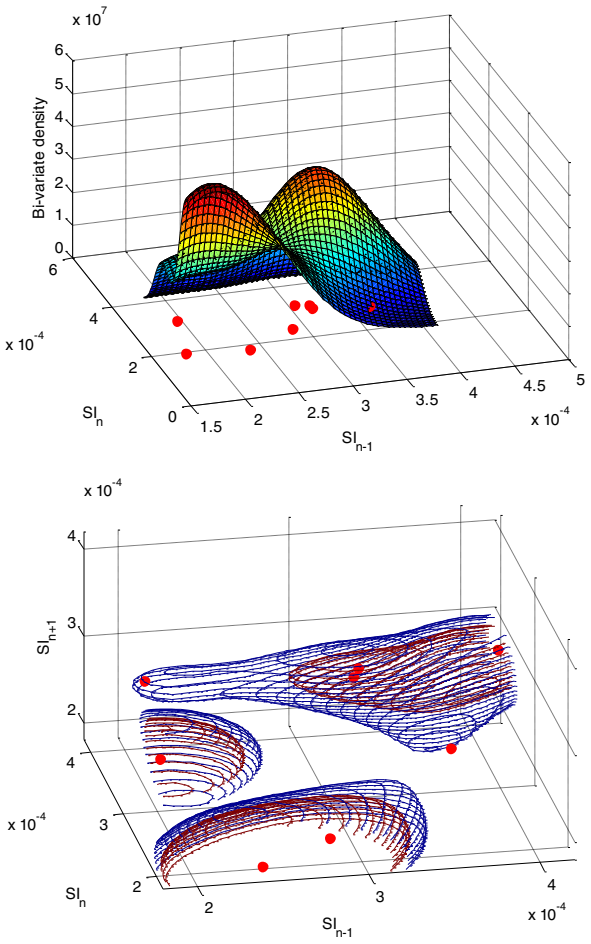

Figure 2 – Bi-variate (top) and tri-variate (bottom) gaussian kernel density estimation for 8 data triplets. Two specific density layers shown for tri-variate case.

Therefore, for any given state (SI_n, SI_{n-1}) exists a conditional probability function of likely future SI_{n+1}: $P(SI_{n+1}|SI_n, SI_{n-1})$, where $\int P(SI_{n+1}|SI_n, SI_{n-1})dSI_{n+1} = 1$ is satisfied. This probability function can be used to determine the 5th-95th percentile of the distribution of future changes in SI and used by the controller to select the best intervention. The new generated 3D model predicts thus future variation of SI based on previous change in SI and can be constructed for 1-3 hourly prediction using data triplets (SI_{n-1}, SI_n, SI_{n+1}), (SI_{n-1}, SI_n, SI_{n+2}), and (SI_{n-1}, SI_n, SI_{n+3}).

2.5 Model comparison analysis.

Cross-validation is used to assess and compare the performance of the 2D and 3D stochastic models. Out of the 65260 total hours of control, 64086 data triplets are created. Both models are constructed on a training set including random 44860 (70%) of total data triplets and tested on the other 19226 (30%). This is repeated 10 times.

The 5th-95th percentile prediction width of the 2D model and the 3D model are compared. Tighter 5th-95th percentile prediction range of SI_{n+1} suggests lower forecasted variability, and thus potentially allows a more aggressive dosing approach, where wider bands suggest higher metabolic variation, and thus more moderate dosing. In addition, the predictive power of both models is compared by computing the percentage prediction of future SI within the interquartile prediction range and within the 5th-95th percentile prediction range. A predictive power of 50% and 90% respectively are expected, which would emphasize how accurately the models are on forward prediction and representation of future SI variability.

3. RESULTS

3.1 2D vs. 3D stochastic model prediction range comparison.

If the 2D stochastic model can be easily represented, it is more difficult for the 3D model, as for each pair (SI_{n-1}, SI_n) corresponds a specific probability density function for SI_{n+1}. Figure 3 shows the 5th-95th percentile (90% likelihood) CI prediction range of SI_{n+1} as a function of SI_n. In this graph, the 2D model is completely shown, as it will be identical for any values of SI_{n-1}. However, the 3D model prediction range depends on specific SI_{n-1} values. Therefore, the 3D model 90% likelihood predictions are shown for two specific values of SI_{n-1}. As shown, the prediction behaviours are different between the 2D and the 3D model. Interestingly, the 3D model prediction range is tighter when $SI_{n-1} \approx SI_n$, thus when SI is stable. However, for larger changes in SI occur, the 3D model prediction range is generally wider.

Compared to the 2D model, the 3D 5th-95th percentile prediction range is affected by sudden shifts in the prediction range. This is a direct impact of low data density in those regions, probably reflecting unusual SI dynamics or measurement and fitting errors. For example, the blue line in Figure 3 representing the 5th-95th percentile range of the 3D model when SI_{n-1}=2.5e-4 is affected by those outliers when SI_n>8e-4. Indeed, above this value, this result suggests an unlikely increase in SI of more than 200%, explaining the low data density in this specific region.

The 5th and 95th percentile of the prediction range of each model are compared in Figure 4. The 2D model, constant in the SI_{n-1} direction, is represented in green. The 3D model is shown in colour and is different for every pair (SI_{n-1}, SI_n). If the green surface is visible (higher) on the 95th percentile surface and invisible (lower) on the 5th percentile surface, it suggests the 2D model has wider prediction bands than the 3D model, and thus the 3D model will have tighter prediction bands. The opposite is also true.

From Figure 4, two regions are clearly identified confirming the previous observation. When SI is stable ($SI_{n-1} \approx SI_n$), along the bisector line, the 3D model prediction ranges are tighter. In contrast, when SI is more variable, the 3D model prediction range are (generally) wider. Sudden bumps are also visible, showing once again the influence of low data density regions.

3.2 Forward predictive power comparison.

The predictive power of both models was tested on 30% of the data, or 19000+ triplets. Table 2 shows 1-3 hourly 2D and 3D stochastic model results. Prediction within the 25th – 75th percentile range are close to the expected value of 50%. The 5th – 95th percentile range results are also similar for both models, and close to the expected 90%. These results show both models accurately predict future SI variability.

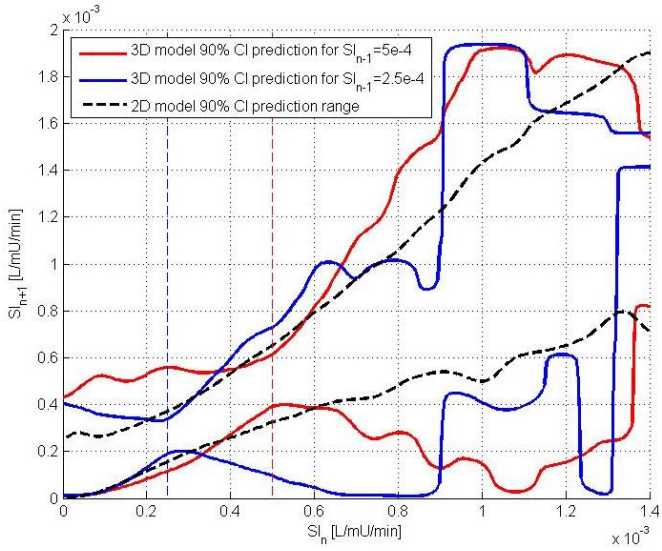

Figure 3 – Resulting 5th-95th percentile prediction range of SI_{n+1} over SI_n. The 2D model is black and is identical for all SI_{n-1}. Red and blue show the 3D model for two specific SI_{n-1}.

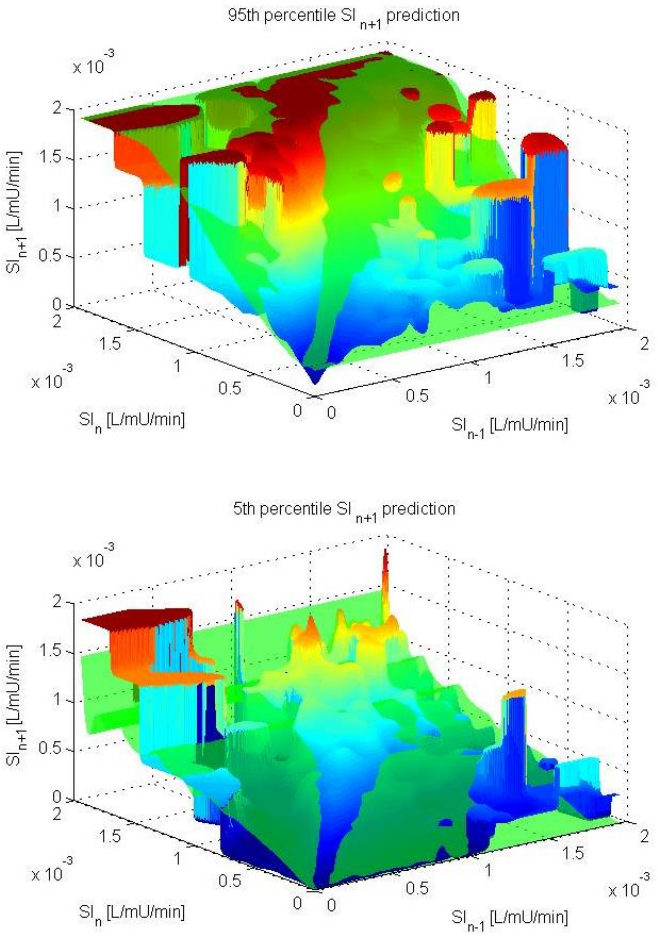

Figure 4 – Comparison between the 2D (green) and 3D (colour) models of the 5th (bottom) and 95th (top) percentiles prediction of future SI_{n+1}. The 2D model is constant across the SI_{n-1} axis, whereas the 3D model is different for every pair of (SI_{n-1}, SI_n).

However, if both models have similar capability to predict patient SI variability, the new 3D model prediction width is shown to be tighter more than 73% of the time. A reduction of the 5th-95th percentile prediction width of 21.7%, 14.9%, and 12.8% compared to the 2D model, for the 1-3 hourly models respectively, is observed. Therefore, the 3D models achieved similar prediction quality, while having much tighter bands. Hence, predictions are made with more precision on future SI variability, and the 2D model presents over-conservative predictive behaviour 73% of the time. In turn, this suggests STAR could use more aggressive dosing for these 73% of hours, for expected improved glycaemic outcomes without compromising safety. Finally, the model could not predict future SI for 1.3% of the testing set data triplets as their inputs (SI_{n-1}, SI_n) were outside of the model definition.

Table 2 – Comparison results of the forward predictive power and reduction in the prediction range for both model. Results are given in median [IQR].

		1-hourly	2-hourly	3-hourly
2D model	% prediction within 25th-75th range	53.8 [53.6, 54.2]	51.9 [51.6, 52.1]	51.3 [50.7, 51.6]
	% prediction within 5th-95th range	90.9 [90.8, 91.0]	90.3 [90.0, 90.4]	90.2 [89.9, 90.3]
3D model	% prediction within 25th-75th range	53.7 [53.5, 53.9]	51.0 [50.8, 51.4]	50.3 [49.9, 50.4]
	% prediction within 5th-95th range	90.8 [90.6, 90.8]	89.8 [89.6, 90.0]	89.5 [89.3 89.6]
3D vs. 2D	% reduction in 5th-95th range width	21.7 [20.6, 20.9]	14.9 [14.8, 15.0]	12.8 [12.6, 19.9]
3D vs. 2D	% prediction tighter	76.4 [75.9 76.5]	74.7 [74.5, 74.8]	73.4 [73.3, 73.6]
2D & 3D	% prediction outside model range	1.3 [1.2, 1.3]	1.3 [1.3, 1.4]	1.3 [1.2, 1.4]

4. DISCUSSION

A new 3D stochastic model is created to better capture future SI variability evolution using not only current SI_n, but also the previous SI_{n-1} value. Both models use the same data and are based on the same principles. Their performance is tested on the same independent test sets.

However, this method may result in skewed probability estimation when low data density is present. In these cases, probably reflecting outliers or uncommon SI dynamics, results in bumps and very local prediction estimation, as shown by the blue lines in Figure 3, and can significantly influence prediction of SI variability. There is thus a question of model definition and resolution to address. More analysis is needed

to balance and assess the impact of removing these outliers to insure safety and improve prediction, without losing information on SI dynamics. An example of the resulting model 5th-95th percentile prediction using lower resolution is shown in Figure 5, resulting in smoother surfaces.

The comparison between models has two outcomes. First, the new 3D model accurately predicts SI variability based on its prior evolution. Second, this prediction is realised with more precision, as the 3D model has tighter prediction bands for more than 73% of the data, and increased patient-specificity. Together with the observation of the resulting 5th-95th percentile prediction range in Figure 4, these results suggest more stable SI for previously stable SI, but higher variation in SI for previously more variable SI.

Figure 6 shows the median [IQR] 3D over 2D ratio in the 5th-95th percentile prediction width of SI_{n+1} for given previous hour-to-hour percentage change in SI (%ΔSI), overlapped with the histogram of the data. It is clear that when (%ΔSI) is in a ±20% range, the median [IQR] prediction range is tighter for the 3D model, which holds for a ~73+% of the total data. This 3D model allows STAR to more aggressively dose insulin when a patient is stable, less aggressively for more variable patients, which could safely increase GC performance.

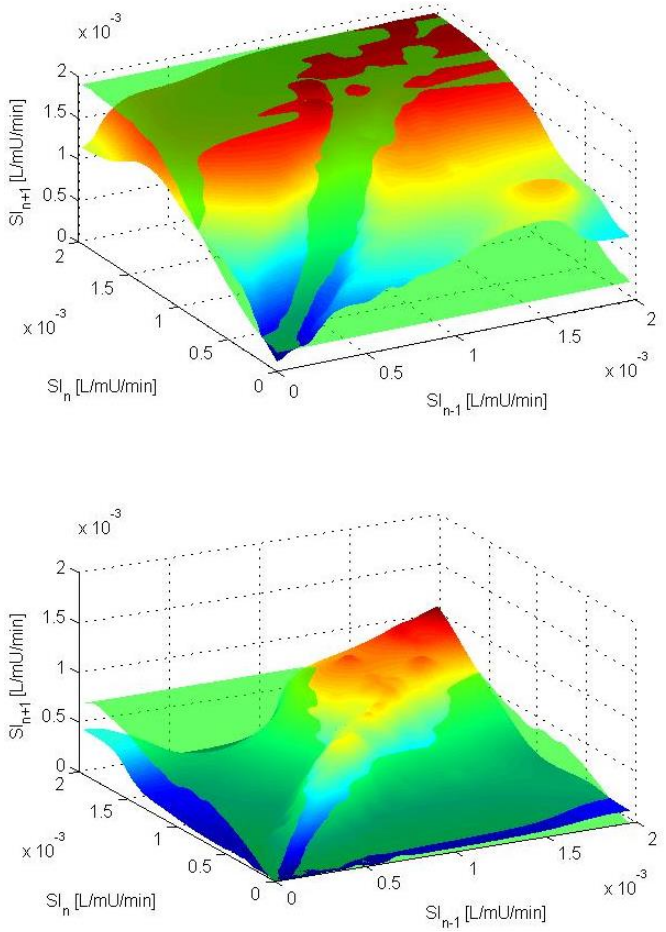

Figure 5 – Updated 5th (bottom) and 95th (top) percentiles prediction for 2D and 3D model constructed without triplets with low data density.

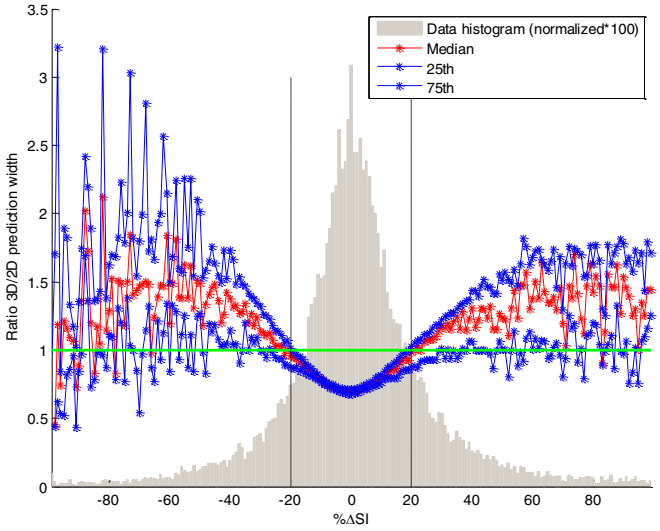

Figure 6 – 3D/2D ratio in 5th-95th percentile prediction width of future SI, for different previous hour-to-hour percentage change in SI.

The reduction in the 5th-95th percentile prediction range decreases from 1 hourly to 3 hourly future prediction. This reduction is expected as it reflects how SI is more likely to vary during a 3 hours timeframe compared to 1 hour. Thus, prediction on future variability are more precise for 1 hourly prediction rather to 2 and 3 hourly prediction. This also reflects the capability of STAR to adapt treatment dynamically, with potential higher insulin dosing for 1 hourly treatment interval compared to 3 hourly treatment intervals.

Future work will evaluate the impact of this new 3D model on GC outcomes. Virtual trials will be designed implementing this new stochastic model within the STAR framework.

5. CONCLUSIONS

This study presents a new kernel density based 3D stochastic model using prior SI evolution to predict future SI variability. New model prediction ranges are 20.5% tighter for more than 73% of the hours/data and give new insight into trends in SI variability compared to the prior 2D model. Further, stable patients are seen to remain stable where more variable patients are more likely to be more variable, enabling better safety. This trend is observed across all prediction horizons. Better predictions of future patient-specific metabolic variability can significantly improve safety and performance of STAR.

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