External Validation and Sub-cohort Analysis of Stochastic Forecasting Models in NICU Cohorts

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Abstract: Hyperglycaemia is a prevalent complication in the neonatal intensive care unit (NICU) and is associated with worsened outcomes. It occurs as a result of prematurity, under developed endogenous glucose regulatory systems and clinical stress. The stochastic targeting (STAR) framework provides patient-specific, model-based glycaemic control with a clinically proven level of confidence on the outcome of treatment interventions, thus directly managing the risk of hypo- and hyper-glycaemia. However, stochastic models that are over conservative can limit control performance. Retrospective clinical data from 61 episodes (25 retrospective and 36 from a prospective blood glucose control study) of insulin therapy in very-low birth weight (VLBW) and extremely-low birth weight (ELBW) neonates are used to create a new stochastic model of model-based insulin sensitivity (S_I [L/mU/min]). Sub-cohort models based on gestational age (GA) and birth weight (BW) are also created. Performance is assessed by the percentage of patients who have 90% of actual intra-patient variability in S_I captured by the 90% confidence bands of the cohort based (inter-patient) stochastic variability model created. This assessment measures per-patient accuracy for any given cohort model.

Per-patient coverage trends were very similar between prospective and retrospective cohorts, providing a measure of external validation of cohort similarity. Per-patient coverage was improved though the use of BW and GA dependent stochastic models, which ensures that the stochastic models more accurately capture both inter- and intra- patient variability. Stochastic models based on insulin sensitivities during insulin treatment periods are tighter and give better and safer glycaemic control. More patient specific methods, particularly in the modeling of endogenous insulin and glucose production, will be required to further improve forecasting and glycaemic control.

Keywords: Insulin sensitivity, control algorithms, physiological models, simulation, intensive care

1.0 INTRODUCTION

Premature infants are a large proportion of neonatal intensive care unit (NICU) populations. Severity of prematurity is commonly quantified by gestational age (GA) and birth weight (BW). Birth weight classifies infants into low birth weight (LBW < 2,500g), very low birth weight (VLBW < 1,500g) and extremely low birth weight (ELBW < 1,000g). Similarly GA classifies prematurity as preterm (< 36 weeks), very preterm (< 31 weeks) and extremely preterm (< 27 weeks). Each classification carries increased risk of long term complications, impaired development, and mortality with decreasing BW and GA.

Persistent hyperglycaemia is reported in 57% of ELBW infants (Hays et al., 2006), and in a study of VLBW infants 80% had blood glucose (BG) >8 mmol/L, 57% had BG>10 mmol/L, and 32% had BG>10 mmol/L for more than 10% of the time (Beardsall et al., 2010). Hyperglycaemia is typically regarded as BG greater than 10mmol/L, but there is no standard definition, nor an accepted threshold for intervention (Alsweiler et al., 2007). Hyperglycaemia has been linked to worsened outcome, but no study has conclusively determined if hyperglycaemia itself is harmful, or simply represents severity of condition. The associated negative outcomes include sepsis, increased ventilator dependence, retinopathy of prematurity, increased hospital length of stay, and mortality (Alaedeen et al., 2006; Heimann et al., 2007).

The approach to managing hyperglycaemia is different for each NICU, but effective treatment remains elusive. Current treatments include glucose restriction, and insulin. However, glucose restriction (Hemachandra et al., 1999) deprives the neonate of energy vital for growth and development (Cowett et al., 2004), and is therefore not ideal. The use of insulin infusions to treat hyperglycaemia and/or promote growth has shown positive outcomes including reduced proteolysis, improved glucose tolerance, increased insulin-like

growth factor (IGF-I) levels, and improved caloric intake and weight gain (Agus et al., 2004; Beardsall, Ogilvy-Stuart, et al., 2007; Beardsall et al., 2008).

However, many insulin trials were unsuccessful in safely providing glycaemic control due to increased hypoglycaemia (Beardsall et al., 2008; Meetze et al., 1998). All reported insulin therapy trials used protocols that fixed insulin dosing based on weight or other factors (Beardsall, Vanhaesebrouck, et al., 2007) or depended on clinical judgement to determine insulin infusion rates. Implicitly, these protocols assume a fixed insulin sensitivity, and so these protocols fail to account for the large intra- and inter-patient variability observed in the insulin sensitivity of neonates (Le Compte et al., 2010; Le Compte et al., 2012). Increased variability with fixed or relatively fixed insulin dosing protocols results in poor control, excessive glycaemic variability and hypoglycaemia (Chase et al., 2011).

STAR (Stochastic TARgeting) is a model based glycaemic control framework (Le Compte et al., 2009; Le Compte et al., 2012) for insulin therapy that uses a time varying insulin sensitivity (S_I [L/mU/min]) to provide an adaptive patient-specfic response that allows for both inter-patient variability and future intra-patient variability over time. This insulin sensitivity characterises a patient's current metabolic state, and likely future changes in that state are forecast using population based stochastic modelling. A range of possible future insulin sensitivity outcomes is generated based on a patient's current insulin sensitivity, and this enables a treatment to be selected that best overlaps the range of possible BG outcomes with a clinically defined target band. The algorithm for STAR is shown in the appendix. STAR has been the clinical standard of care in Christchurch Women's Hospital since 2009.

The performance of STAR is dependent on the effectiveness of stochastic modelling; poor stochastic forecasting results in poor glycaemic control. High variability in insulin sensitivity over time and between patients has been shown to limit possible performance of glycaemic control in simulation (Dickson et al.). High variability results in overly conservative stochastic models for some neonates, with wide stochastic forecasting bands that are not representative of all neonates resulting in low doses of insulin and persistently high BG. To enable better and equally safe control for all patients, the stochastic models need to be improved. One avenue is to create stochastic models for the variation of S_I over specific sub-cohorts by GA and BW, which are variables readily available at bedside. The goal is to create models that not only account for inter-patient variability over cohorts, but also capture intra-patient variability (per-patient) more accurately. This is done through a retrospective analysis of insulin sensitivities from clinical data. Quantification of variability and its sources will enable tighter glycaemic control without sacrificing safety.

2.0 METHODS

2.1 System model

The clinically validated NICING model (Le Compte et al., 2009) describes glucose-insulin dynamics in the extremely preterm neonate. The model is described by the ordinary differential equations (ODEs) shown in Equations 1-7. Model parameters and variables are defined in Table 1, and the model is shown pictorially in Figure 1.

The rate of change of plasma glucose ($\dot{G}$) is defined in Equation. 1:

$$\dot{G} = -p_G G(t) - S_I G(t) \frac{Q(t)}{1 + \alpha_G Q(t)} + \frac{P(t) + EGP * m_{body} - CNS * m_{brain}}{V_{g,frac}(t) * m_{body}} \quad (1)$$

Insulin-mediated glucose clearance is determined by insulin sensitivity (S_I) and non insulin-mediated uptake includes a general clearance term, including kidney clearance, (p_G) and a central nervous system uptake (CNS). Glucose sources include exogenous glucose ($P(t)$) and endogenous production (EGP).

The rate of change of plasma ($\dot{I}$) and interstitial ($\dot{Q}$) insulin are defined in Equations 2-4:

$$\dot{I} = -\frac{n_L I(t)}{1 + \alpha_I I(t)} - n_K I(t) - n_I\big(I(t) - Q(t)\big) + \frac{u_{ex}(t)}{V_{I,frac} * m_{body}} + (1 - x_L)u_{en} \quad (2)$$

$$u_{en} = \mathrm{I_B} e^{\frac{-k_I u_{ex}}{V_I}} \quad (3)$$

$$\dot{Q} = n_I\big(I(t) - Q(t)\big) - n_C \frac{Q(t)}{1 + \alpha_G Q(t)} \quad (4)$$

Plasma insulin is cleared via the liver (n_L), the kidney (n_K) and transport into interstitial fluid (n_I). Insulin enters the system exogenously (u_{ex}) or endogenously (u_{en}) through pancreatic secretion, as described in Eqn. 3. Insulin leaves the interstitial fluid through degradation (n_C). Appearance of glucose via the enteral route is modelled via two intermediary compartments, the stomach (P_1) and the gut (P_2), and is described in Equations 5-7.

$$\dot{P}_1 = -d_1 P_1 + P(t) \quad (5)$$

$$\dot{P}_2 = -\min(d_2 P_2, P_{max}) + d_1 P_1 \quad (6)$$

$$P(t) = \min(d_2 P_2, P_{max}) + PN(t) \quad (7)$$

Transport rates between the stomach and gut, and gut and blood (d_1 and d_2 respectively) are limited to a maximum flux (P_{max}). Solutions to equations 1-7 (giving profiles for G,I,Q,P_1 and P_2) are generated simultaneously in the time domain using a Runga-Kutta 4 based ODE solver.

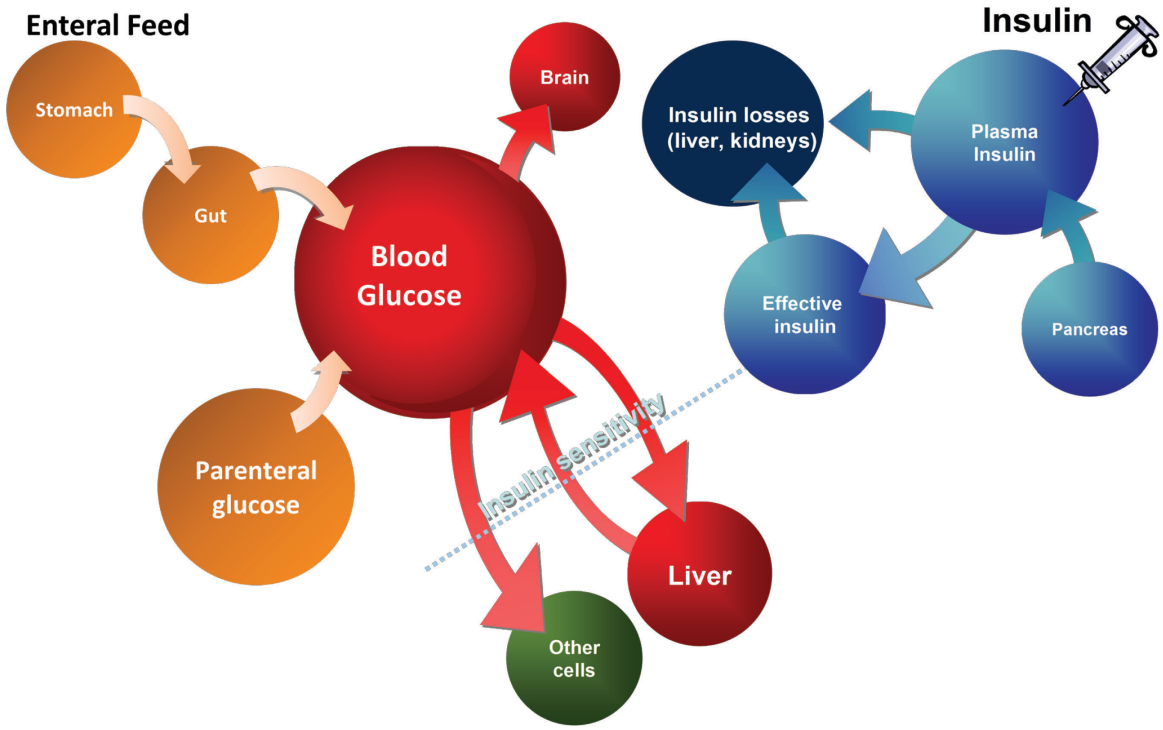


Figure 1: Pictorial representation of the NICING model.

S_I is patient specific and time varying, describing a patients current metabolic state. It is fit using integral based fitting methods (Hann et al., 2006) on a retrospective hour-to-hour basis, and assumed constant over an hour-long period. In addition to being a marker of peripheral insulin sensitivity, S_I also incorporates uncertainty around patient-specific endogenous insulin and glucose production. A S_I of zero represents the lower physiological bound in insulin sensitivity where no glucose is leaving the blood plasma via the insulin-mediated uptake path.

Table 1: Glucose-insulin metabolic model variable definition

Variable	Description	Values
G	Blood glucose level	(mmol/L)
I	Plasma insulin concentration	(mU/L)
Q	Interstitial insulin concentration	(mU/L)
p_G	Endogenous glucose clearance	0.0030 (min^{-1})
α_G	Saturation parameter for insulin mediated glucose removal	0 (L/mU)
α_I	Saturation parameter for plasma insulin clearance	0.0017 (L/mU)
S_I	Insulin sensitivity	(L/mU/min)
EGP	Endogenous glucose production	0.0284 (mmol/kg/min)
CNS	Central nervous system glucose uptake	0.088 (mmol/kg/min)
$P(t)$	Glucose appearance in plasma from dextrose intake	(mmol/min)
PN	Parenteral Nutrition	(mmol/min)
P_{max}	Maximal glucose flux from gut to plasma	6.11 (mmol/min)
$P1$	Glucose level in stomach	(mmol)
$P2$	Glucose level in gut	(mmol)
V_G	Plasma glucose distribution volume	0.5961 (L)
k_I	Interstitial insulin transport rate	0.1 (min^{-1})
I_B	Endogenous insulin production	15 (mU/L/min)
n_I	Rate of transport between plasma and interstitial insulin compartments	0.003 (min^{-1})
n_K	Renal insulin clearance	0.150(min^{-1})
n_L	Hepatic insulin clearance	1 (min^{-1})
n_C	Interstitial insulin degradation	0.003 (min^{-1})
x_L	First-pass hepatic insulin clearance	0.67
$u_{ex}(t)$	Exogenous insulin	(mU/min)
$u_{en}(t)$	Endogenous insulin production	(mU/L/min)
V_I	Plasma insulin distribution volume	0.0450 (L)
d_1	Glucose absorption rate from stomach	0.0347 (min^{-1})
d_2	Glucose absorption rate from gut	0.0069 (min^{-1})
$D(t)$	Dextrose intake	(mmol/min)
m_{body}	Body mass	(kg)
m_{brain}	Brain mass (14% $\boldsymbol{m_{body}}$)	(kg)

2.2 Clinical Patients and Insulin Sensitivity Fitting

S_I profiles were fit using integral based fitting (Hann et al., 2006) from clinical data using Equations 1-7. This clinically validated metric and method (Chase et al., 2010) allows the performance and stochastic forecasting of STAR to be optimised before clinical trials. The integral based fitting method can be used since S_I is constant across an hour long time interval. If this time interval is bounded by t_1 and t_2, SI can be solved for by the re-arranging of the integrated form of Equation 1 for S_I, giving Equation 8.

$$S_I = \frac{-\left(G(t_2) - G(t_1)\right) + \int_{t_1}^{t_2}\left\{-p_G G(t) + \frac{P(t) + EGP * m_{body} - CNS * m_{brain}}{V_{g,frac}(t) * m_{body}}\right\}dt}{\int_{t_1}^{t_2}\left\{\frac{Q(t)}{1 + \alpha_G Q(t)}\right\}dt} \quad (8)$$

The start and end BG for each hour of clinical data, $G(t_2)$ and$G(t_1)$, is approximated using linear interpolation between BG measures. The S_I profile of a patient consists of a constant S_I identified for each hour of clinical data.

The patient cohort, summarised in Table 2, consists of data from 21 retrospective patients (with 25 patient episodes), and 8 short term and 22 long term patients from a prospective BG control study using STAR. The 8 short term patients received insulin therapy for 24 hours in a validation trial of the existing model and controller (Le Compte et al., 2009). Long term patients were treated using STAR as a standard of care at Christchurch Women's Hospital. There are 61 clinical patient datasets, as there are 28 treatment episodes for the 22 long term patients.

Table 2: Clinical patient summary statistics.

	Short-term (N=8)		**Long-term (N=28)**		**Retrospective (N=25)**	
	Median	[IQR]	Median	[IQR]	Median	[IQR]
Gestational age at birth (weeks)	25.6	[24.9 - 26.4]	[25.4	[25.0 - 26.8]	26.6	[25.4 - 27.7]
Weight at birth (grams)	745	[681 - 814]	760	[601 - 925]	845	[800 - 904]
Age at start of trial (days)	6.6	[3.6 - 7.7]	3.6	[1.5 - 6.4]	n/a	

2.3 Improving Stochastic Forecasting with Increased Cohort

The current stochastic model used in the STAR controller was designed using a retrospective cohort of 25 patients (Le Compte et al., 2010). Hence, the relevance of its performance in virtual trials may be limited. A stochastic matrix created using the larger 61 virtual patient cohort is compared to the current stochastic matrix.

The stochastic model used for S_I forecasting is generated from changes in insulin sensitivity across a retrospective representative clinical patient population. Changes in S_I can be seen when a S_I value ($S_{I,n}$) is plotted against the $S_I$value 1-4 hours forward ($S_{I,n+1}$), as shown in Figure 2. No change would result in a straight line with gradient 1. Kernel density methods are used to generate a distribution of likely future values of S_I for each sensitivity for which an example is shown in Figure 2. Forecasting is achieved using the 5th and 95th percentiles of likely S_I outcome.

Performance of retrospective and prospective clinical sub-cohort based stochastic models is compared with a whole cohort model over 3-hour forecast intervals. A perfect stochastic model would capture 90% of each individual patient's variations in the 5-95th percentile interval, but this may vary for individual patients. Performance of each stochastic model is assessed by the percentage of patients whose individual stochastic performance comes close to this ideal, for a more accurate and general the stochastic model.

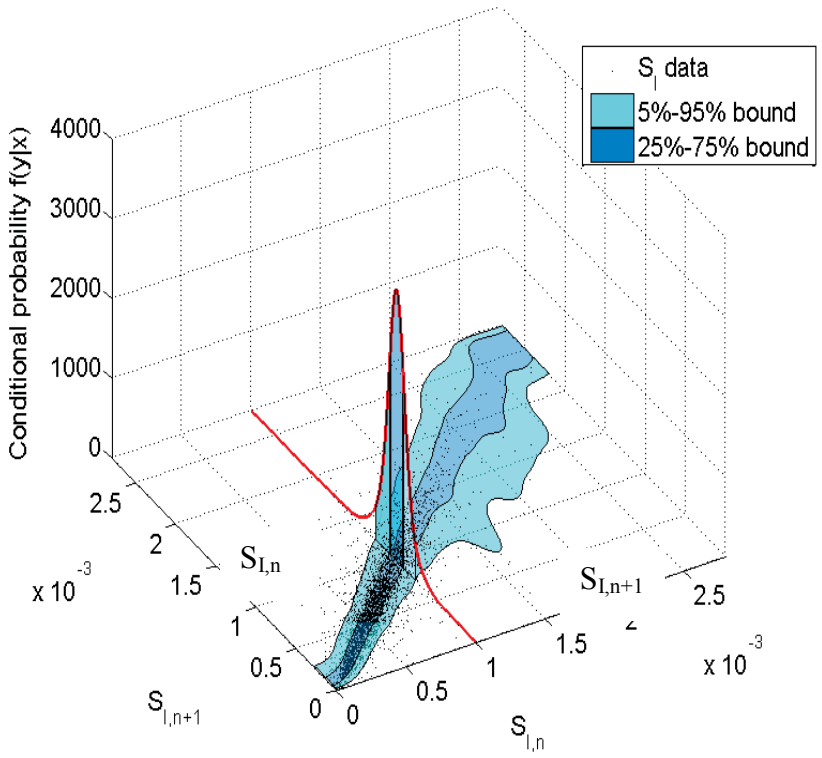


Figure 2: Hourly insulin sensitivity variation data with probability bounds and example curve showing probability bounds (Le Compte et al., 2010).

2.4 Improving Stochastic Forecasting in Sub-Cohorts

Two variables easily identified at the bedside are birth weight (BW) and gestational age (GA). Stochastic model matrices are created for each sub-cohort generated by tertiles in BW or GA. A Kolmogorov–Smirnov (KS) test was used to identify the most significantly different patient sub-cohort groupings by absolute S_I and hour-to-hour changes in S_I. Sub-cohort groupings were arranged by BW or GA. BW based sub-cohorts were arranged in several ways: 1) by tertiles and 2) into two groups with the critical BW ranging from 700 to 1300g in 5 gram steps. Similarly GA sub-cohorts were arranged by: 1) tertiles, and 2) two groups with the critical GA ranging from 24 to 25 weeks. From the patient sub-cohort groupings that were most different ($p<0.005$) additional stochastic models were created to differentiate behaviours in S_I. Performance is assessed using per-patient coverage.

2.5 Improving Stochastic Forecasting using only Insulin Sensitivities from Insulin therapy periods

Inherent in the clinical data are periods of several hours in length where the patient has not received at exogenous insulin. These periods tend to occur at the conclusion of a patient episode and reflect the improving ability of a patient to regulate their own plasma glucose levels. Stochastic models were developed using only the patient data in which exogenous insulin had been given sometime within the last two hours. Performance is assessed using per-patient coverage, and is directly compared to the non-insulin specific case.

2.6 Clinically validated virtual trial methods

The effect of stochastic modelling on the tightness and performance of glycaemic control can be evaluated through clinically validated virtual trial methods (Chase et al., 2010). Virtual trials test the effect of insulin and nutrition treatments on a virtual patient's blood glucose by using a known, treatment independent (Chase et al., 2010), insulin sensitivity profile derived from clinical data. Future information is ignored and the simulation algorithm in Appendix 2 is followed. The change in blood glucose levels over the intervention interval is then simulated using the known insulin sensitivity profile. Control performance outcomes are measured in the percentage time in the 4-8mmol/L band, percentage BG>10 mmol/L, and safety is evaluated in the percentage BG<4.0 mmol/L and number of incidences of BG<2.6 mmol/L.

3.0 RESULTS

3.1 Stochastic Forecasting with Increased Cohort

Figure 3 shows the per-patient coverage of the 5th to 95th percentile of forecasted change in S_I for the current (N=25) and new (N=61) whole-cohort stochastic models. There is no significant difference between the per-patient coverage of the different stochastic matrices. Both stochastic matrices have a minimum coverage over 70% and tight distributions around 90%. This result provides a measure of external validation in that the retrospective (N=25) cohort showed similar behaviour and performance to the prospective (N=36) cohort. The same results can be seen for 2 and 4 hour measurement intervals (not shown). However, small improvements can be seen in the coverage distribution for the new whole-cohort stochastic matrix (N=61). It is important to note that Figure 3 is the per-patient coverage, and not all patients have equal numbers of measurements and thus, do not have the same weighting on stochastic model forecast limits. In addition, manipulation of stochastic matrices to bring the overall whole-cohort percentage coverage closer to the target 90% tends to adjust the percentiles to capture a single data point, thus making the matrix more cohort-specific and adding no extra value for use outside of the existing cohort.

3.2 Gestational Age and Birth Weight Sub-Cohort

The cumulative distribution functions (CDFs) of S_I for tertiles of is shown in Figures 3. The CDFs of SI when separated by GA (<25.1 weeks, >26.9weeks, and between 25.1 and 26.9 weeks) are almost identical to Figure 4. The lower tertile has significantly lower S_I than the other groups for both GA and BW ($p < 0.05$, KS-test). In both cases, the relative changes in S_I (lower plot) are not significantly different. Thus, these tertiles are different in absolute S_I, but not in hour-to-hour variability.

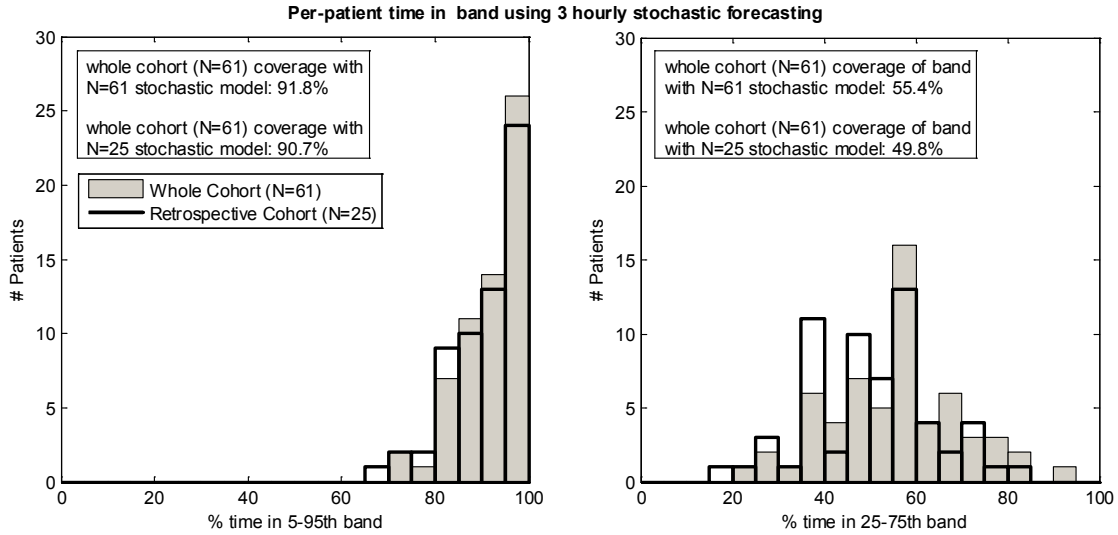


Figure **3**: Per-patient coverage between the forecasted 5th and 95th, and 25th and 75th, percentile change in insulin sensitivity using the current stochastic matrix compared with new stochastic matrix. (N = number of patients used to create stochastic matrix).

Table 3 shows the results for the tertiles in Figures 4, as well as other statistically significant cut-off values found ($p < 0.05$) for S_I over BW and GA sub-cohorts. Figure 5 shows the resulting per-patient coverage for stochastic forecasting using stochastic model for each of the weight tertiles, on comparison to a whole cohort stochastic model. There is noticeable improvement from the whole cohort (N=61) result shown for comparison, with increased patient coverage around 90%. This result was typical for all the stochastic model combinations shown in Table 3. Thus, the BW and GA dependent models add greater resolution and per-patient accuracy.

Table 3: Effect of weight and gestational age on insulin sensitivity statistics.

Data Set	S_I -Median [IQR] (L/mU/min)	Relative delta S_I – Median (P) [IQR]	# hours	#Patients
Whole Cohort	0.0017 [0.0010 - 0.0027]	0.004204 [-0.0303 - 0.0351]	6968	61
BW<700g	0.0013 [0.0007 - 0.0020]	0.004116 [-0.0299 - 0.0339]	3032	20
BW>865g	0.0020 [0.0013 - 0.0031]	0.006074 [-0.0289 - 0.0376]	1426	20
700g<BW<865g	0.0021 [0.0013 - 0.0032]	0.003114 [-0.0312 - 0.0360]	2510	21
BW<805g	0.0015 [0.0008 - 0.0025]	0.003640 [-0.0310 - 0.0344]	4566	32
BW>925g	0.0024 [0.0015 - 0.0037]	0.008583 [-0.0194 - 0.0353]	748	12
805g<BW<925g	0.0019 [0.0013 - 0.0030]	0.003678 [-0.0312 - 0.0385]	1654	17
BW<700g	0.0013 [0.0007 - 0.0020]	0.004116 [-0.0299 - 0.0339]	3032	20
BW>700g	0.0021 [0.0013 - 0.0032]	0.004254 [-0.0305 - 0.0369]	3907	40
BW<800g	0.0014 [0.0007 - 0.0021]	0.003866 [-0.0289 - 0.0334]	3519	27
BW>800g	0.0021 [0.0013 - 0.0033]	0.004446 [-0.0315 - 0.0382]	3449	34
GA<25.1wks	0.0013 [0.0007 - 0.0021]	0.004001 [-0.0314 - 0.0343]	3196	22
GA>26.9wks	0.0020 [0.0013 - 0.0032]	0.008319 [-0.0215 - 0.0370]	1200	16
25.1<GA<26.9 wks	0.0020 [0.0013 - 0.0031]	0.002614 [-0.0316 - 0.0364]	2572	23
GA<26.15wks	0.0015 [0.0008 - 0.0026]	0.003139 [-0.0316 - 0.0340]	4561	34
GA>27.05wks	0.0021 [0.0014 - 0.0033]	0.008422 [-0.0205 - 0.0374]	1141	14
26.15wks< GA <27.05 wks	0.0019 [0.0013 - 0.0027]	0.004314 [-0.0315 - 0.0389]	1266	13
GA<26.3 wks	0.0015 [0.0008 - 0.0026]	0.003138 [-0.0310 - 0.0340]	4842	37
GA>26.3 wks	0.0020 [0.0014 - 0.0030]	0.007230 [-0.0287 - 0.0385]	2126	24
GA<27.05 wks	0.0016 [0.0009 - 0.0026]	0.003364 [-0.0316 - 0.0349]	5827	47
GA>27.05 wks	0.0021 [0.0014 - 0.0033]	0.008422 [-0.0205 - 0.0374]	1141	14

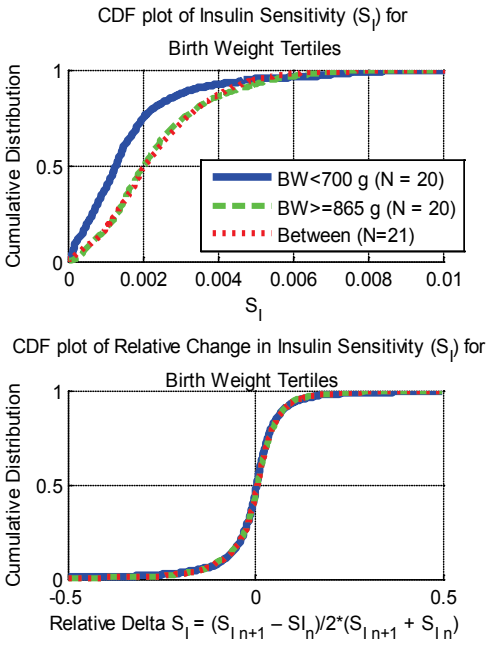


Figure 4: Correlation of insulin sensitivity and change in insulin sensitivity with birth weight

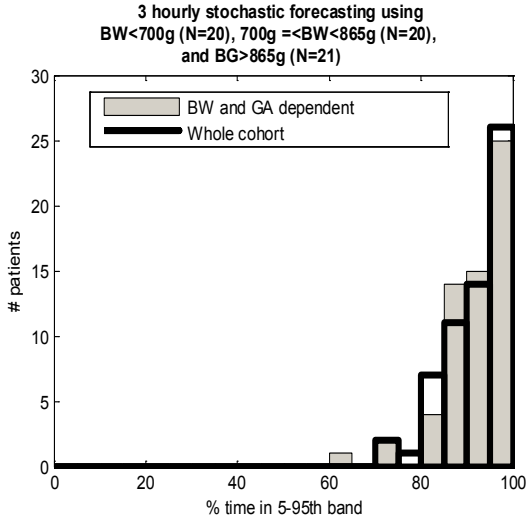


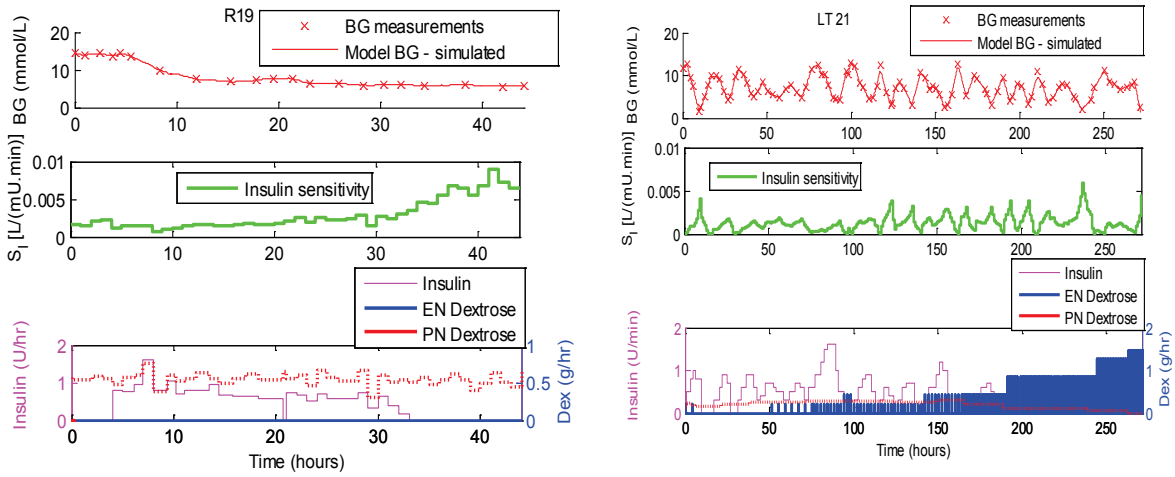
Figure **5**: Comparison of per-patient coverage for BW and GA dependent point to point 3 hourly stochastic forecasting.

3.4 Low patient coverage case studies

Given that the whole cohort stochastic models have ~ 90% overall coverage in the 5-95th percentile band, patients with individual coverage less than 85% were extracted for further analysis. As can be seen in Table 4 there is no common characteristic that could potentially be used to identify such patients as more variable. The patients summarised in Table 4 cover the entire range for both gestational age and birth weight. Furthermore, analysis of the per-patient coverage statistics of the entire patient cohort shows no trends with birth weight, gestational age or gender, and while, in general, a patient with low coverage of the 5th to 95th percentile band also had low coverage of the 25th-75th band (defined as coverage less than 45%), the same was not true in reverse.

Table 4: Highly variable patient statistics. LT denotes patients from the long term cohort, R denotes patients from the retrospective cohort

Patient Number:	**# Hours**	**% in 5th – 95th band**	**% above 95th percentile**	**% in 25th – 75th band**	**% above 75th percentile**	**Birth weight**	**Gestational age**
LT 21	272	75.1	10.0	30.9	33.5	0.605	25
LT 27	28	80.0	12.0	28.0	48.0	0.69	24.6
R 6	93	73.3	17.8	33.3	38.8	0.900	25
R 10	66	76.2	19.0	38.9	42.8	1.28	27.9
R 12	34	80.6	19.4	29.0	35.5	0.845	28.6
R 19	44	82.9	17.1	43.9	36.5	0.93	28.6



a) b)

Figure 6: Clincial data and SI profiles for two highly variable patients: a) Retrospective patient 19 and b) Long Term patient 21

Figure 6 shows two high variability profiles derived from clinical data. In Figure 6 a) the S_I rises unusually fast and unusually high, whereas in Figure 7 b) the S_I exhibits sudden peaks and drops. In particular, it is the sudden increases in S_I beyond the forecasted bounds that can result in unexpectedly low BG. For this reason, when carrying out virtual trials, the highly variable patients tend to constitute unrepresentative, larger proportions of the low BG (BG<4.0 mmol/L) time periods, which means the stochastic matrices remain overly conservative for the remainder of the cohort. The S_I of the other high variability patients from Table 4 generally exhibit aspects of both these example profiles, and are difficult to visually identify as differing from the rest of the cohort without looking at per-patient coverage. Patients that are variable with respect to the cohort are thus hard to identify in the clinical situation with the limited bedside metrics available.

3.5 Stochastic matrices based on periods of insulin therapy

The analysis was carried out using S_I from time periods in clinical data when a patient had been on insulin within the last two hours. This removed the increase in S_I common at the end of a patient's clinical data, when they are not receiving insulin treatments and their BG is basal and stable. This increase in S_I reflects an improvement in patient condition. Figure 6 shows the difference made to per patient coverage. The narrowing of stochastic forecasting bands is evident in Figure 7 with the lower overall patient coverage, and the clear distribution around 90% coverage. There was no difference in the results for trends with BW and GA.

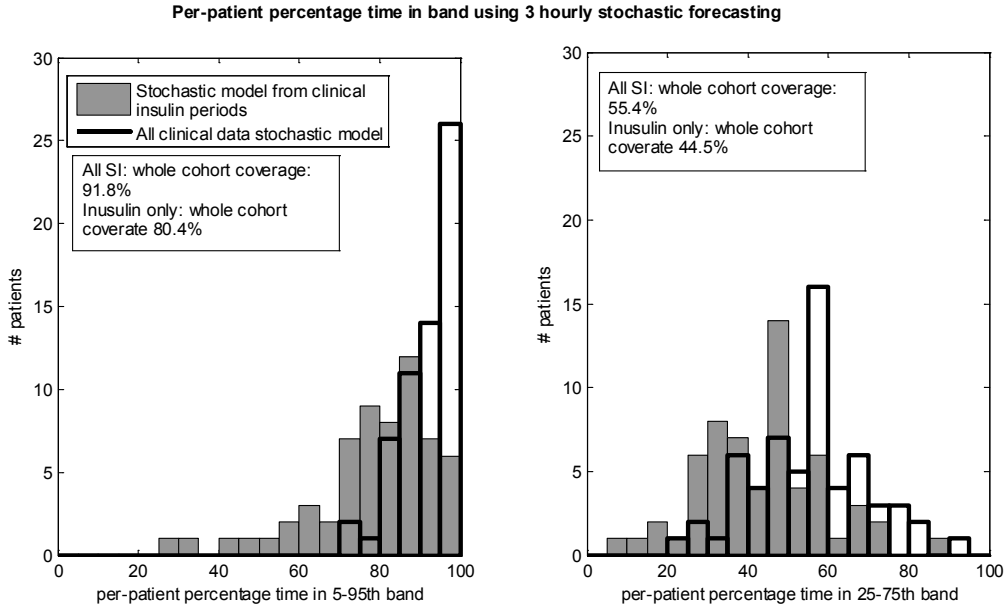


Figure 7: Per-patient coverage between the forecasted 5th and 95th percentile change in insulin sensitivity using the current stochastic matrix compared with an insulin periods only stochastic model. The clinical data used to generate the insulin periods stochastic model ignores any data where insulin has not been given within the last 2 hours.

3.6 Simulation Results

Clinically validated virtual trials using the stochastic matrix from insulin periods showed a 10% increase in performance (% BG between 4.0 and 8.0 mmol/L), and a drop in the number

of hypoglycaemic events (BG <2.6 mmol/L) from 4 to 2 patients. This result shows that using insulin-period-based stochastic modelling increases the performance and safety of glycaemic control.

	Original N=25 Stochastic Model	**N=61 Stochastic Model**	**BW<700g and BG>=700g Stochastic Models**	**Insulin Periods only Stochastic Model**
% Time in Band (4.0-8.0mmol/L)		64.1		76.6
%BG <4.0 mmol/L		1.7		2.2
%BG<2.6 mmol/L (# patient episodes)		0.09 (3)		0.1 (6)
% BG >10 mmol/L		14.3		7.6

4.0 DISCUSSION

Comparison of per-patient percentile band coverage for different cohort based stochastic matrices has shown that the cohorts are essentially similar in behaviour. The addition of 36 patient episodes (N=25 to N=61) has improved per-patient stochastic model coverage slightly, but not to an extent that is likely to be clinically significant in use. This similarity in coverage with the use of different cohort stochastic forecasting verifies that the original data set is as representative of the NICU population as previously thought, where initial work with stochastic matrices in adult ICU patients indicated N = 25 would be suitable (Lin et al., 2006).

The high proportion of coverage above 90%, and in particular above 95% in the 5-95th band suggests that this band width is determined by the behaviour of a relative few patients. Ideally, for patient specificity, the majority of per-patient coverage would be close to the target 90%. The patient coverage of the 25-75th percentiles is much wider, indicating significant inter-patient variability and lack of patient-specific coverage within these central tendency bounds. In particular, the short and long term cohorts tend to have higher average coverage in the 25th-75th band suggesting that differences between cohorts arise within the extremes of behaviour, and that estimates of variability are over conservative in the majority of cases. Overall it seems that inter-patient variation is more significant than intra-patient variation as a limiting factor in this stochastic forecasting model, and that a relative few more variable patients are quite different in behaviour.

BW and GA dependent stochastic models can be used to further improve per-patient coverage, as seen in Figure . The proportion of coverage around the 90% target for the 5-95th percentiles is much greater, indicating BW and GA can be used to introduce greater patient specificity in stochastic forecasting. Due to the relatively small number of patients used, the ideal combinations of BW and GA found may not fully represent all NICU populations or be

perfect divisions for other NICU cohorts. Equally, there may be differences between NICUs due to differences in cohort or case mix. However, the results clearly illustrate potential to improve patient-specific forecasting and glycaemic control based on easily measured variables. Further investigations using larger independent cohorts should be completed to validate these initial insights, and create more generalisable results. However, these results provide a template for further analysis.

A small proportion of patients from this cohort exhibit changes in S_I that is not well predicted by the whole cohort and birth weight divisional stochastic models. These patients do not have any readily identifiable patient descriptor, such as birth weight or gestational age, in common. However, these patients can be roughly divided according to their exogenous insulin requirements. Several patients had high insulin sensitivity and did not require exogenous insulin to maintain constant BG. Their S_I was not well predicted by the model due to improvement of patient condition, exacerbating per-patient variability and deviance from modelled insulin and glucose secretion, and thus they are in no danger as high insulin sensitivity will result in no treatment. These cases highlight model specificity for describing glucose and insulin dynamics in the neonate with deficient glycaemic control.

The other type of patient with S_I profiles that were not well predicted by the model were those with high variability due to rapid fluctuations in patient condition, most likely due to changes in insulin and glucose secretion. This case is more serious as exogenous insulin is required, and a rapid increase in insulin sensitivity can lead to a decrease in BG levels. Such patients highlight the need for well designed insulin dosing protocols with safety checks. Currently, in addition to forward prediction of likely BG outcomes, STAR applies a maximum limit on the amount by which insulin can increase from treatment to treatment. This limit is dependent on BG and protects highly variable patients from excessive insulin therapy.

There was a decrease in average percentage time in band and shift in distribution to around 90% when using S_I only from periods where a patient had received insulin. The new stochastic bands are tighter and therefore less conservative, but better reflect patient condition and variability for patients actually receiving insulin, as shown in the improved coverage of the target band (4.0-8.0 mmol/L) and lower number of patients with hypoglycaemic events. It also suggests that the 7 patients with percentage time in band less than 60% have higher insulin sensitivity, and thus, as seen in the data, received less insulin therapy. In addition, uncertainty around the endogenous glucose and insulin secretion is highlighted, particularly in the patient recovery stage. This result gives direction for future work in better quantification of variability around endogenous secretion of insulin and glucose. It also underlines the models specificity for use in patients requiring insulin therapy.

5.0 CONCLUSIONS

Stochastic model based forecasting based on a larger patient database provides a more accurate representation of the NICU population, but is limited by inter-patient variability. Birth weight and gestational age dependent stochastic forecasting can be used to further increase per-patient accuracy and coverage. The use of stochastic models based on insulin sensitivities from insulin treatment periods better reflected patient condition in control, as reflected by the 10% increase in percentage time in band and the halving of the number of patients with hypoglycaemic events. Further improvement can be achieved through investigations into the variability associated with endogenous insulin and glucose production.

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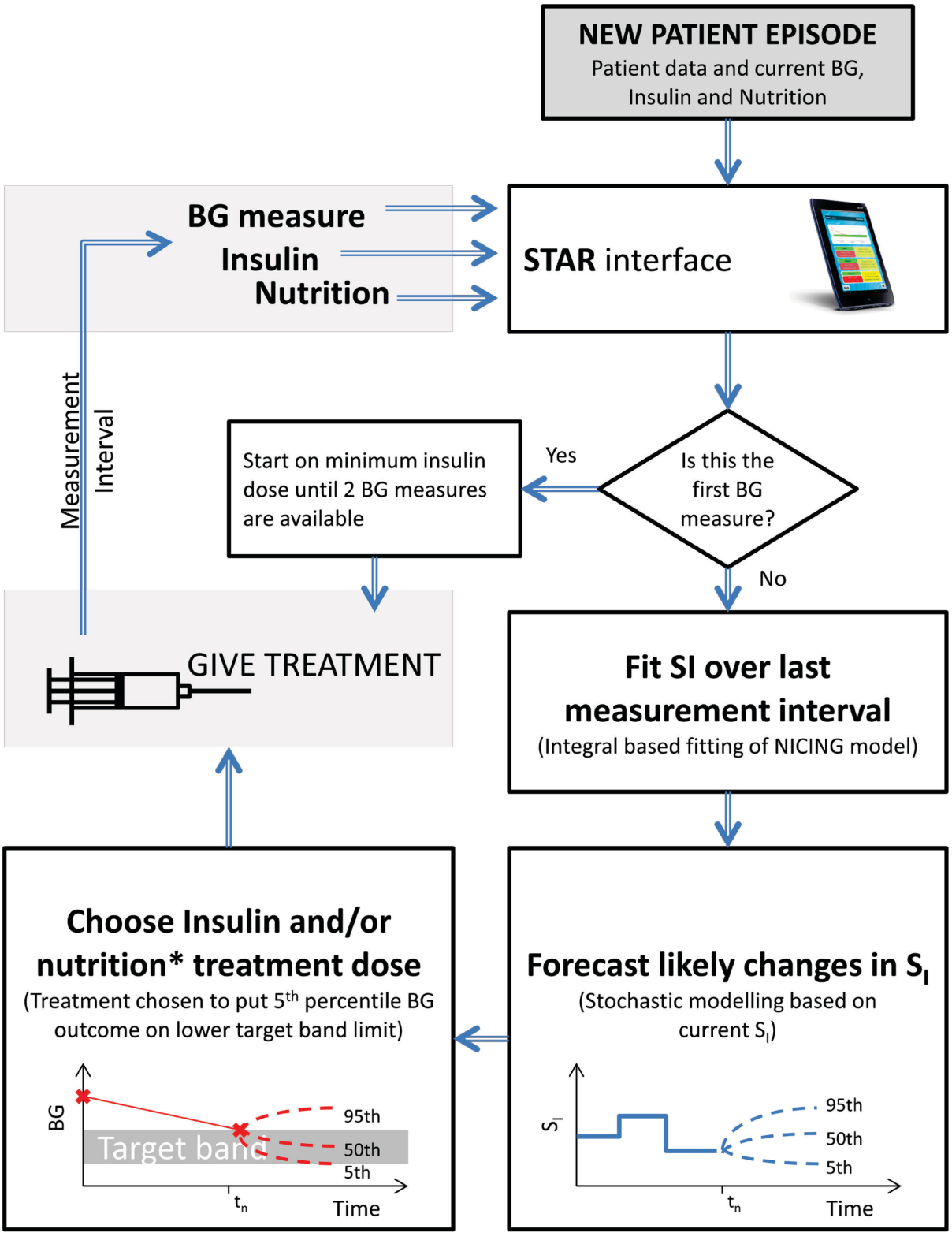
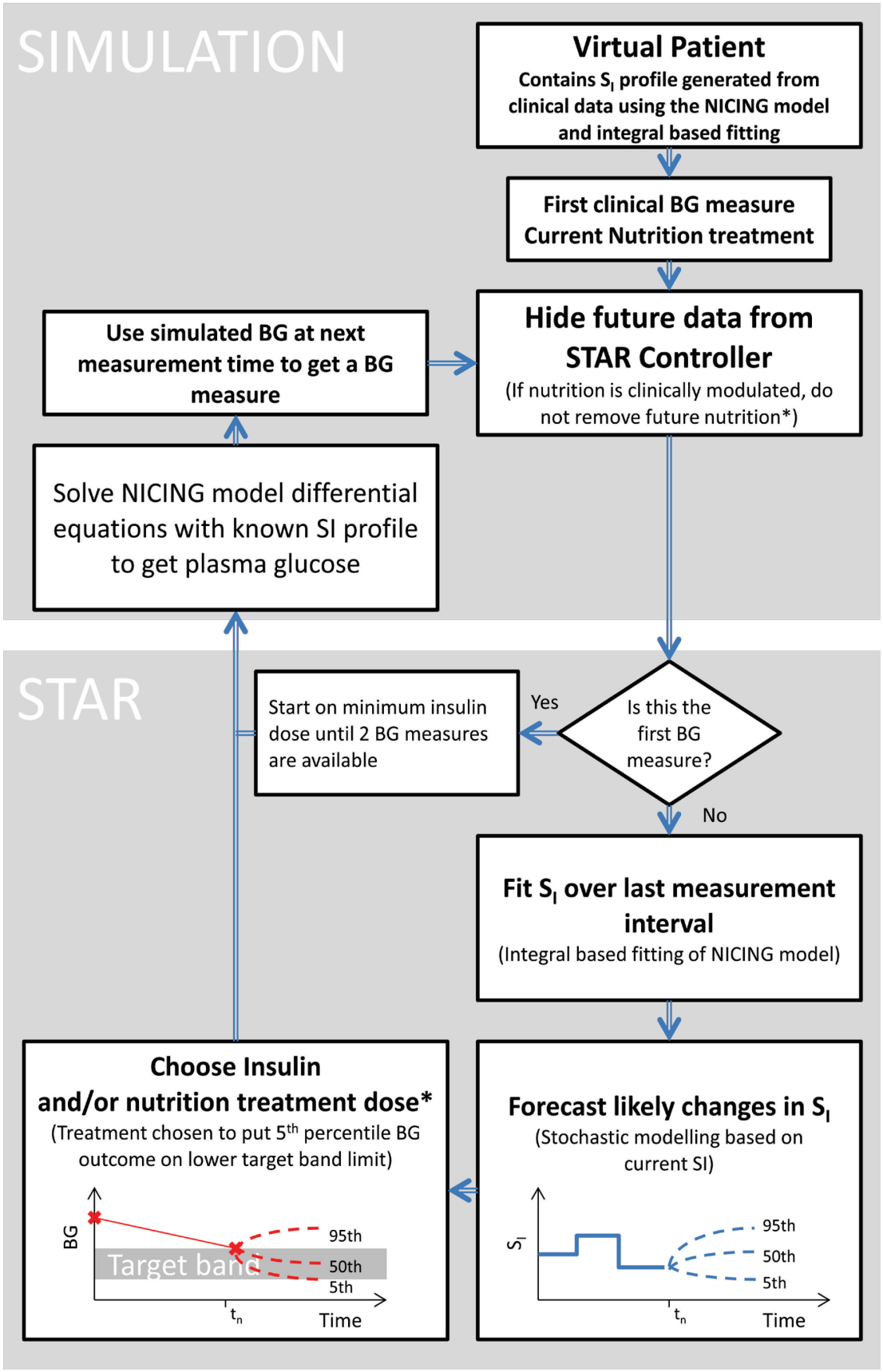
APPENDIX 1: STAR algorithm



*Currently nutrition is clinically modulated. In the adult ICU STAR modulates both nutrition and insulin to optimise glycaemic control.

APPENDIX 2: Virtual trial simulation algorithm



*Currently nutrition is clinically modulated. In the adult ICU STAR modulates both nutrition and insulin to optimise glycaemic control.