Blood Glucose Prediction Using Stochastic Modeling in Neonatal Intensive Care

Aaron J. Le Compte*, Dominic S. Lee, J. Geoffrey Chase, Jessica Lin, Adrienne Lynn, and Geoffrey M. Shaw

Abstract—Hyperglycemia is a common metabolic problem in premature, low-birth-weight infants. Blood glucose homeostasis in this group is often disturbed by immaturity of endogenous regulatory systems and the stress of their condition in intensive care. A dynamic model capturing the fundamental dynamics of the glucose regulatory system provides a measure of insulin sensitivity ($S_I$). Forecasting the most probable future $S_I$ can significantly enhance real-time glucose control by providing a clinically validated/proven level of confidence on the outcome of an intervention, and thus, increased safety against hypoglycemia. A 2-D kernel model of $S_I$ is fitted to 3567 h of identified, time-varying $S_I$ from retrospective clinical data of 25 neonatal patients with birth gestational age 23 to 28.9 weeks. Conditional probability estimates are used to determine $S_I$ probability intervals. A lag-2 stochastic model and adjustments of the variance estimator are used to explore the bias-variance tradeoff in the hour-to-hour variation of $S_I$. The model captured 62.6% and 93.4% of in-sample $S_I$ predictions within the (25th–75th) and (5th–95th) probability forecast intervals. This overconservative result is also present on the cross-validation cohort and in the lag-2 model. Adjustments to the variance estimator found a reduction to 10%–50% of the original value provided optimal coverage with 54.7% and 90.9% in the (25th–75th) and (5th–95th) intervals. A stochastic model of $S_I$ provided conservative forecasts, which can add a layer of safety to real-time control. Adjusting the variance estimator provides a more accurate, cohort-specific stochastic model of $S_I$ dynamics in the neonate.

Index Terms—Forecasting, human factors, stochastic approximation.

I. INTRODUCTION

HYPERGLYCEMIA occurs in 40%–80% of very low-birth-weight infants in the neonatal intensive care unit (NICU) [3], [4]. Low-birth-weight neonates and preterm neonates are at the highest risk of developing hyperglycemia [5], [6], even in patients with no family history of diabetes. Hyperglycemic infants are often treated by glucose restriction [11]–[13]. However, prolonged severe glucose restriction may adversely affect the infant’s nutritional status, and may also be a reason for poor growth observed in these infants [11]. Avoiding hyperglycemia, while providing adequate nutrition to promote growth and development, is a major challenge for healthcare providers in the NICU.

Several mechanisms are thought to contribute to neonatal hyperglycemia. Persistent endogenous glucose production (EGP) during glucose infusions has been demonstrated in several studies [9], [16]. Hyperglycemia is also common during times of neonatal stress and increased secretion of counter-regulatory hormones leads to a prominent rise in endogenously produced glucose, as well as a reduction in insulin sensitivity ($S_I$). Nutritional support regimes with high carbohydrate content are also provided to increase neonate weight, but often compound the counter-regulatory response [17]. Immaturity of the glucose transport system and a limited number of insulin-dependent tissues are also thought to be contributing factors [18].

Insulin is an anabolic hormone and promotes growth, while lowering glucose levels. However, endogenous deficiency or lack of effect due to high insulin resistance will have a negative impact on glycaemic levels [11]. Immature insulin processing in the neonate produces excessive proinsulin, which is approximately 16× less effective than regular adult insulin, which may also explain why some poor control is exhibited in this population [21]. Preterm infants require higher insulin concentrations that term infants to maintain euglycemia [21], and a high insulin concentration compared to adults may be required to promote peripheral glucose uptake [9]. Besides glucose control, reduced proteolysis, and thus, preservation of muscle mass has been associated with insulin therapy in this cohort [7], [8], independent of glucose infusion [26].

Several recent studies have associated hyperglycemia with increased morbidity and mortality in neonatal cohorts [27]–[29]. Limited trials of glucose control using insulin in neonates have been reported [7], [11], [34]–[39], and insulin therapy did help to improve glucose tolerance in these limited trials. Insulin therapy in preterm neonates is gaining wider acceptance [40], [41], but still carries the risk of hypoglycemia and possible neurological complications [3].

Model-based glycaemic control methods using both insulin and/or nutrition modulation have been employed successfully in the control of hyperglycemia in adult critical care populations, as reviewed by Chase et al. [42]. Model-based methods allow information about the fundamental metabolic state of the patient, $S_I$ in this case, to be inferred from serial blood
glucose (BG) measurements, and records of nutrition and insulin administration [2], [43]. Once the current $S_I$ of the infant has been identified, prediction of future $S_I$ would allow predictions of outcome BG concentration for an intended clinical intervention. Changes in the $S_I$ parameter reflect variations in patient condition such as clinical stress [44], [45] and drug therapy [13]. Thus, tracking and forecasting this parameter is important to provide safe glycaemic control in the highly dynamic preterm neonate.

Stochastic models provide a means to quantify this probability of a future $S_I$ [46]. Thus, the resulting distribution of BG concentrations that would result from a given intervention can be determined [47]. This information can then be used to guide dosing to avoid low blood sugar concentrations, improve overall glycaemic control, and identify periods of potential high glucose variability that may be indicative of emerging clinical events.

This paper presents the adaptation of a stochastic model for $S_I$ prediction from adult critical care to the unique clinical and physiological case of the neonate. Several modifications to the initial kernel density estimation model are used to explore the relationship between the model and the underlying dataset. In addition, the stochastic modeling approach is extended to include more than the prior hour values to determine if improved prediction can be obtained in this neonatal case.

II. METHODS

A. Patient Cohort

Retrospective data from 25 episodes of insulin therapy treatment in Christchurch Women’s NICU were used in the study. Ethics approval for the collection and publication of data was obtained from the Upper South Regional Ethics Committee. The 25 episodes of insulin usage were composed of 21 individual patients representing 3567 h of patient data. Gestational age at birth ranged from 23 to 28.9 weeks, and birth weight ranged from 600 to 1280 g. Inclusion criteria were birth weight less than 1500 g and a period of treatment with insulin of at least 12 h.

B. System Model

The system model used in this research is based on a clinically validated glucose regulatory system model for adult intensive care patients [2], [43]. The model has been modified to better account for the main physiological differences in neonates based on available clinical data and kinetic studies. The overall model is defined as

$$\dot{G} = -p_GG - S_I G \frac{Q}{1+\alpha_GQ} + \frac{P(t) + (P_{END}m_{body}) - (CNSm_{brain})}{(V_G,frac(t)m_{body})} \tag{1}$$

$$\dot{Q} = -kQ + kI \tag{2}$$

$$\dot{I} = -\frac{nI}{1 + \alpha_I I} + \frac{u_{ex}(t)}{(V_I,frac n_{body})} + e^{-(k_I u_{ex}(t))}I_B \tag{3}$$

where $G(t)$ (in millimols per liter) is the total plasma glucose and $I(t)$ (in millimols per liter) is the plasma insulin, exogenous insulin input is represented by $u_{ex}(t)$ (in milliunits per minute), and basal endogenous insulin secretion $I_B$ (in milliunits per liter-minute), with $k_I$ representing the suppression of basal insulin secretion in the presence of exogenous insulin. The effect of previously infused insulin being utilized over time is represented by $Q(t)$ (in milliunits per liter), with $k$ (1/min) accounting for the effective life of insulin in the system. Body weight and brain weight are denoted by $m_{body}$ (in kilograms) and $m_{brain}$ (in kilograms), respectively. Patient endogenous glucose clearance and insulin sensitivity are $p_G$ (1/min) and $S_I$ (in liters per (milliunits-minutes), respectively. The parameter $V_I,frac$ (in liters per kilogram) is the insulin distribution volume per kilogram body weight and $n$ (1/min) is the constant first-order decay rate for insulin from plasma. Total plasma glucose input is denoted $P(t)$ (in millimols per minute), EGP is denoted by $P_{END}$ (in millimols per (kilogram-minutes)) and $V_G,frac$ (in liters per kilogram) represents the glucose distribution volume per kilogram of body weight. CNS (in millimols per (kilogram-minutes)) represents noninsulin-mediated glucose uptake by the central nervous system, as well as the liver, kidneys, and red blood cells [48]. Michaelis–Menten functions are used to model saturation, with $\alpha_G$ (in liters per milliunit) used for the saturation of plasma insulin disappearance, and $\alpha_I$ (in liters per milliunit) for the saturation of insulin-dependent glucose clearance.

Table I summarizes the parameters used in this model. For the simulations in this study, $k$, $n$, $\alpha_I$, $\alpha_G$, CNS, $I_B$, $V_I,frac$, $P_G$, and $P_{END}$ are set to generic population values based on reported data. Prior clinical and model sensitivity studies with the similar adult model [2], [49] have shown this choice to be robust. The glucose compartment (1) in this model was modified from [2] and [49] to account for available neonatal data [50]. In particular, the CNS and $P_{END}$ terms were introduced to take advantage of available neonatal glucose kinetic studies. The endogenous glucose clearance term $p_G$ was set to 0.003 min$^{-1}$ based on parameter sensitivity studies [1], and is considered effectively constant, similar to the adult case [2]. Insulin-mediated glucose uptake saturation represented by the parameter $\alpha_G$ was set to zero based on the results of [9] and [51], which showed no saturation in glucose uptake with increasing insulin concentration.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>$k$</td>
<td>0.0086 min$^{-1}$</td>
<td>[2]</td>
</tr>
<tr>
<td>$n$</td>
<td>0.90 min$^{-1}$</td>
<td>[7-10]</td>
</tr>
<tr>
<td>$\alpha_I$</td>
<td>1.70 x 10$^{-3}$ L/min</td>
<td>[2]</td>
</tr>
<tr>
<td>$\alpha_G$</td>
<td>0.14 * $m_{body}$ kg</td>
<td>[15]</td>
</tr>
<tr>
<td>CNS</td>
<td>0.088 mmol/kg/min</td>
<td>[14]</td>
</tr>
<tr>
<td>$m_{brain}$</td>
<td>0.14 * $m_{body}$ kg</td>
<td>[15]</td>
</tr>
<tr>
<td>$I_B$</td>
<td>10 mU/L/min</td>
<td>[9, 10]</td>
</tr>
<tr>
<td>$V_I,frac$</td>
<td>0.045 L/kg</td>
<td>[19, 20]</td>
</tr>
<tr>
<td>$V_G,frac$</td>
<td>ECF proportion L/kg</td>
<td>[22-25]</td>
</tr>
<tr>
<td>$P_{END}$</td>
<td>0.02318 mmol/kg/min</td>
<td>[1, 10, 16, 26, 30-33]</td>
</tr>
<tr>
<td>$p_G$</td>
<td>0.003 min$^{-1}$</td>
<td>[1]</td>
</tr>
</tbody>
</table>
within typical clinical usage ranges. Fig. 1 shows the model fit and 1–4 h prediction error for a range of physiological $p_G$ and $P_{END}$ values over the 3567 h of retrospective patient data. Model fit and prediction performance metrics were robust to a range of $p_G$ and $P_{END}$ values. Further parameter sensitivity analysis found that model performance was robust to variations of the parameters presented in Table I [1].

The parameter $S_I$ is explicitly determined from the data. The integral-based fitting method of Hann et al. [2] was employed for identifying $S_I$ over time using retrospective BG concentrations ($G$), insulin administration ($u_{ex}(t)$), and nutritional infusion rates ($P(t)$). The resulting time-varying $S_I$ profile was constrained to a lower bound of $1 \times 10^{-5}$ L/(mU·min) to prevent nonphysiological negative values for $S_I$ [46], [47].

C. Stochastic Model (Lag-1)

A 2-D kernel density estimation method is used to construct the stochastic model that describes the hourly transition of $S_I$. The kernel density method combines probability distribution functions for each point of data to generate an overall density function for the dataset. This method has the advantage of producing a smooth, physiologically likely, continuous function across the parameter range to provide continuity when interpolating $S_I$ forecasts to account for each particular patient state, and automatically accounts for any possible multimodality where the density of data may show several distinct peaks corresponding to patterns of changes in $S_I$. The overall result is a bivariate probability density function for the potential parameter values. The goal of this statistical model is to quantify the range of $S_I$ one hour ahead in time ($S_{I,n+1}$) based on available data ($S_{I,n}, S_{I,n-1}, S_{I,n-2}, \ldots, S_{I,0}$) to guide real-time clinical control. Thus, it is important that the model formulation is computationally feasible for real-time applications on typical hardware.

The 2-D kernel density method is chosen for creating the stochastic model because the distribution of $S_{I,n+1}$ varies with $S_{I,n}$, as shown in Fig. 2, and cannot be simply described with a single standard statistical distribution. Thus, the variations in $S_I$ can be treated as a Markov process. A Markov process has the property that the conditional probability density function of future states of the process, given the current state, depends only upon the current state. Therefore, using the Markov property of the stochastic behavior of $S_I$, the conditional probability density of $S_{I,n+1}$ taking on a value $y$ can be calculated by knowing $S_{I,n} = x$

$$p(S_{I,n+1} = y | S_{I,n} = x) = \frac{p(S_{I,n+1} = y, S_{I,n} = x)}{p(S_{I,n} = x)}.$$  \hspace{1cm} (4)

Considering the fitted $S_I$ in a 2-D space, as shown in Fig. 2, the joint probability density function across the $x$-$y$ ($S_{I,n}-S_{I,n+1}$) plane is defined by the fitted values shown by the dots, whose coordinates are $x_i$ and $y_i$

$$p(x, y) = \frac{1}{n} \sum_{i=1}^{n} \frac{\phi(x; x_i, \sigma_x^2) \phi(y; y_i, \sigma_y^2)}{p_{x_i} p_{y_i}}.$$  \hspace{1cm} (5)
Thus, knowing \( S_{I,n} = x \) at hour \( n \), the probability of \( S_{I,n+1} = y \) at hour \( n + 1 \) can be calculated using (8) and (9) across the \( x-y \) plane. Where there is a higher density of data, more certainty can be drawn on the “true” behavioral pattern.

The model was cross validated by splitting the 25 patient cohort into five groups, each containing five patients. For each group, the model was fitted on the remaining 20 patients of the cohort representing approximately 2800 h of data. Out-of-sample \( S_I \) predictions were generated for the five patients of the unused group and compared to the actual fitted \( S_I \) from these five patients.

Based on the in-sample, where the stochastic model is generated from the entire retrospective dataset and tested on the same data, and out-of-sample, where different subsets of data are used for model generation and testing, the kernel density estimator was modified by multiplying the variance estimators by a constant \( c \) (i.e., \( c\sigma_x \) and \( c\sigma_y \)) to explore the model bias-variance tradeoff for this data. This adjustment to the variance estimator effectively adjusts the kernel bandwidth and the degree of smoothing over the data.

D. Stochastic Model (Lag-2)

The stochastic model was extended to incorporate lag-2 effects to investigate any further reliance on \( S_I \) time-history to provide justification for more complex Markov-like models. The lag-2 model produces probability intervals for \( S_I \) at hour \( n+1 \), given the \( S_I \) for the previous two hours: \( S_{I,n-1} = x \) and \( S_{I,n} = y \). The derivation of the model is similar to that of the lag-1 case in that the extension to 3-D data involves the product of three univariate probability distributions. Further details on higher dimensional kernel density smoothing methods are available in [53]. The resulting conditional probability estimator is defined as shown in (10) at the bottom of the next page, where

\[
p_{xy}(x,y) = \frac{\int \phi(x; x_i, \sigma^2_{x_i}) p_{x_i} \phi(y; y_i, \sigma^2_{y_i}) p_{y_i}}{\int \phi(x; x_i, \sigma^2_{x_i}) p_{x_i} \phi(y; y_i, \sigma^2_{y_i}) p_{y_i}}
\]

\[ p_z = \int \phi(z; z_i, \sigma^2_{z_i}) dz. \]

Greater details of the general modeling approach, theoretical background, and specific computations are given in [46] and [47].

III. RESULTS

Fig. 2 shows the distribution of hourly variation in \( S_I \) for the 3567 h of patient data. Approximately 95% of the values are below \( 1.5 \times 10^{-3} \) L/(mU·min). Fig. 3 shows the conditional probability plot for the lag-1 model. Fig. 4 shows the 5th, 25th, 50th, 75th, and 95th percentile probability bounds computed by integrating Fig. 3, overlaid on the raw data of Fig. 2. For a given value \( S_{I,n} \), the 25th–75th percentile prediction bound for \( S_{I,n+1} \) is found by determining the intersection of the 25th percentile bound and the 75th percentile bound on Fig. 4 with the line \( y = S_{I,n} \), shown in Fig. 4 for \( S_{I,n} = 1 \times 10^{-3} \) L/(mU·min). These values can then be sequentially substituted
Fig. 3. Conditional probability density function for $S_{I,n+1}$ knowing $S_{I,n}$. The structure of the plot is largely unimodal in the region $S_{I,n} < 1.5 \times 10^{-3}$ and $S_{I,n+1} < 1.5 \times 10^{-3}$, corresponding to the region of densest data.

for $S_I$ into (1) to produce BG concentration forecasts based on an equal-tailed calculated 25th–75th percentile range of likely future $S_I$ [47].

Table II shows the in-sample results for the lag-1 model for $n = 3530$ predictions. The number of predictions is less than the total hours of $S_I$ due to end effects where the patient data record was not evenly divisible by 1 h, and because predictions can only be computed after the second hour of patient data. The overall median 1-h absolute prediction error comparing predicted BG based on the 50th percentile of predicted $S_I$ to the interpolated value from retrospective data is 4.3%, corresponding to an average BG error of 0.34 mmol/L. The width of the (25th–75th) BG probability interval is 0.78 mmol/L. Similarly, the (5th–95th) BG probability interval width is 2.32 mmol/L. $S_I$ predictions (62.6%) were within the (25th–75th) probability intervals, corresponding to 59.1% of BG predictions. Similarly, 93.4% of $S_I$ predictions were within the (5th–95th) probability intervals, corresponding to 92.2% of BG predictions. Thus, the proportion of fitted $S_I$ and predicted BG values that fell within the (25th–75th) and (5th–95th) probability intervals were measurably higher than the expected 50% and 90%.

The results of Tables II and III suggest that the model prediction coverage for $S_I$ is overconservative by approximately 7%–12% for the (25th–75th) prediction interval. The lag-2 model was used to investigate whether these effects could be mitigated by incorporating $S_I$ information from two previous hours. A comparison of the lag-1 and lag-2 models revealed 61.3% of $S_I$ fell within the (25th–75th) for the lag-2 model, similar to the 62.6% result for the lag-1 case. Similarly, 94.6% of $S_I$ fell within the lag-2 (5th–95th) interval compared to 93.4% for the lag-1 model. These results suggest that lag-2 effects play no significant major role in the evolution of $S_I$ compared to the simpler lag-1 case.

A comparison of the lag-1 and lag-2 models revealed 61.3% of $S_I$ fell within the (25th–75th) for the lag-2 model, similar

TABLE II

<table>
<thead>
<tr>
<th>Prediction Width</th>
<th>25th–75th</th>
<th>5th–95th</th>
</tr>
</thead>
<tbody>
<tr>
<td>BG</td>
<td>0.78 mmol/L</td>
<td>2.32 mmol/L</td>
</tr>
<tr>
<td>Median absolute percent BG point prediction error</td>
<td>4.3%</td>
<td>0.34 mmol/L</td>
</tr>
</tbody>
</table>

Data are expressed as cohort medians ($n = 3530$ predictions).

\[
p(S_{I,n+1} = z | S_{I,n-1} = x, S_{I,n} = y) = \frac{\sum_{i=1}^{n} \left( \frac{\phi (x; x_i, \sigma_x^2)}{p(x)} \right) \left( \frac{\phi (y; y_i, \sigma_y^2)}{p(y)} \right) \left( \frac{\phi (z; z_i, \sigma_z^2)}{p(z)} \right)}{\sum_{i=1}^{n} \left( \frac{\phi (x; x_i, \sigma_x^2)}{p(x)} \right) \left( \frac{\phi (y; y_i, \sigma_y^2)}{p(y)} \right)} \]

(10)
TABLE III

<table>
<thead>
<tr>
<th>Group</th>
<th>Groups used to create model</th>
<th>% SI within interval</th>
<th>% BG within interval</th>
<th>BG interval width (mmol/L)</th>
<th>BG point prediction error (mmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>[25th - 75th]</td>
<td>[5th - 95th]</td>
<td>[25th - 75th]</td>
<td>[5th - 95th]</td>
</tr>
<tr>
<td>Group 1:</td>
<td>[-, 2, 3, 4, 5]</td>
<td>57.4%</td>
<td>92.2%</td>
<td>56.4%</td>
<td>90.9%</td>
</tr>
<tr>
<td>Group 2:</td>
<td>[1, -, 3, 4, 5]</td>
<td>68.7%</td>
<td>92.1%</td>
<td>64.3%</td>
<td>91.5%</td>
</tr>
<tr>
<td>Group 3:</td>
<td>[1, 2, -, 4, 5]</td>
<td>67.0%</td>
<td>94.8%</td>
<td>62.4%</td>
<td>94.0%</td>
</tr>
<tr>
<td>Group 4:</td>
<td>[1, 2, 3, - , 5]</td>
<td>59.2%</td>
<td>91.8%</td>
<td>56.2%</td>
<td>90.8%</td>
</tr>
<tr>
<td>Group 5:</td>
<td>[1, 2, 3, 4 , -]</td>
<td>61.7%</td>
<td>95.6%</td>
<td>57.1%</td>
<td>92.7%</td>
</tr>
<tr>
<td>Overall</td>
<td>[1, 2, 3, 4, 5]</td>
<td>62.6%</td>
<td>93.4%</td>
<td>59.1%</td>
<td>92.2%</td>
</tr>
</tbody>
</table>

Fig. 5. Proportion of in-sample predicted SI within the 25%–75% prediction bounds and number of predictions (=number of data points) grouped by SI range.

Fig. 6 shows probability plots for c = 1.0, c = 0.5, and c = 0.1. As expected, the probability distribution becomes less smooth for lower values of c, particularly for higher values of SI, where data are less dense due to the modification of the kernel bandwidth and subsequent degree of smoothing. Additionally, for lower values of c, the (25th–75th) and (5th–95th) percentile probability bounds for SI_{i,n}+1 are essentially equal for some regions of SI_{i,n} due to sparse data, which may contribute to the increase in coverage proportion for c less than 0.1, and show that the model is possibly overfitting the data.

IV. DISCUSSION

The lag-1 stochastic model presented in this paper has also been employed on a cohort of adult intensive care patients [46], [47]. The results of Lin et al. also show that the model produces...
TABLE IV

<table>
<thead>
<tr>
<th>$c$</th>
<th>% of $S_I$ within probability bounds</th>
<th>% of BG within prediction bounds</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>[25th - 75th]</td>
<td>[5th - 95th]</td>
</tr>
<tr>
<td>0.05</td>
<td>50.8%</td>
<td>90.5%</td>
</tr>
<tr>
<td>0.08</td>
<td>50.8%</td>
<td>90.6%</td>
</tr>
<tr>
<td>0.1</td>
<td>50.7%</td>
<td>90.9%</td>
</tr>
<tr>
<td>0.2</td>
<td>51.7%</td>
<td>90.8%</td>
</tr>
<tr>
<td>0.3</td>
<td>52.2%</td>
<td>90.6%</td>
</tr>
<tr>
<td>0.5</td>
<td>54.7%</td>
<td>90.9%</td>
</tr>
<tr>
<td>1.0</td>
<td>62.6%</td>
<td>93.4%</td>
</tr>
<tr>
<td>2.0</td>
<td>75.4%</td>
<td>96.9%</td>
</tr>
<tr>
<td>Ideal</td>
<td>50%</td>
<td>90%</td>
</tr>
</tbody>
</table>

Fig. 6. Probability-bound determination using local variance estimator modified by a constant $c$. The lower values of $c$ produce a less smooth probability distribution with greater variance at higher $S_I$. The individual points represent raw $S_I$ data. The solid lines represent the 5%, 25%, 50%, 75%, and 95% probability bounds.

Fig. 7. Comparison of in-sample predicted $S_I$ within arbitrary probability bounds ($2a$) against ideal proportion of predictions within bounds (45° line) for $c = 1.0$ and $c = 0.5$, where interquartile range is the $2a = 50\%$ case.

The kernel density estimator method employed in this stochastic model produces a smooth, physiologically likely distribution, and a conservative model. This conservatism can provide a layer of safety as wider probability bounds would be more likely to capture dynamics and changes not observed in the cohort used to fit the model. However, wider coverage bands may also impact on glycemic control performance, as using a conservatively wide probability band to avoid potential hypoglycemia may needlessly force a controller to maintain a mildly hyperglycemic state. The overall BG width of the (5th–95th) percentile probability band for $c = 1.0$ was 2.32 mmol/L, which would likely have a significant impact on performance for a controller targeting a typical 4–7 mmol/L target range.

A tradeoff between model bias and variance is thus required. The cross validation showed consistent results, suggesting that the cohort dataset is large enough to satisfy the assumption that the model contains enough data points to reasonably reflect the vast majority of target patients presented in the Christchurch Women’s Hospital NICU. Modifying the local data density variance estimator showed that less variance ($c < 1.0$) resulted in distributions that more accurately reflected the observed data prediction coverage. The ideal value of the adjustment parameter $c$ was found to be in the range of 0.1–0.5. However, Fig. 6 shows that the probability bounds of the distribution for relatively small $c$ are not smooth, suggesting that this particular distribution is overmodeling the data, where a smoother variation is physiologically more likely. The method shown in Fig. 7
provides a means to produce smooth probability bounds with a customizable tradeoff between glycaemic control performance and hypoglycemic protection. Overall, \( c = 0.5 \) appeared to provide the most suitable tradeoff between model bias and variance for this cohort.

The results in Fig. 5 suggest that the overestimation of the probability bounds does not occur in regions of sparse data, but rather in regions of dense data. The extension of the model to incorporate lag-2 effects in (10)–(12) had a minimal effect on this dataset. Thus, the local data density variance estimator may be a source of the overestimation. The variance estimator employed here is aligned with the cardinal axes—the major and minor axis of the ellipse that forms from the contours of each individual distribution in (8) is aligned in the x and y directions. A further modification may incorporate a rotation of the distribution—such that the variance in each distribution is described by three parameters (\( \sigma_x, \sigma_y, \) and \( \theta \)) [54] to represent scaling in the x and y directions and rotation, respectively.

Clinically, the absence of lag-2 effects is interesting. It says that variation is hour-to-hour in these neonates and effectively random over that period with no buildup. A second clinical outcome or interpretation is that major changes in the neonate’s condition are not likely over a longer period and are, thus, more acute. The lack of significant lag-2 effects appears to indicate that significant changes in \( S_I \), and thus, infant condition may occur largely within 1-h windows. A detailed prospective study, possibly utilizing continuous glucose monitoring, may provide more data to further clarify this preliminary result.

The cohort data represents 3567 h of fitted \( S_I \) data over 25 patients. BG measurement density for these patients was typically 2–4 per hour. Thus, there may be some effect introduced by interpolating between BG measurements to fit \( S_I \). However, a lag-1 model produced by only taking values of the \( S_I \) parameter one hour before and one hour after each BG measurement still yielded 64.0\% of predicted \( S_I \) within the 25th–75th percentiles, overshooting the 50\% expected value. This result suggests that the BG interpolation is not playing a significant role in this dataset. Higher BG measurement density may reveal more dynamics that could be used to refine the BG system model, and subsequently, the stochastic model. However, such greater measurement density is ethically difficult in the very low-blood-volume NICU population [3].

The nonparametric formulation of the kernel density model automatically accounts for multimodality, which may reveal patterns in large changes in \( S_I \). Clinically, such a sudden or large change could be due to a sudden worsening of condition. Thus, the multimodal model may provide some measure of estimating the risk of sudden significant change (for the worse), particularly at higher \( S_I \), which might offer some significant clinical benefit.

Overall, this stochastic method provides predictions based on a cohort-wide dataset. The prediction bounds for less dynamic patients would typically be more conservative than necessary to account for more dynamic patients that make up the patient population. Thus, the probability bounds are optimized in a cohort sense, but not necessarily on a per-patient basis. Statistical methods, such as autoregressive integrated moving average error.
(ARIMA) modeling, may provide enhanced prediction performance by customizing the model to the individual patient in real time. However, such models require substantial individualized patient data (e.g., 12–48 h) that may not be available at the commencement of real-time glycaemic control for a given infant. Real-time continuous glucose monitors have been used in neonatal cohorts [55] and may provide additional data for more accurate parameter fitting and forecasting; however, readings on current devices exhibit wide confidence bands, and lower sensitivity and specificity at low BG [55]. Thus, the cohort-wide model presented here could be employed to provide prediction bounds until a suitable amount of data are generated to employ a reliable patient-specific model. Semi-Markov methods may also be employed in \( S_I \) forecasting, and can provide an avenue to assess the variable of BG measurement and control intervention timings to test robustness to real-world uncertainties and delays.

V. CONCLUSION

Lag-1 and lag-2 stochastic models are developed to provide \( S_I \) predictions based on a set of identified, time-varying \( S_I \) data for a neonatal intensive care cohort. The model provides prediction estimators with greater, more conservative, coverage than expected from the probability bounds. Incorporating lag-2 effects did not improve the coverage proportion, and greater coverage overestimation in regions of higher data density pointed to the variance estimator based on local data density as a likely source of overestimation. Modifying the data density estimator by introducing a constant scaling factor showed that appropriate coverage was obtained at approximately 10%–50% of the original value. However, the probability bounds were no longer smooth or as physiologically realistic for very low values near 10%. A value of \( c = 0.5 \) provided the best tradeoff of bias and variance. Smooth probability bounds containing an appropriate proportion of prediction coverage can be obtained by choosing probability bounds to obtain the desired prediction and glycaemic control performance.

Finally, the model and approach has also provided useful clinical insight. The model skew in distribution at higher \( S_{1,n} \) values to account for sudden, larger negative changes in \( S_I \) that appears to match clinical reality and provides insight, for at least this cohort, into the risk or likelihood of such changes.

REFERENCES


Authors’ photographs and biographies not available at the time of publication.