Sensitivity of Re-calibrated Continuous Glucose Monitor Data: *How do errors in calibration measurements affect reported hypoglycemia?*

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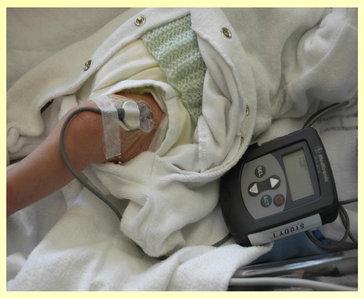
INTRODUCTION

Continuous Glucose Monitors (CGMs) are increasingly used in research settings to examine glucose metabolism in newborn babies, typically with a focus on neonatal hypoglycemia.

Accuracy of these devices depends on the accuracy and timeliness of calibration blood glucose (BG) measurements entered into the CGM device.

This study investigated the effects of calibration timing and measurement errors on output CGM data. There was a focus on the impact these errors had on metrics used to quantify hypoglycaemia.



METHODS

Patient Data

CGM data and blood-gas analyzer reference BG measurements from 155 neonates were used in this study.

Cohort and CGM data details:

No. patients	Age at birth	Avg. length of CGM trace (days)	Avg. calibrations per day
155	>35 weeks	1.79	5.90

Timing Error Models

The delay between measuring BG and entering the value into the CGM for calibration formed the basis of these models. Data from two different critical care units were used to create two models:

1. Waikato Model
2. Christchurch Model

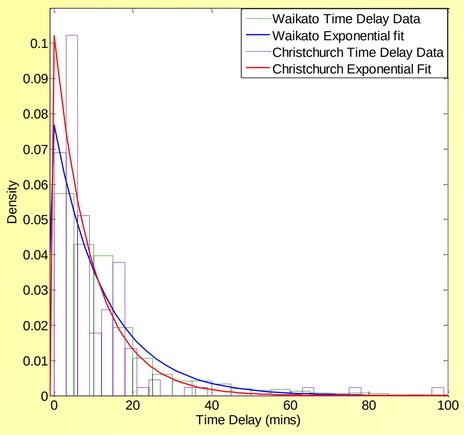


Figure 1: Binned time delay data with exponential fit applied

Measurement Error Models

Measurement error models were created to emulate the performance of three glucometers:

- Abbott Optimum Xceed
- Nova Statstrip GLU
- Roche Accu-chek Inform II

Glucometer BGs were compared to blood gas BGs to determine errors. Errors were stratified based on blood gas BGs and modeled using Gaussian distributions.

Abbott Error Model					
Reference BG (mmol/L)	**< 5.9**	**6.0 - 6.9**	**7.0 – 7.9**	**8.0 – 8.9**	**> 9.0**
Number of measurements	141	277	224	42	40
Error mean (mmol/L)	0.5099	0.5433	0.2299	0.1952	0.635
Error std. dev. (mmol/L)	0.4982	0.7519	0.5521	0.8748	0.3965
Nova Error Model					
Reference BG (mmol/L)		**<6.9**	**7.0 – 7.9**	**>8.0**	
Number of measurements		67	141	21	
Error mean (mmol/L)		-0.0134	-0.0823	-0.1905	
Error std. dev. (mmol/L)		0.2564	0.2471	0.3463	
Roche Error Model					
Number of measurements		174	160	10	
Error mean (mmol/L)		-0.181	-0.4212	-0.27	
Error std. dev. (mmol/L)		0.2615	0.2645	0.0949	

Recalibration

CGM data were recalibrated to make use of accurate calibration BG measurements. Recalibration forced CGM data to pass through the blood gas BG measurements.

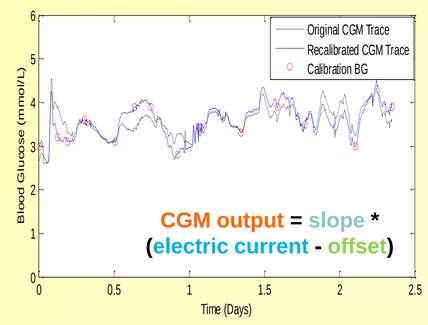


Figure 2 Example of Original CGM output vs. Recalibrated CGM output

Monte Carlo Simulation

Randomly sampled timing and measurement errors were added to calibration BG, prior to recalibration. This process was repeated 1,000 times, resulting in 1,000 different CGM traces for each patient. Hypoglycemia in each trace was quantified using: 1) number of events, 2) duration of hypoglycemia, and, 3) hypoglycemic index. The median difference in hypoglycemia across 1,000 runs per patient is presented as median [25th - 75th] (5th - 95th) percentiles for the cohort.

RESULTS

Overall Cohort Results

Baseline hypoglycemia in cohort	
Number of events	1 [0 4] (0 13)
Duration (%)	1.10 [0 10] (0 29)
Hyperglycemic Index	0.878 [0 17] (0 87)

Baseline hypoglycemia in this cohort and **variation in hypoglycemia** due to timing and measurement error

Change to hypoglycaemia metrics due to timing and measurment error - Median [25th-75th percentile] (5th-95th percentile)				
Number of events	*No measurement error*	*Abbott*	*Nova*	*Roche*
No Timing Error		-1 [-3 0] (-8 0)	0 [0 1] (-3 2)	0 [0 2] (-3 4)
Waikato	0 [0 1] (-2 2)	-1 [-2 0] (-8 0)	0 [0 1] (-3 2)	1 [0 2] (-3 4)
Christchurch	0 [0 0] (-2 2)	-1 [-2 0] (-8 0)	0 [0 1] (-3 2)	1 [0 2] (-3 4)
Duration (%)	*No measurement error*	*Abbott*	*Nova*	*Roche*
No Timing Error		-4.68 [-9.0 -1.0] (-17 0)	0.49 [0.1 1.6] (-0.1 6.7)	4.45 [1.8 10] (0 23)
Waikato	0.21 [0 1.3] (-1.7 4.1)	-4.25 [-9.0 -1.0] (-15 0)	1.02 [0.1 3.2] (-0.5 8.7)	5.36 [2.1 11] (0 26)
Christchurch	0.17 [0 0.9] (-1.5 3.6)	-4.40 [-8.5 -0.6] (-15 0)	0.84 [0 2.7] (-0.4 8.1)	5.23 [2.2 11] (0 25)
Hyperglycemic Index	*No measurement error*	*Abbott*	*Nova*	*Roche*
No Timing Error		-7.64 [-22 0] (-59 0)	2.93 [0.5 8.2] (0 16)	19.4 [4.2 38] (0 70)
Waikato	0.27 [0 3.1] (-3.3 14)	-6.84 [-22 -0.3] (-48 0)	3.84 [0.7 12] (-0.1 27)	20.8 [4.1 42] (0 82)
Christchurch	0.18 [0 2.3] (-2.9 11)	-7.24 [-21 -0.4] (-50 0)	3.77 [0.60 11] (0 23)	21.3 [4.7 42] (0 80)

Impact of Bias

Comparing Abbott results to Roche results, the impact of bias on hypoglycemia metrics was clear. The positive bias in the Abbott error caused hypoglycemia to be under reported, while the negative bias in Roche error caused hypoglycemia to be over reported.

Figure 3: CGM traces showing the effect of Abbott measurement error (top), Nova measurement error (middle), and, Roche measurement error (bottom). The colored band in each plot shows the 5th-95th percentile range in CGM data over 1000MC simulations.

State of the Trace

Generally, timing Error was dominated by measurement error **BUT** the state of the trace at the time of calibration played a substantial role in how measurement and timing errors affected hypoglycemia metrics

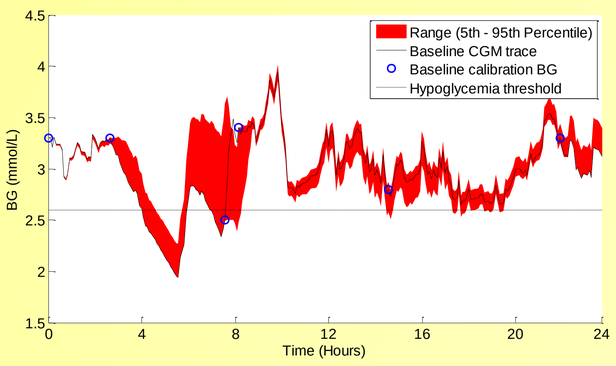


Figure 4: Example CGM trace with Waikato timing error only

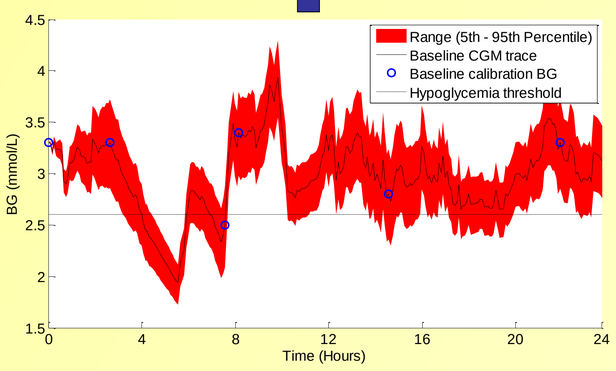


Figure 5: Example CGM trace with Nova Measurement error only

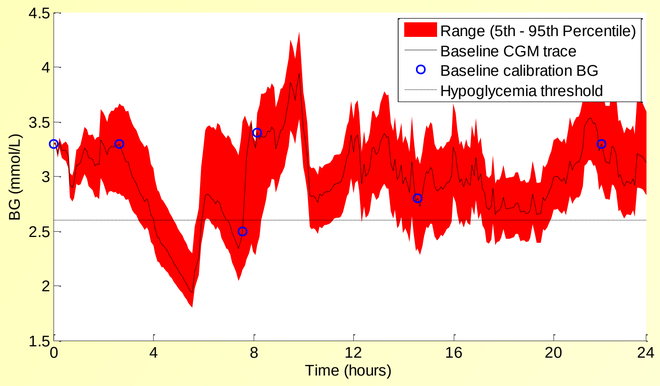


Figure 6: Example CGM trace with Waikato timing and Nova measurement error

CONCLUSION

Bias can have a significant effect on hypoglycemia metrics and bias can differ between glucometers. Hence, results from studies of hypoglycemia may contain substantial variation simply due to the technology used to measure BG. If the CGM trace is changing rapidly during calibration timing error can have an increased impact on the hypoglycemia metrics – it is vital the calibration BG is obtained and entered quickly. If the trace is steady around 2.6mmol/L measurement error can have a large impact on hypoglycemia metrics.