Model-based targeted control with stochastic forecasting for regulation of glycemia in ELBW neonates

A. Le Compte, A. Lynn, J.G. Chase, G.M. Shaw, D.S. Lee, X.W. Wong, J. Lin, C.E. Hann

INTRODUCTION

Hyperglycemia occurs in 40-80% of very premature, low birthweight infants. The pathogenesis of hyperglycemia in critically ill adults and preterm infants may differ. The mechanisms responsible for hyperglycemia in preterm infants are related to immaturity of the glucose regulatory system, in addition to clinical stress.

This condition has been linked to worsened outcomes, including increased incidence of sepsis, increased ventilator dependence, retinopathy of prematurity, hospital length of stay and mortality

Often, glucose restriction is used to control high blood glucose levels, but this can deprive the neonate of crucial energy required to promote growth. Continuous insulin infusion has thus been proposed as a solution to reduce plasma glucose concentrations and optimize nutrition in these small infants.

However, great heterogeneity is the hallmark of neonatal glucose metabolism. Thus, the emerging use of insulin carries a significant risk of hypoglycemia due to patient response variations to insulin over time.

An adaptive model of the fundamental glucose regulatory dynamics in neonates can track an infant's sensitivity to exogenous insulin in real-time. Targeted control forecasts the range of likely future glucose levels to select the optimal insulin rate, adapting control to the infant's current metabolic state.

MODELS AND METHODS

A metabolic computer system model, clinically validated in adult intensive care patients and virtual trials using neonatal data, is used to provide tight control in very low birth weights infants. Median model BG fit error is 2.4% on retrospective data and forecast errors are 5.2% to 13.6% for 1 to 4 hour BG predictions.

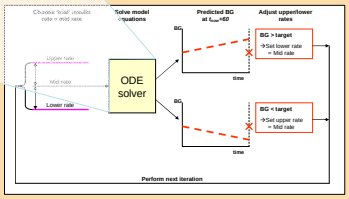
$$\dot{G} = -p_G.G - S_I.G.\frac{Q}{1+\alpha_G Q} + \frac{P(t) + \left(P_{END} * m_{body}\right) - \left(CNS * m_{brain}\right)}{\left(V_{G,frac}(t) * m_{body}\right)}$$

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

$$\dot{I} = -\frac{nI}{1+\alpha_I I} + \frac{u_{ex}(t)}{\left(V_{I,frac} * m_{body}\right)} + e^{-(k_d + k_{sc}(t))} I_B$$

Insulin infusions were modulated using an iterative bisection algorithm to match forecasted BG to a pre-determined target based on measurements every 2-3 hours (max 12 measurements/day).

Stochastic forecasting models quantify the expected variation of insulin sensitivity based on retrospective patient data. BG system equations are solved using successive values of forecasted insulin sensitivity using to yield forecast BG range.

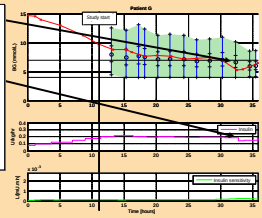


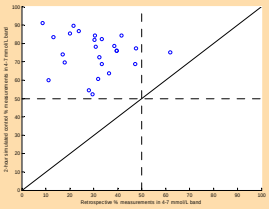
SIMULATION STUDIES

Simulation studies performed using insulin sensitivity profiles generated from 25 retrospective episodes of insulin. Controller refined *in-silico* before clinical implementation.

Stochastic model forecasts drove controller decisions for more insulin resistant and/or dynamic patients, preventing episodes of hypoglycaemia.

- Change in insulin sensitivity contained
- Insulin infusion rate adjusted
- More aggressive control may have created hypo event for this patient
- Controller tolerated period of higher BG to balance risk of changes in patient condition.

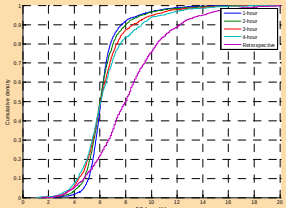


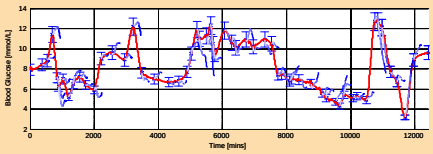


Comparison of percentage of BG measurements within the 4 – 7 mmol/L BG range for retrospective and 2-hour simulated control. Each circle represents one of 25 patient profiles.

Improved control in simulation with up to 65% - 82% more measurements inside target 4 – 7 mmol/L BG range indicated on both per-patient (left) and whole-cohort (below) scales.

Insulin sensitivity exhibits greater inter-patient variance in neonates versus adults. Therefore, optimal control requires adaptive methods in this population.





(Above) Empirical cumulative distribution functions of BG measurements for retrospective hospital control versus simulated model-based control trials of 1, 2, 3 and 4-hour measurement and intervention frequency.

(Left) Example of model generated BG response (blue) over 1-4 hour prediction interval. Predictions are generated assuming a constant insulin sensitivity over prediction interval.

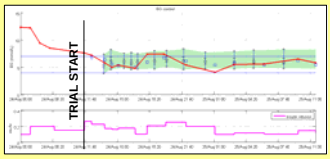
CLINICAL TRIALS

Seven clinical trials up to 24 hours each were performed based on initial blood glucose over 10 mmol/L to initiate insulin. Over all trials median BG was 6.9 (IQR: 5.6 – 7.9, 90%CI: 4.6 – 11.2) mmol/L over 74 measurements. Minimum BG was 3.8 mmol/L.

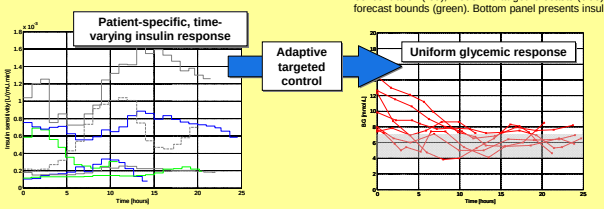
Clinical glycemic variables during trials. Infusion rates are computed as hourly averages.
BG mean and standard deviation are computed using lognormal statistics. EBM = Expressed Breast Milk.

Patient	Median dextrose rate		Total EBM [mL]	Median insulin rate [U/kg/hr]	Geometric BG mean [mmol/L]	Geometric BG StDev [mmol/L]	Max. BG [mmol/L]	Min. BG [mmol/L]	Measurement period, hours	Median insulin sensitivity [L/(mU.min)]
	mg/kg/min	kcal.kg.day								
A	7.1	40.6	0.0	0.025	7.7	1.04	8.7	6.9	2.1	0.45
B	9.4	54.4	5.0	0.040	6.7	1.16	12.3	4.1	1.7	1.25
C	4.1	23.3	0.0	0.068	8.7	1.19	14.4	5.2	1.7	0.14
D	9.6	55.0	3.0	0.052	6.5	1.08	8.0	5.0	2.5	0.7
E	6.8	39.1	11.0	0.116	9.0	1.12	12.6	6.5	2.1	0.2
F	8.2	47.5	4.5	0.069	7.0	1.23	14.5	3.8	1.7	0.5
G	9.4	54.3	2.0	0.191	8.7	1.17	14.7	5.3	1.9	0.14

Within the relatively small study population, a 2.3x spread of dextrose infusion rates were used, and an 8.9x spread of insulin sensitivity was computed. In response, the controller used a 7.6x spread of median insulin infusion rates.



Real-time control trial. Top panel presents measured BG concentration (red), model BG target forecasts (blue) and stochastic forecast bounds (green). Bottom panel presents insulin infusion rate.



Model-fitted insulin sensitivity during trials. Each line represents the hourly evolution of patient sensitivity to exogenous insulin.

Per-patient BG concentration during computerised insulin dosing. The shaded region represents the 4-7 mmol/L target band.

Overall cohort BG target error was 7.6% (0.54 mmol/L) during clinical trials. Distribution of BG prediction errors revealed 69% and 84% of BG measurements within ±10% and ±20% of forecasted value.

BG prediction accuracy and stochastic model prediction coverage.

Patient	Median BG prediction error (absolute)		BG within IQR forecast range	BG within 5%-95% forecast range
	[%]	[mmol/L]		
A	19.20%	1.47	33%	83%
B	8.60%	0.52	31%	85%
C	7.60%	0.77	80%	90%
D	8.40%	0.53	33%	100%
E	6.40%	0.48	100%	100%
F	8.50%	0.72	50%	83%
G	5.90%	0.44	92%	100%
Whole cohort	**7.60%**	**0.54**	**62%**	**92%**

Canterbury District Health Board
Te Poari Hauora o Waitaha
UC BIOMEDICAL ENGINEERING
UC UNIVERSITY OF CANTERBURY