

Analysis of Insulin Sensitivity Stochastic Models Between STAR Original and Malaysian Cohorts

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Abstract: Maintaining healthy blood glucose (BG) levels is vital in ensuring the health of intensive care unit patients. In present work, there exists model-based glycemic control protocols that capture insulin-glucose dynamics that can provide patient-specific treatments. The Stochastic Targeted Glycemic Control (STAR) protocol is a model-based glycemic control protocol that utilizes stochastic modelling together with the Intensive Control Insulin Glycemic Control (ICING) model. STAR has shown its effectiveness in Christchurch and Hungary. However, it is currently less effective in Malaysia. A study is conducted to compare the stochastic model between the STAR original and Malaysian cohort to identify if the difference in effectiveness is due to a difference in stochastic insulin sensitivity (S_I) models between cohorts. Results from this study show that there could be a difference of up to 49.4% in predictive ability of the stochastic models from the two cohorts, suggesting that it could play a role in being the cause for its lack in effectiveness. With further patient data collection, this hypothesis could be proven or otherwise eliminated from the possible causes for the lack of effectiveness of the STAR protocol in Malaysia.

Keywords: Decision support; Control of physiological and clinical variables; Stochastic control

1. INTRODUCTION

Hyperglycemia is a medical condition that describes an abnormally increased blood glucose (BG) level, which can greatly threaten the lives of intensive care unit (ICU) patients. Stress-induced hyperglycemia can occur to ICU patients with no medical history of diabetes (McCowen et al., 2001). Some complications of hyperglycemia include a weakened immune system, neuropathy, retinopathy and more. (Turina et al., 2005; Malone, 2016; Engerman and Kern, 1986). Hyperglycemia has been associated with higher mortality rates in ICU patients (Ousman, 2002). On the other extreme is hypoglycemia, which describes an abnormally low BG level. While most occurrences of hypoglycemia are treatment related, it poses just as much a threat as hyperglycemia or even more. In a landmark study by Van den Berghe et al. (2001), good regulation of BG levels has shown to decrease mortality rates by up to 45%.

The current standard used for BG level regulation in Malaysian hospitals are known as the Insulin Infusion Protocol and the Enteral and Parenteral Nutrition Protocol (Cawangan Kualiti Penjagaan Kesihatan Bahagian Perkembangan Perubatan Kementerian Kesihatan Malaysia et al., 2012). These protocols are sliding scale approaches and do not employ model theory of any kind. This along with unpredictable metabolic changes may produce highly variable BG levels, which makes it difficult to maintain glycemic control. Computational physiological models can help overcome this by using patient specific data to create personalized solutions to highly variable ICU patients (Chase et al., 2018).

The Stochastic Targeted Glycemic Control (STAR) protocol is a model-based protocol that recommends specific insulin and nutrition input values to individual patients. This protocol utilizes both the Intensive Control Insulin Glycemic Control (ICING) model along with stochastic modelling to predict insulin sensitivity (S_I) and subsequently help generate BG outcomes for potential nutrition and insulin combinations. In pilot trials by Fisk et al. (2012), STAR managed to keep the percentage time spent of patient BG levels within the 4.4 mmol/L – 8.0 mmol/L range at 89.4%. STAR has also undergone pilot trials in University Hospital of Liège, Belgium showing similar results of up to 78% in the target band (Uyttendaele et al., 2018).

In virtual trials of the STAR protocol carried out in Hospital Tunku Ampuan Afzan (HTAA), Kuantan, Malaysia by Jamaludin et al. (2016), where percentage time spent of BG levels within the 4.4 mmol/L – 10.0mmol/L range at 82% for non-diabetics and 70.6% for diabetics, compared to the 76.3% and 59.6% from the current standard sliding scale protocol. Further virtual trials (Ahamad et al., 2016) and pilot patient trials (Abu-Samah et al., 2018) further validated previous works with 79.25% and 71.96% in the 4.4 mmol/L – 10.0mmol/L range. However, percentage time spent within the tighter BG range of 4.4 mmol/L – 8.0mmol/L was only 51.95% and 43.93%. The reason for this stark difference as compared to the Christchurch trials is currently still being investigated.

Hence, this paper aims to specifically investigate the possible stochastic S_I model differences between the Malaysian and the STAR original cohort. An initial stochastic S_I model of a Malaysian cohort is created in order to compare it with the model currently used in the STAR protocol in hopes to

determine if the lack of effectiveness of the STAR protocol in Malaysia is truly due to a S_I difference between cohorts.

2. METHODOLOGY

2.1 STAR Protocol

The STAR protocol (Fisk et al., 2012) is a glycemic control tool for use in intensive care units. STAR controls both insulin and nutrition input to the patient, making it different from most standard protocols. STAR functions by predicting patient insulin sensitivities and its future variability. This is combined with the ICING model to accurately capture the physiological model of the glucose-insulin regulatory dynamic system in the human body. The starting criteria for STAR is two consecutive BG readings of above 8.0 mmol/L. The clinical target range is 4.4 mmol/L to 8.0 mmol/L. STAR has been implemented into an application that can be used through a tablet or smart device to provide a comfortable user interface. When at least two consecutive BG levels have been obtained, integral-based parameter identification is used to identify the S_I from the ICING model. Since S_I varies hourly and changes between patients, stochastic-based forecasting is then used in conjunction with the ICING model to predict likely BG levels for given insulin and nutrition inputs. At every intervention, STAR provides the user with a free choice of measurement of either 1, 2, or 3 hourly intervals based on personal clinical judgement. Nutrition and insulin combinations that best overlaps the resulting BG range with the target clinical band is then provided to the user.

2.2 Intensive Control Insulin Nutrition Glucose (ICING)

The Intensive Control Insulin Nutrition Glucose (ICING) model is a set of differential equations is the glucose-insulin regulatory model used in the STAR protocol. The equations of the ICING model have been studied along with each of its parameters. Some parameters are determined through various literatures (Fisk et al., 2012; Lin et al., 2011; Kovács et al., 2011; Pistikopoulos and Knovel, 2018) while some others are obtained from bedside data of patients. The only unknown time-varying patient specific model is S_I . The model equations are presented below:

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

$$\dot{Q} = n_I (I(t) - Q(t)) - n_c \frac{Q(t)}{1 + \alpha_G Q(t)} \quad (2)$$

$$\dot{I} = -n_K I(t) - \frac{n_L I(t)}{1 + \alpha_I I(t)} - n_I (I(t) - Q(t)) + \frac{u_{ex}(t)}{V_I} + (1 - x_L) \frac{u_{en}(G)}{V_I} \quad (3)$$

$$\dot{P}_1 = -d_1 P_1 + D(t) \quad (4)$$

$$\dot{P}_2 = -\min(d_2 P_2, P_{max}) + d_1 P_1 \quad (5)$$

$$P(t) = \min(-d_2 P_2, P_{max}) + PN(t) \quad (6)$$

$$u_{en} = \min(\max(16.67, k_1 G(t) + k_2), 266.67) \quad (7)$$

The symbol G [mmol/L] represents the total plasma BG in the body. The interstitial insulin and plasma insulin are represented by the parameters Q [mU/L] and I [mU/L] respectively. S_I [L/mU/min] represents insulin sensitivity. The parameters u_{ex} [mU/min] and u_{en} [mU/min] are the exogenous insulin input and endogenous insulin production respectively. The parameter P [mmol] represents the total external nutrition, where P_1 [mmol] represents the glucose in the stomach and P_2 represents the glucose in the gut. The exogenous parenteral dextrose input is expressed by PN [mmol]. The parameter D [mmol/min] represents the amount of dextrose provided from external feeding.

The ICING model requires three main steps for application in the STAR protocol. The first step is parameter fitting, which is obtaining all the known parameters. All parameter constants are known (Table 1) and the initial values for G , I , Q , P_1 and P_2 are computed using patient bedside data. Second is to identify the last unknown variable, S_I integral-based parameter identification. Finally, forward simulation can be performed to predict future BG values and therefore provide different treatment recommendations.

Table 1: Constants used in ICING model

| Model variable | Description | Numerical value |
|----------------|--------------------------------------------------------------------|--------------------------|
| p_g | Patient endogenous glucose removal | 0.006 min ⁻¹ |
| EGP_b | Basal endogenous glucose production | 1.16 mmol/min |
| CNS | Central nervous system glucose uptake | 0.3 mmol/min |
| V_G | Glucose distribution volume | 13.3 L |
| V_I | Insulin distribution volume | 4.0 L |
| α_G | Saturation of insulin stimulated glucose removal | 1/65 L/mU |
| α_I | Saturation of plasma insulin disappearance | 0.0017 L/mU |
| n_I | Transfer rate between plasma and interstitial insulin compartments | 0.0075 min ⁻¹ |
| n_C | Cellular insulin clearance rate from interstitium | 0.0075 min ⁻¹ |
| n_K | Kidney clearance rate of insulin from plasma | 0.0542 min ⁻¹ |
| n_L | Liver clearance rate of insulin from plasma | 0.1578 min ⁻¹ |
| x_L | Fraction of first pass hepatic extraction | 0.67 |
| P_{max} | Maximum disposal rate from gut | 6.11 mmol/min |
| d_1 | Transport rate between stomach and gut | 0.0347 |
| d_2 | Transport rate between gut and bloodstream | 0.0069 |
| k_1 | Pancreatic insulin secretion glucose sensitivity | 14.9 |
| k_2 | Pancreatic insulin secretion offset | -49.9 |

2.3 Extraction and Processing of Patient Data

From International Islamic University Hospital, Kuantan, Malaysia, patient data of 2,585 collective hours from 61 ICU patients were analysed in this study. Written informed consent was obtained for all patients, and approval (IREC 657) was granted for this study by the International Islamic University Malaysia Medical Centre (IIUMMC) Research Ethics Committee and National Institutes of Health Malaysia (NIH).

Integral-based parameter identification (Hann et al., 2005) using the ICING model is then used to gain 2,584 pairs of hourly S_I data.

The probability distribution of possible future S_I at time $n+1$ depends on the S_I values at time n , and hence can be treated as a Markov chain. The Markov property states that the future state of a process depends only on its current state. Hence, the conditional probability of S_I can be written as $P(S_{I_{n+1}}|S_{I_n})$.

Additionally, according to Bayes' Theorem, conditional probability has the statistical property as follows:

$$P(A|B) = \frac{P(A, B)}{P(B)} \quad (8)$$

Hence, $P(S_{I_{n+1}}|S_{I_n})$ can be written as

$$P(S_{I_{n+1}}|S_{I_n}) = \frac{P(S_{I_n}, S_{I_{n+1}})}{P(S_{I_n})} \quad (9)$$

$P(S_{I_n})$ and $P(S_{I_{n+1}}, S_{I_n})$ are obtained using univariate and multivariate kernel density estimation respectively. $P(S_{I_{n+1}}|S_{I_n})$ is then plotted and will be presented as a 3-D stochastic S_I model. The 5th, 25th, 50th, 75th and 95th percentiles are then plotted. These lines represent the probability interval for potential $S_{I_{n+1}}$ values, one hour after having identified the current hour S_{I_n} value. Then, it is converted into a cumulative distribution function curve (CDF).

The stochastic S_I model from the STAR original cohort model is also extracted from the STAR protocol application (Lin et al., 2008). The 5th, 25th, 50th, 75th and 95th percentile lines for S_{I_n} against $S_{I_{n+1}}$ is obtained and similarly, a cumulative distribution density curve is generated in order to compare the Malaysian against the STAR original cohort.

2.4 Comparison Between Cohorts

In order to compare the predictive ability of the stochastic S_I models of the two cohorts, the mean percentage difference between each percentile is calculated using Eq. (10).

$$\text{Mean percentage difference} = \sum_{i=1}^N \left| \frac{M_i - S_i}{\frac{M_i + S_i}{2}} \right| \times 100 \quad (10)$$

Where N is the total number of data points along the S_{I_n} axis.

3. RESULTS

The mean hourly S_I values for each patient was calculated and the median of the mean hourly patient S_I value for the entire cohort was found to be 0.00028 L/mU/min with a median of mean standard deviation of 0.00018. The interquartile range (IQR) for mean hourly patient S_I value was 0.00020-0.00044 [L/mU/min] while the interquartile range for the standard deviation was 0.00013-0.00028.

A graph of S_I at hour n (S_{I_n}) against S_I at hour $n+1$ ($S_{I_{n+1}}$) as shown in Fig 1. A conditional density plot of $P(S_{I_{n+1}} | S_{I_n})$ is constructed using the hourly S_I data as shown in Fig 2. Each slice of the surface along the $S_{I_{n+1}}$ axis has an area under the curve summing to 1. Note that Fig 2 is generated from Eq. (9).

The 5th, 25th, 50th, 75th and 95th percentile range is then plotted, which is shown in both Fig 2 and Fig 3 (left). These lines represent the probability interval for potential $S_{I_{n+1}}$ values, one hour after having identified the current hour S_{I_n} value. The probability density curve is then converted to a cumulative distribution density curve as shown in Fig 4. Similar data for the STAR original cohort is plotted in Fig 3 and Fig 4.

In a similar manner, the CDF graphs of both cohorts will be compared by obtaining the absolute percentage difference of the two CDFs. This allows us to see at what range of S_I values do the predictive abilities of the stochastic models differ.

With reference to Fig 3, each percentile line from 5th to 95th is compared in terms of mean percentage difference and is shown in Table 2. The gap between 5th and 95th percentile lines represent the 0.90 probability interval. The largest difference in percentage difference comes from the 5th percentile line with 79.15%.

Table 2: Mean percentage difference for each percentile between Malaysian and STAR original cohorts

| Percentile | Mean Percentage difference between Malaysian and STAR original Cohort (%) |
|------------------|---------------------------------------------------------------------------|
| 5 th | 79.15 |
| 25 th | 40.50 |
| 50 th | 19.66 |
| 75 th | 11.30 |
| 95 th | 18.34 |

Fig 5 shows the percentage absolute difference between the cumulative distribution density curves between the Malaysian in and STAR original cohort. A maximum difference of up to 49.4% can be found between the Malaysian and STAR original cohort conditional probability for S_I .

4. DISCUSSION

From the results, the median S_I value for the entire cohort is 2.8×10^{-4} L/mU/min with an IQR of 2.0×10^{-4} to 4.4×10^{-4} L/mU/min. This verifies that the ICING model is performing well at identifying the hourly S_I values as the range of S_I matches those found from various literatures which approximately ranges from 2×10^{-5} to 2.26×10^{-3} L/mU/min

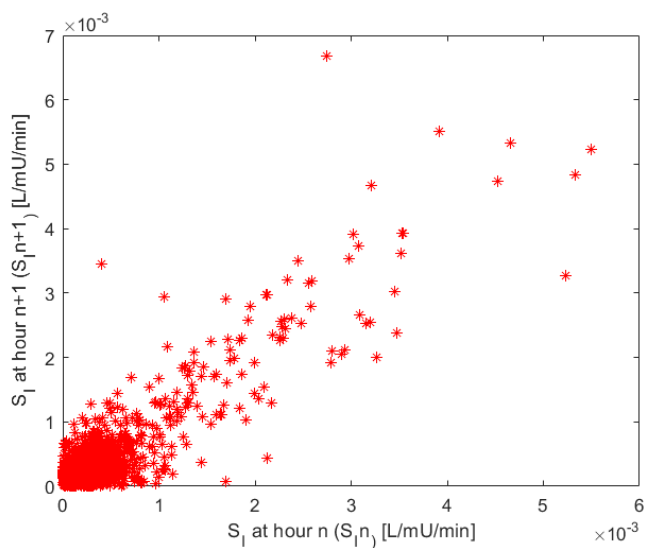


Fig 1. Fitted hourly S_I data on 65 Malaysian ICU patients

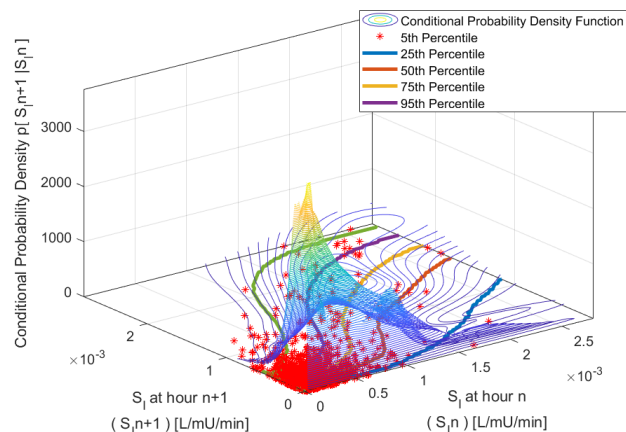


Fig 2. Stochastic S_I model with percentiles plotted and raw S_I data points for Malaysian cohort

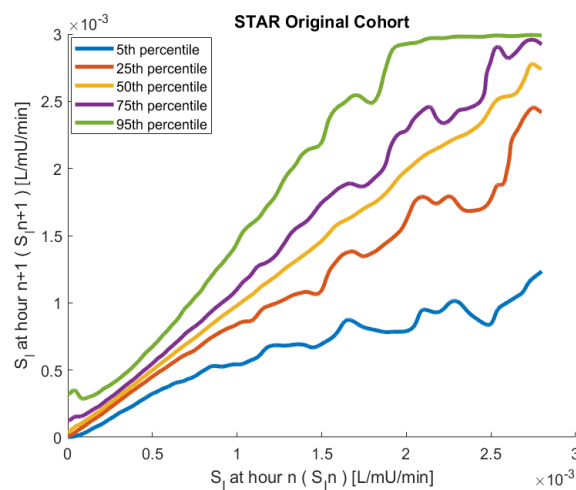
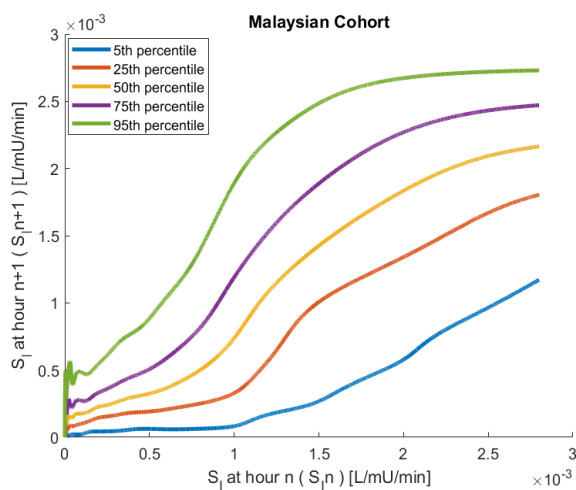


Fig 3. Percentile lines for Malaysian (left) and STAR original cohort (right)

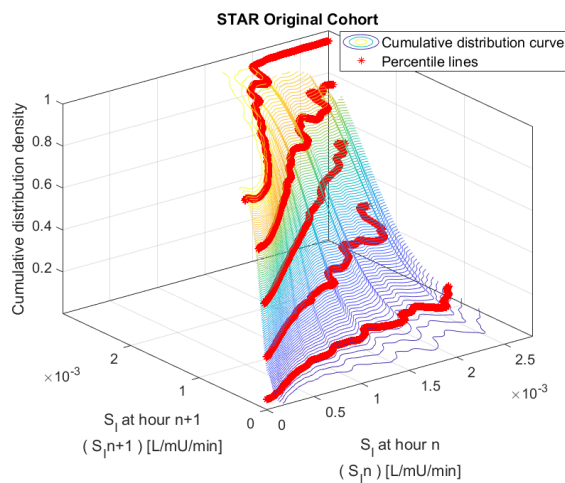
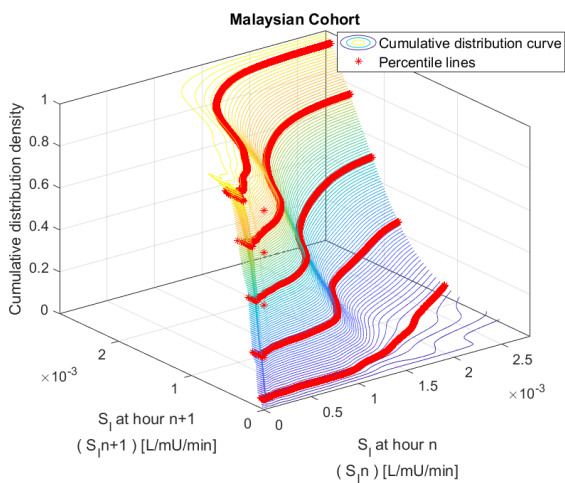


Fig 4. Cumulative distribution density with percentile lines superimposed for Malaysian cohort (left) and for STAR original cohort (right)

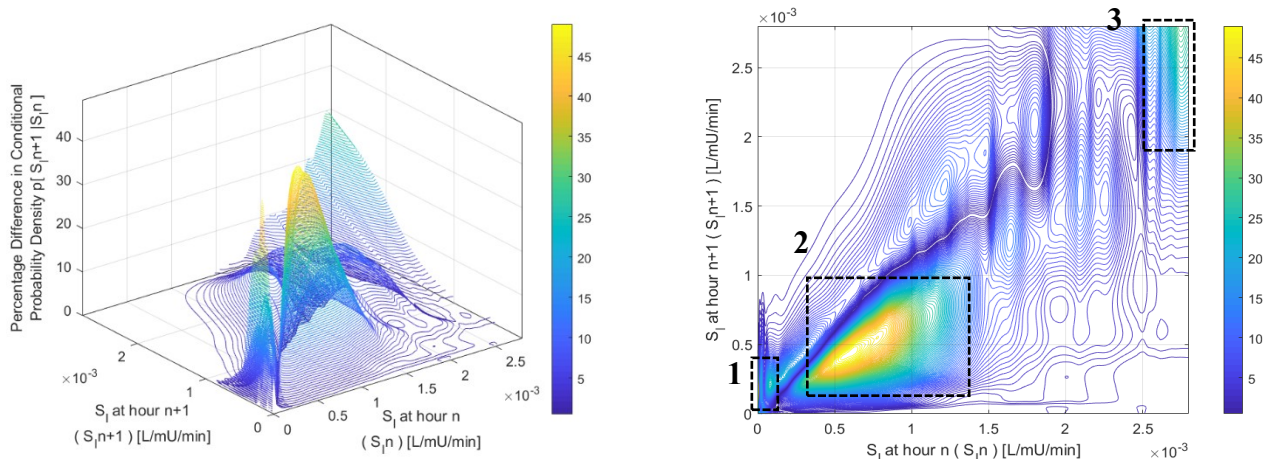


Fig 5. Absolute percentage difference for cumulative distribution density Curves between Malaysian and Christchurch cohort. (Left) An isometric view of graph, (Right) A top view of the graph

(Bergman et al., 1987; McDonald et al., 2000). These values also matches the values found from a Malaysian cohort in a study by Ahamad et al. (2016) in which the interquartile range for S_I values was 1.19×10^{-4} to 2.28×10^{-4} L/mU/min.

In Fig 3, the wide gap between the 5th and 95th percentile line for the Malaysian cohort could imply that the S_I values of the Malaysian cohort may vary more widely within the span on an hour. However, this could also be caused by the relatively low amount of patient data in the Malaysian cohort which can be seen in Fig 1, especially in the 2×10^{-3} to 3×10^{-3} L/mU/min range. The largest differences between percentile lines comes from the 5th and 25th percentile, as shown in Table 2. These two percentiles for the Malaysian cohort are lower. However, the 50th, 75th and 95th percentiles do not show very high differences. This could possibly indicate that while the Malaysian stochastic model predicts similar S_I values with the original cohort. The only difference would be that the Malaysian stochastic model overestimates the possible range of the S_I at the next hour, especially to lower values.

From Fig 5, most of the graph have low values, implying that both stochastic S_I models have similar predictive capabilities. However, on the three zones highlighted by dotted lines in Fig 5, the differences between the cohorts shoot up to 49.4%, especially at Zones 1, 2 and 3 of the graph. This indicates that at these S_I values within these zones, the stochastic models of the two cohorts predict S_I values at the $n+1$ hour that differ quite a bit. For example, at the $S_{I,n}$ value of 0.75×10^{-3} L/mU/min, the stochastic model of the Malaysian cohort would predict an $S_{I,n+1}$ range that could be up to 40% than what the STAR original stochastic model would have predicted.

The higher variability in S_I values could suggest that a different target range would be recommended for the Malaysian cohort. Having a target range too tight can be hard to achieve and may lead to less time spent within the target BG range. As such, the STAR protocol achieves a decent percentage time in the BG range of 4.4 to 10.0 mmol/L in a Malaysian cohort in works done by Abu-Samah et al. (2018).

It is noted that there are were various limitations in this study. One major limitation was the relatively low number of Malaysian data as compared to the STAR original cohort. Moreover, raw patient data of the original STAR cohort from Christchurch were at this time not available. Hence, the CDF graph for the original STAR cohort were fitted with sigmoid curves which is the cause for the lack of fit with the percentile lines as shown in Fig 4.

Future works include further validating the Malaysian stochastic model by generating BG probability intervals with the ICING model, which can then be compared with other Malaysian BG data to check how much percent of the time the real measurements lay within the probability intervals generated. Furthermore, collecting more patient data to make a more accurate stochastic model for the Malaysian cohort so that a better comparison can be made. If the stochastic S_I models between STAR original and Malaysian cohorts are in fact significantly different, the next step would be to build a full stochastic model for S_I which can be used in conjunction with the STAR protocol, making it more effective for a Malaysian cohort. However, if there are no significant differences between the two cohorts, it can at least be eliminated as a potential cause of difference in effectiveness in a Malaysian cohort. Investigation into other potential reasons for difference of effectiveness of the STAR protocol in Malaysia can also be done, such as compliance analysis of the staff or even a cohort study to investigate other potential cohort differences. These can include medical differences, diabetic status of the patients or even different target feed practices, which all could potentially bring different explanations for the problem at hand.

5. CONCLUSIONS

A stochastic model of insulin sensitivity for a Malaysian cohort has been successfully modelled. The interquartile range for S_I values for this cohort ranged from 1.3×10^{-4} to 2.8×10^{-4} L/mU/min which is relatively low. The results from comparing this stochastic model with the STAR original cohort show

differences of up to 49.4% in conditional probability which could be a possible reason for differences in effectiveness of the STAR protocol between Malaysia and Christchurch. To obtain more conclusive evidence that there is a significant difference in S_1 between the STAR original and Malaysian cohort, the created stochastic S_1 model for the Malaysian can be further validated and more Malaysian patient data should be obtained to create a more accurate stochastic model to enable a better comparison against the STAR original cohort.

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