Continuous Glucose Monitoring: Using CGM to Guide Insulin Therapy Virtual Trials Results

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Abstract: Continuous glucose monitoring (CGM) devices can measure blood glucose levels through interstitial measurements almost continuously (1-5min sampling period). However, they are not as accurate as glucose readings from blood measurements. The relation between tissue and blood glucose is dynamic and the sensor signal can degrade over time. In addition, CGM readings contains high frequency noise and can drift between measurements. However, maintaining continuous glucose monitoring has the potential to improve the level of glycemic control achieved and reduce nurse workload. For this purpose, a simple model was designed and tested to see the effect of inherent CGM error on the insulin therapy protocol, STAR (Stochastic TARgeted).

An error model was generated from 9 patients that had one Guardian Real-Time CGM device (Medtronic Minimed, Northridge, CA, USA) inserted into their abdomen as part of an observation trial assesing the accuracy of CGM measurements compared to a blood gas analyser and glucometer readings. A resulting error model was then used to simulate the outcomes if the STAR protocol was guided by CGM values on 183 virtual patients. CGM alarms for hyper- and hypo-glycaemic region were included to improve patient safety acting as 'guardrails'. The STAR CGM protocol gave good performance and reduced workload by ~50%, reducing the number of measurements per day per patient from 13 to 7. The number of hypoglycaemic events increased compared to the current STAR from 0.03% <2.2mmol/L to 0.32%. However, in comparison to other published protocols it is still a very low level of hypoglycaemia and less than clinically acceptable value of 5% <4.0mmol/L. More importantly this study shows great promise for the future of CGM and their use in clinic. With the a newer generation of sensors, specifically designed for the ICU, promising less noise and drift suggesting that a reduced nurse workload without compromising safety or performance is with in reach.

1. INTRODUCTION

Continuous glucose monitoring (CGM) devices, with their 1-5 minute measurement interval, have recently been used to monitor critical care patients' blood glucose (BG) in a more effective, less invasive manner than intermittent bedside BG measurements alone (Pretty et al., 2010, Signal et al., 2010, Beardsall et al., 2005, Harris et al., 2010, Holzinger et al., 2010, Brunner et al., 2011). CGM devices typically consist of a small pager-like monitoring device that receives a signal from a sensor inserted into the subcutaneous layer, just beneath the skin. Calibration algorithms convert the signal into a meaningful glucose concentration by comparing it to known calibration BG measurements, which are entered into the monitor by the user every 6-12 hours.

Typical glycaemic control protocols require BG measurements every 1-4 hours (Evans et al., 2012, Lonergan et al., 2006, Plank et al., 2006, Blaha et al., 2009), resulting in approximately 13 blood draws a day per patient. This represents a significant part of nurse workload(Carayon et al., 2005, Holzinger et al., 2005). CGM devices have the potential to drastically reduce the number of BG measurements per day while ensuring patient safety and increased time in the desired BG target band.

However, CGM devices can display suboptimal accuracy resulting from error or delay in calibration measurement, sensor drift and delayed glucose diffusion (Castle et al., 2010, Facchinetti et al., 2014). Thus, before CGM can become ubiquitous in the care of critically ill patients these errors and the effects of these errors on BG control must first be quantified and understood.

This paper presents a simple CGM error model, including drift, created by comparing CGM readings and true BG values using data from 9 patients admitted to the Christchurch Intensive Care Unit (ICU). The impact of the CGM error is then evaluated in virtual trials using the STAR protocol (Stochastic TARgeted) (Evans et al., 2012), which is now standard care in Christchurch ICU. Alarms and guardrail threshold settings were also investigated to insure patient safety especially in the hypoglycaemic region. These alarms are typically built in to CGM devices and would thus require no extra programming to use.

2. PATIENTS & METHODS

2.1 CGM Error Model

2.1.1 Patients

This part of the study uses data from 9 patients admitted to the Christchurch Hospital ICU that were enrolled in an observational pilot study of CGM (Signal, 2013). Inclusion criteria was two consecutive BG measurements greater than 8mmol/L, indicating the need for insulin therapy using the STAR protocol. Exclusion criteria were an anticipated ICU admission period of less than 3 days. All patients had one Guardian Real-Time CGM device (Medtronic Minimed, Northridge, CA, USA) inserted into their abdomen, providing real-time CGM values every 5 minutes. The patients all remained under insulin therapy treatment for > 24 hours. This study was approved by the Upper South Regional Ethics Committee, New Zealand. Table 1 summaries the patient demographics.

Table 1. Summary of CGM study patient characteristics. Data are show as median [interquartile range] where appropriate.

N	9
Age (years)	57 [38-64]
Gender (M/F)	5/4
APACHE II score	22 [17 – 28]
Hospital mortality (L/D)	(5/4)
Duration of CGM (days)	3.6 [2.5 – 5.7]

2.1.2 Model

A simple CGM error model was created, separating the error in to two distinct parts of noise and drift defined:

$$CGM = BG_{real} + noise + drift \qquad \text{Eq.1}$$

Where drift was assumed to be a constant linear bias. It was defined as the rate of increase in discrepancy between the CGM trace and reference BG measurements over time between calibration BG measurements. Thus, drift was assumed to start at a calibration measurement and finish at the following calibration measurement.

The magnitude of the accumulated drift between any two calibrations was found using a drift distribution created by comparing true BG values and CGM values for each paired data. The absolute values of the drift error was taken and the errors were normalised with regards to the time spent since last CGM calibration to obtain a drift per hour value. Figure 1 shows the error distribution achieved for each patient and the entire cohort.

The error distribution of the entire cohort was best described by an exponential distribution with a mu = 0.4764. It was assumed that positive and negative drifts are equitably distributed (50-50).

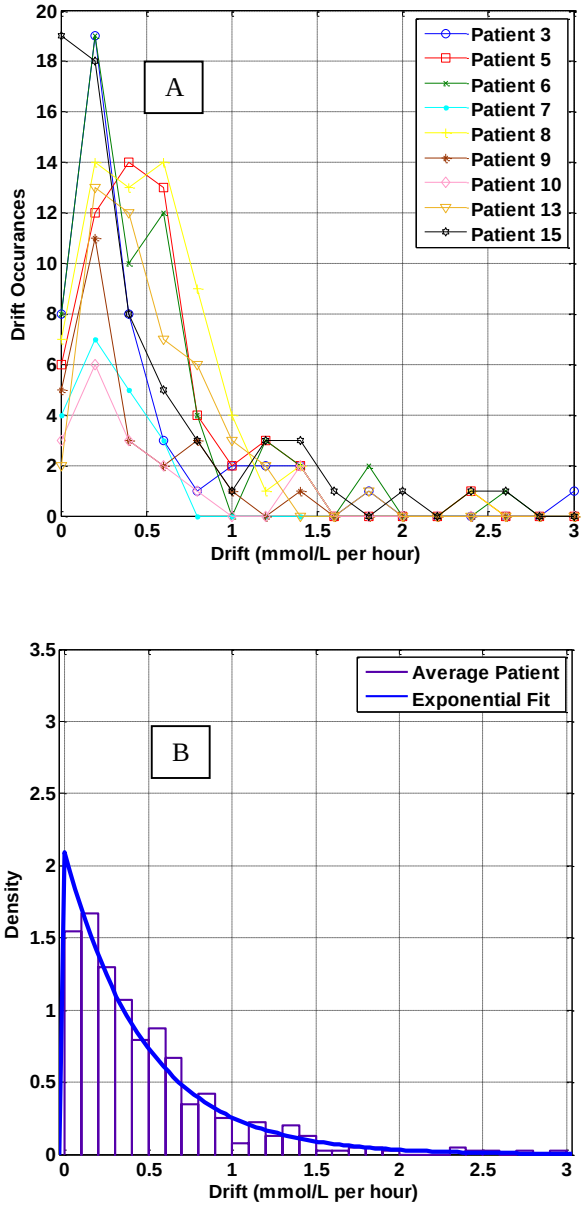

Figure 1: Distribution for each individual patient (A) and the entire cohort (B)

High frequency sensor noise was generated using Gaussian noise distribution from Golberg et al. (Goldberg et al., 2004). This distribution can been seen in Figure 2 where it is ¼ of the size of the original distribution published. This value was selected to match the data observed in the observational trials. The reduction represents the significant improvement in sensor noise since its publication. It is evident then from Figure 3 that this combination of error models to create a CGM trace in simulation displays trends and measurement error to that of a real CGM trace. A range of type CGM traces were chosen to be displayed in Figure 3 to illustrate the robustness of the model.

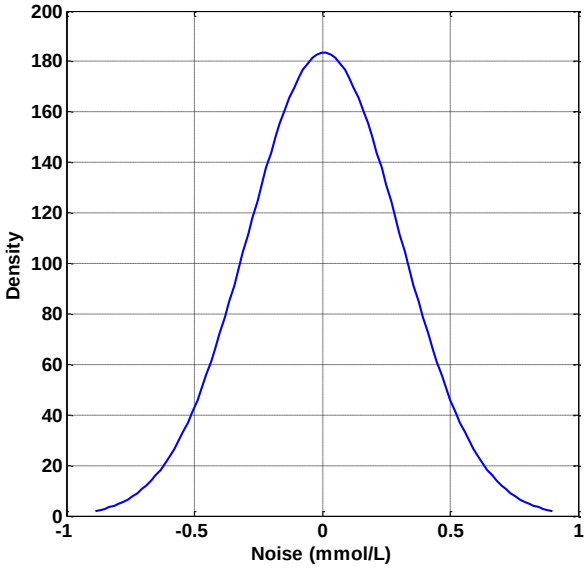

Figure 1: 1/4 Goldberg noise distribution used to model the high frequency noise seen in CGM signals

2.2 Virtual Trials

The effect of CGM error on insulin therapy was tested using a clinically validated virtual trial approach (Chase et al., 2010). This approach uses virtual patients, each comprising an insulin sensitivity (SI) profile identified from the clinical data of a real patient using a pharmacokinetic-pharmacodynamic (PK-PD) model of the glucose-insulin system (Lin et al., 2011). The SI profile can then be used with the PK-PD model to simulate the glycaemic outcome of different insulin and nutrition interventions.

In this study the STAR protocol was tested. In addition, CGM measurements were simulated using Equation 1. The impact on performance and safety using CGM instead of the ~13 measurements/day required by STAR (Fisk et al., 2012) was then assessed.

2.2.1 Patients

Virtual trials were performed using retrospective data from 183 patients treated by accurate glycaemic control protocols at Christchurch Hospital ICU between 2011 and 2013. All patients were treated with the tablet-based STAR protocol for > 24hrs. Cohort demographics are presented in Table 2.

Table 2. Cohort demographics of the patients used for virtual trials. Data are presented as median [interquartile range] where appropriate.

N	183
Age (years)	65 [54-72]
Gender (M/F)	123/60
APACHE II score	21 [15 – 25]
Hospital mortality (L/D)	131/52

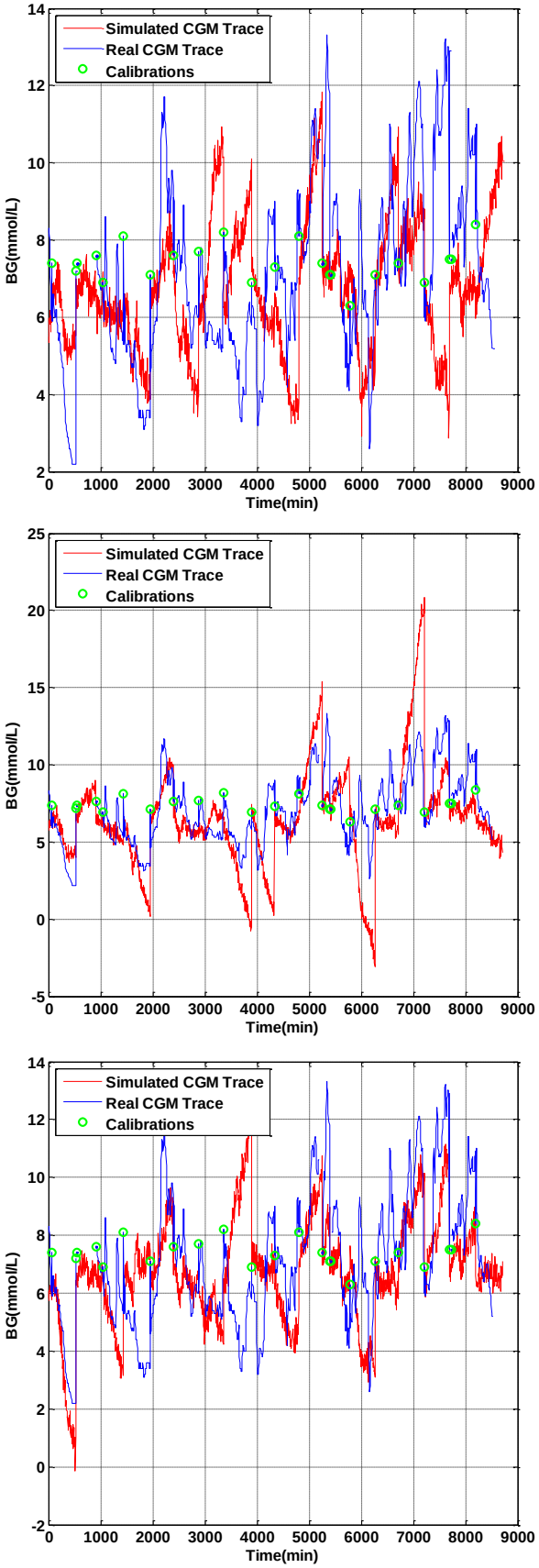

Figure 3: Comparing CGM traces simulated using the CGM error model and BG calibration measurements to the real CGM trace from observational trials.

2.2.2 Alarm Design

To ensure patient safety from hypoglycaemia (BG < 4.5 mmol/L) or hyperglycaemia (BG > 9 mmol/L), CGM alarms were used in simulation. Every time CGM BG values reach the upper or lower threshold, a BG measurement was performed. If the BG value at the lower threshold (CGM BG < 4.5 mmol/L) differed by more than 0.5mmol/L the CGM device was recalibrated, correcting the sensor drift. The same process was undertaken at the upper threshold (CGM BG > 9 mmol/L) if the measurements differed by more than 1.0mmol/L. The threshold values were selected to optimise performance, safety and workload. Otherwise CGM measurements were used as BG measurements in STAR to determine insulin and nutrition. These alarms values were optimised by repeated simulation with hypoglycaemic alarm values ranging from 3-5mmol/L and hyperglycaemic alarm values ranging from 8-10mmol/L both in steps of 0.5mmol/L. The alarm values selected provided the best trade off between performance, safety and workload.

2.3 Analysis Methods

Monte Carlo (MC) methods were employed to reduce the impact of randomly sampled outliers on results. A 50-run MC simulation was completed for each virtual patient. Blood glucose values were generated using the clinically validated Intensive Control Insulin-Nutrition-Glucose (ICING) model of the glucose-insulin system (Lin et al., 2011) was used. Sensor drift and noise was added to the measurements using the CGM model. These BG measurements were then given to the STAR protocol generate insulin and nutrition interventions. This situation simulates what it would be like if CGM devices were being used to guide the protocol in clinic.

Metrics such as %time in the desired 4.4 – 8mmol/L band, %time below 2.2mmol/L and number of blood draws per patient per day were used to assess the performance, safety and resulting workload of using CGM devices to guide the STAR protocol. Results were compared to a 50-run MC of the STAR protocol without CGM error and the clinical results of the 183 patients.

3. RESULTS & DISCUSSION

3.1 Virtual Trials Results

During virtual trials, the STAR protocol guided by CGM measurements achieved a median BG of 7.0 mmol/L with 72.2% time in the desired 4.4-8.0 mmol/L target band. Table 3 summarises the performance of the STAR CGM protocol and, for comparison, also shows clinical data and results from virtual trials of the same patients with the STAR protocol without the additional CGM error model.

Table 3 illustrates the compromise in target-band performance that was necessary with the STAR CGM protocol to meet safety and workload requirements. Compared with clinical results and STAR, time in the 4.4-8.0 mmol/L band was reduced by approximately 15%. However, the average measurement interval increased by ~50%.

Importantly, the STAR CGM protocol is still safe for patients even with the increased error in BG measurements. STAR CGM has less time in the hypoglycaemic region than many other published protocols (Finfer et al., 2012, Preiser et al., 2008, Brunkhorst et al., 2008, Bagshaw et al., 2009, Treggiari et al., 2008) which require much hire number of blood draws per day. The time below 4.0mmol/L is below a clinically specified value of 5%.

Table 3. Results of virtual trial simulations as well as clinical data. Data are presented as median [interquartile range] where appropriate. STAR MC contains no variation as error is not added to the measurements generated in simulation. Hence, there is no median [IQR] for these values.

Whole cohort statistics	**STAR MC**	**STAR CGM MC**	**Clinical**
N	183	183	183
BG meas/day/ patient	13.5 [12-16]	7.00 [5.9-8.6]	13.0
BG (mmol/L)	6.99 [6.0-8.2]	7.06 [6.0-8.3]	6.80 [5.9-8.0]
% time in 4.4-8.0 mmol/L	81.0	72.2 [72-73]	81.3
% time < 4.4 mmol/L	1.59	4.7 [4.6-4.9]	1.69
% time < 2.2 mmol/L	0.03	0.320 [0.28 - 0.37]	0.01

It is worth to noting that these results represent a worst case scenario as the STAR protocol was not modified to take into account the real-time BG readings available or the trend data. Thus, additional dextrose/insulin boluses when hypo/hyper alarms are triggered and proved accurate would most likely increase the performance and safety seen. However, this would increase the workload required and this initial investigation aimed to see how much the current workload could be reduced using the current standard of care.

Also the real-time Guardian devices the error model was created from were not designed for clinical use. These CGM devices are designed to help Type I and II diabetic patients regulate their BG levels. Thus, there are many factors when using these devices in critical care that are known to impact the performance, such as patients diagnosed with sepsis, septic

shock and peripheral oedema (Lorencio et al., 2012). Additionally certain medications/therapies commonly used in ICU, such as paracetamol, can influence CGM performance (Moser et al., 2010). Therefore, the newer generation of sensors that are emerging specifically designed for hospital use, such as the Medtronic Sentrino (Medtronic, 2012), are likely to be more accurate and be less affected by these factors all of which would improve performance.

Drift reduces performance the most as it is an unseen bias. To investigate the effect of reduced drift half guardian noise was simulated with on the same cohort. This produced less draws per day, only 1.38% time <4.4mmol/L and 78% time in the desired 4.4-8mmol/L band. These results are much improved and show great promise for the future CGM devices being developed to aid in reducing nurse workload.

4. CONCLUSIONS

The study aimed to show the effects of using a CGM device to guide insulin therapy. The STAR CGM protocol gave good performance and reduced workload by ~50%. The increase of hypoglycaemic events compared to the current STAR protocol was of concern but in comparison to other published protocols it is still a very low level of hypoglycaemia and is well under the clinically acceptable value of 5% below <4.0mmol/L. The amount of hypoglycaemic could be reduced by integrating trend data and hypoglycaemic alarms in to the STAR protocol allowing glucose boluses to be delivered after alarms identified as accurate.

More importantly this study shows great promised for the future of CGM and their use in clinic. With the newer generation of sensors being specifically designed for the ICU environment promising less error and drift. Results from MC using half the noise of guardian data suggests that a workload can be significantly reduced without compromising safety or performance.

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