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SYMPOSIUM

Hypoglycemia Detection in Critical Care Using Continuous Glucose Monitors: An *in Silico* Proof of Concept Analysis

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Abstract

Background:

Tight glycemic control (TGC) in critical care has shown distinct benefits but has also been proven difficult to obtain. The risk of severe hypoglycemia (<40 mg/dl) has been increased significantly in several, but not all, studies, raising significant concerns for safety. Continuous glucose monitors (CGMs) offer frequent measurement and thus the possibility of using them for early detection alarms to prevent hypoglycemia.

Methods:

This study used retrospective clinical data from the Specialized Relative Insulin Nutrition Titration TGC study covering seven patients who experienced severe hypoglycemic events. Clinically validated metabolic system models were used to recreate a continuous blood glucose profile. *In silico* analysis was enabled by using a conservative single Gaussian noise model based on reported CGM clinical data from a critical care study [mean absolute percent error (MAPE) 17.4%]. A novel median filter was implemented and further smoothed with a least mean squares-fitted polynomial to reduce sensor noise. Two alarm approaches were compared. An integral-based method is presented that examined the area between a preset threshold and filtered simulated CGM data. An alarm was raised when this value became too low. A simple glycemic threshold method was also used for comparison. To account for random noise skewing the results, each patient record was Monte Carlo simulated 100 times with a different random noise profile for a total of 700 runs. Different alarm thresholds were analyzed parametrically. Results are reported in terms of detection time before the clinically measured event and any false alarms. These retrospective clinical data were used with approval from the New Zealand South Island Regional Ethics Committee.

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Abbreviations: (APE) absolute percent error, (BG) blood glucose, (CGM) continuous glucose monitor, (FIR) finite impulse response, (ICU) intensive care unit, (IQR) interquartile range, (LMS) least mean squares, (MAPE) mean absolute percent error, (SD) standard deviation, (SPRINT) Specialized Relative Insulin Nutrition Titration, (TGC) tight glycemic control

Keywords: alarm, blood glucose, continuous glucose monitor, glycemic control, hypoglycemia, sensor

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Abstract cont.

Results:

The median filter reduced MAPE from 17.4% [standard deviation (SD) 13%] to 9.3% (SD 7%) over the cohort. For the integral-based alarm, median per-patient detection times ranged, *t*, from –35 minutes (before event) to –170 minutes, with zero to two false alarms per patient over the cohort and different alarm parameters. For a simple glycemic threshold alarm (three consecutive values below threshold), median per-patient alarm times were –10 to –75 minutes and false alarms were zero to seven; however, in one case, five of seven subjects never alarmed at all, despite the hypoglycemic event.

Conclusions:

A retrospective study used clinical hypoglycemic events from a TGC study to develop and analyze an integral-based hypoglycemia alarm for use in critical care TGC studies. The integral-based approach was accurate, provided significant lead time before a hypoglycemic event, alarmed at higher glycemic levels, was robust to sensor noise, and had minimal false alarms. The approach is readily generalizable to similar scenarios, and results would justify a pilot clinical trial to verify this study.

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Introduction

Critically ill patients often experience stress-induced hyperglycemia and high levels of insulin resistance, even with no prior diabetes.[1–7] Hyperglycemia worsens outcomes, increasing the risk of severe infection,[8] myocardial infarction,[1] and critical illness such as polyneuropathy and multiple organ failure.[7] The occurrence of hyperglycemia, particularly severe hyperglycemia, is associated with increased morbidity and mortality in this group of patients.[1,3]

Some studies have shown that tight glucose control (TGC) reduced intensive care unit (ICU) patient mortality by 45% following control limits of 110 to 140 mg/dl.[7,9–11] However, there is a little agreement on what constitutes desirable glycemic performance,[12–14] particularly with regard to how TGC affects outcome. Thus, despite the potential, many ICUs do not used fixed protocols.[4,12,13,15,16]

Overall, any glycemic control protocol must reduce elevated blood glucose (BG) levels with minimal hypoglycemia, thus minimizing risk in the presence of significant variability in insulin resistance resulting from conflicting drug therapies and dynamically evolving physiological condition, among others. As the patient condition evolves, particularly acutely, TGC and intensive insulin therapy can prove difficult. Protocols or clinical practices that utilize large insulin doses can thus suffer from high glycemic variability and excessive hypoglycemia.[17] As a result, several clinical trials have not achieved the benefit of TGC.[17–20]

Hence, there is significant difficulty in providing protocols that simultaneously provide good performance and TGC without excessive hypoglycemia. The two major reasons or causes of hypoglycemia are often reported to be clinical error and, or combined with, infrequent measurement using bedside glucometers or blood gas analyzers.[19,21–24] Thus, the use of continuous glucose monitors (CGMs) with their rapid 2- to 5-minute measurement rates offers the opportunity to better monitor patients so that hypoglycemia could be avoided, mitigating this risk significantly.

Typically, in most ICU studies, blood glucose is measured every one to four hours, faster only if the levels are already hypoglycemic. The result can be very variable glycemic control, especially with longer measurement intervals.[25] Thus, CGMs would also provide the potential to control glycemic levels better or more tightly, minimizing variability, which has also been strongly linked with mortality, independent of glycemic levels, in these cohorts.[26,27]

However, there have been relatively few successful investigations of CGMs in critical care use,[28] although they are well studied in type 1 diabetes.[29,30] In particular, one set of TGC trials that used them was not particularly successful.[31,32] They offer the trade-off of sometimes significant added sensor noise with their far higher, automated sampling rate.[28,33] However, because these sensors and their algorithms are improving every year, the technology is in a state of constant evolution. Hence, their eventual effective use is potentially inevitable and will free clinicians to provide tighter control in the face of highly dynamic metabolic behavior.

This article used data from the Specialized Relative Insulin Nutrition Titration (SPRINT) TGC study.[11] It examined each of the seven cases of hypoglycemia that was not a function of sensor error. Conservative sensor noise based on reported data in the literature was added to model results fitted to data to simulate the use of CGM. A novel integral-based algorithm with a median filter was used to develop a robust and readily generalized alarm approach and to prove the concept in this *in silico* study.

Subjects and Methods

Subjects

This research was conducted as a retrospective study using records from seven patients admitted to the Christchurch Hospital ICU between 2005 and 2007. Patients were included if they had one or more severe hypoglycemic episodes (BG <40 mg/dl) while on the SPRINT glycemic control protocol.[11] Patients were excluded if the hypoglycemic episode appeared to be due to sensor failure[34] or to a recording error. Details of the cohort are shown in **Table 1**.

Table 1.
Cohort Details, Presented as Median (100% Range) Where Applicable[a]

N	7
Male/female	4/3
APACHE II score	25
	(12–30)
APACHE II ROD (%)	53
	(5–72)
Age (years)	63
	(37–81)
Hypoglycemic blood glucose level (mg/dl)	38
	(31–40)

[a] APACHE II, Acute Physiological and Chronic Health Evaluation II; ROD, risk of death.

The requirement for patients in this study to be on the SPRINT protocol ensured that they had regular, consistent, and accurate records of blood glucose levels (every one to two hours) and insulin and nutrition administration.[11] The use of these patient records fell under existing ethics approval granted by the Upper South Regional Ethics Committee, New Zealand.

Continuous Glucose Monitor Noise Model. Continuous glucose monitor sensor error consisted of a bias due to calibration drift with a random or quasi-random noise superimposed on top. Calibration drift due to sensor degradation over time was not considered in this study, as this is controlled by the specific calibration protocol used with the sensor. The random component of noise modeled in this study was assumed to be independent and normally distributed.

This research used a single-Gaussian noise model. The model was derived to produce similar errors on a similar cohort to those reported by Goldberg *et al.*[28] in a 2004 study of the Medtronic continuous glucose monitoring system (MiniMed Medtronic, Northridge, CA) in a medical ICU. In the study by Goldberg and associates,[28] calibration of the CGM sensors was performed retrospectively with all available data and at least four reference BG measurements per day, removing any bias. This report was used as it was critical care specific and reported a wide range of error statistics versus a reference measure. Goldberg and colleagues[28] reported errors for measurements in five BG ranges. The noise model was thus created to match the reported noise statistics over the same five ranges.

More specifically, it is a Gaussian distributed random error with a mean absolute percentage error (MAPE) of 12.8% and a standard deviation (SD) of 10% on a cohort similar to Goldberg's. However, the percentage error was greater for lower blood glucose levels here (MAPE 17.8%) given the relatively constant mean absolute difference in milligrams per deciliter seen. Because such lower measurements are encountered more frequently in this study involving tightly controlled patients on SPRINT, which are limited to the time periods around hypoglycemic episodes, the errors in MAPE are conservatively higher. However, these errors are also more relevant as they are specific to the hypoglycemia alarm situation studied here.

In Silico CGM Measurements. Using a model derived from the clinically validated glucose–insulin model of Lin and colleagues[35] and hospital records, a blood glucose profile was generated for each patient at 5-minute intervals based on their model-fitted, time-varying insulin sensitivity. These profiles were generated in a data window starting 9 hours before the severe hypoglycemic event at a normoglycemic level and ending 4 hours after an actual measured hypoglycemic event. Random noise was added to this "actual" blood glucose profile using the single-Gaussian model, creating a sequence of virtual CGM sensor outputs.

Continuous Glucose Monitor Filtering. To simulate the real-time use of a CGM device, an algorithm was implemented in MATLAB™ (MathWorks, Natick, MA) to step through the sequence of virtual CGM readings and filter them without knowledge of "future" values, as would be the case clinically. Thus, the clinical situation can be simulated for developing an alarm methodology.

A combination median filter and least mean squares (LMS) curve fit was used to smooth the noisy virtual CGM sequence. Initially, a weighted median filter was applied to the prior 30 minutes of noisy data, followed by a linear least squares fit over previous hour median-filtered data.

The fundamental steps to implement the median filter at any given time, $t = x$, are

1. Take current and two prior CGM readings (three samples, 10-minute window) and find median value M_3
2. Take current and six prior CGM readings (seven samples, 30-minute window) and find median value M_7
3. Take average of M_3 and $M_7 = M_A$
4. Take current M_A value and 12 prior M_A values (1-hour window of median-filtered values)
5. Fit LMS first-order polynomial line
6. Output value at time $t = x$ is the value of this fitted line at $t = x$

This set of steps is based on well-known median filtering[36] and LMS polynomial fitting methods. Multiple windows give an empirically designed trade-off between fast dynamics and response, and longer windows and smoother filtered outputs with lag.[37] This approach is also less computationally expensive than integral-based approaches or Kalman filtering.[38–40]

Alarm Design. An algorithm was required to trigger an alarm when the filtered blood glucose sequence appeared to be heading toward a hypoglycemic event. While better than raw data, filtered data were still too noisy to apply a simple set of conditions such as m measurements below a threshold BG value. Therefore, a windowed integral method [essentially a finite impulse response (FIR) filter[41]] was implemented using filtered data. This approach is both simple and robust to noise.

Specifically, the area between the BG curve and a specified level was calculated within a window of prior samples. When this integral became less than a preselected threshold value, an alarm was triggered, indicating an impending hypoglycemic episode. Several combinations of these parameter values were simulated. **Figure 1** shows an example.

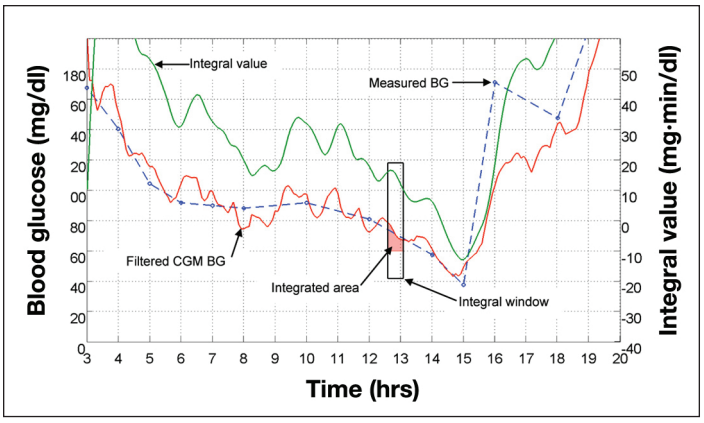

Figure 1. An example showing the blood glucose integral used to trigger a hypoglycemic alarm.

An alarm was considered false if the following conditions held:

- There was more than one alarm for each actual hypoglycemic episode per patient and
- For two clinical blood glucose measurements either side of the alarm, no value was less than or equal to 40 mg/dl.

It should be noted that this use of prior knowledge of clinical BG measurements was only used after filtering and processing to identify any false alarms and would thus not be part of a real-time implementation.

Analysis. For analysis, the timing of this alarm was compared with the time that the episode was actually detected in the hospital. This value essentially measures

the lead time to intervene and the minimization of minor or moderate hypoglycemia. The number of false alarms was also recorded to ensure that the method was accurate.

To get meaningful results with random noise, this study used a Monte Carlo analysis approach. Each patient's model-based, true BG profile was passed through the single-Gaussian random noise generator 100 times, creating 100 different virtual CGM sequences per patient. Results of these 700 trials with the filter and alarm algorithm were analyzed using nonparametric statistics to determine overall cohort and per-patient results.

Results were reported in terms of alarm lead time and number of false alarms for several analyses and thresholds. A simple glycemic threshold method is also shown for comparison.

Results

Filter Results

Median and LMS-based filter design resulted in a significant noise reduction. Specifically, the MAPE on raw noisy virtual outputs was reduced from 17.4% (SD 13%) to 9.3% (SD 7%) over the cohort. However, given relatively smaller numbers of hours (N = 91 hours over seven patients), the distributions were not perfectly normal. Thus, the nonparametric filtering output was a reduction from a median absolute percent error (APE) of 14.4% [interquartile range (IQR): 6.8–24.9] to a median APE of 7.6% (IQR: 3.6–13.2). Mean absolute differences were 14.7 and 7.7 mg/dl, respectively. All these values compare well with results reported in the literature.[28,39,40]

Alarm Analysis Results

The primary result for this study was the time difference between an alarm triggered by simulated CGM data and when a hypoglycemic episode was detected by actual measurement. As a secondary result, the number of false alarms triggered was also reported as a measure of the reliability of the alarm algorithm. **Table 2** shows results for the integral-based alarm for different window lengths and trigger threshold values. Negative time values indicate that an alarm was triggered before a hypoglycemic event was measured. These results were counted over all 700 Monte Carlo simulation runs.

Despite sensor noise, there was a clear improvement in the time of detection of hypoglycemic episodes using CGM sensors compared to standard clinical procedures measuring one to two hourly with, in this case, SPRINT. The degree of improvement depends on the design and parameters of the alarm algorithm presented. The reliability of the alarm, as measured by the number of false alarms, decreases with increasing advanced detection time.

As a comparison, **Table 3** shows results of using a simple glycemic level alarm algorithm. The alarm was triggered in this case by three consecutive CGM readings below the threshold BG value and a negative average gradient over those three points. It is obvious that the performance is significantly worse than the integral-based algorithm. False alarm values of –1 indicate that no alarms were triggered at all, despite the hypoglycemic event occurring in each case. Thus, results in **Table 3** show that for more than 75% of the time, with a threshold value of 50 mg/dl, no alarm was triggered despite the oncoming, glycemically near, hypoglycemic event.

Table 2.
Early Detection of Hypoglycemic Episodes Reported for Integral-Based Alarm Algorithm with a Range of Parameter Values[a]

Integration window length (samples)	5			7			13		
Integral threshold (mg·min/dl)	5	10	20	5	10	20	5	10	20
Hypo detection time cohort (min)	-65 [-110, -35]	-95 [-120, -55]	-145 [-180, -120]	-55 [-95, -30]	-85 [-120, -50]	-130 [-180, -115]	-35 [-73, -15]	-55 [-95, -25]	-120 [-160, -85]
Hypo detection time patient median (min)	-65 [-94, -33]	-90 [-118, -56]	-170 [-180, -124]	-60 [-83, -31]	-80 [-110, -47]	-150 [-180, -123]	-35 [-66, -16]	-55 [-88, -26]	-120 [-166, -101]
BG level at alarm (mg/dl)	58 [55, 60]	64 [62, 66]	78 [74, 79]	55 [53, 57]	62 [60, 64]	75 [71, 77]	52 [48, 54]	55 [51, 60]	72 [61, 75]
false alarms	1 [0, 2]	1 [0, 2]	2 [1, 3]	1 [0, 1]	1 [0, 2]	2 [1, 3]	0 [0, 1]	1 [0, 1]	1 [1, 2]

[a] Data are median (IQR) for all 700 Monte Carlo runs (100 per patient).

Figure 2 shows a typical example of filtered CGM data for one patient run plotted alongside the actual measured one to two hourly blood glucose values. The dark band and line show the median (line) and IQR (shaded band) of the CGM hypoglycemic event detection for the entire 100 Monte Carlo runs over this patient for a window length of seven samples and an integral threshold of 10 mg·min/dl. First, it is evident that even when filtered, CGM data are still relatively noisy. This noise can cause false alarms and impact the reliability of the method.

Second, the range of hypoglycemia detection is still well in advance of the measured hypoglycemic event at 15 hours. The hypoglycemic value is 39 mg/dl and thus it may also be assumed that it likely occurred very near this time. The IQR of detection is 50–120 minutes before the event, which was preceded by a stable range of glycemia around 90 mg/dl for several hours.

Figure 3 illustrates how false alarms can occur. The integral window length and threshold were seven samples and 10 mg·min/dl, respectively. There were two false alarms recorded at 14.8 and 17.2 hours. Although the actual blood glucose measurements remain fairly constant, noisy CGM data pulled the value of the integral below the threshold value, triggering an alarm. The actual alarm was not triggered until 21.3 hours, 45 minutes before it was detected by clinical measurements. Hence, in this case, the actual event was detected and reliably alarmed but minor hypoglycemia at 15–18 hours (60–65 mg/dl) triggered false alarms in this particular Monte Carlo run. Other Monte Carlo runs did not trigger false alarms.

Discussion

While CGMs are well studied in ambulatory type 1 diabetes patients,[29,30] there have been relatively few successful investigations of CGMs in critically ill inpatients.[28] There are several important differences between critically ill patients and ambulatory type 1 diabetes patients, which may have an impact on the performance of the CGM device. Critically ill patients are generally insulin resistant[1–7] due to high levels of counterregulatory stress hormones and consequently hyperglycemic without adequate control. Insulin resistance, coupled with continuous feeding and sedation, limits the rate of change of blood glucose levels, preventing rapid changes that can occur with meals and exercise, possibly resulting in improved CGM performance compared to ambulatory individuals. However, peripheral edema, a lack of dynamic circulation of interstitial fluid due to a nonambulatory state,[42] may reduce performance.

Table 3.
Early Detection of Hypoglycemic Episodes Reported for Simple Glycemic Threshold Value-Based Alarm Algorithm for All 700 Monte Carlo Runs[a]

Consecutive points below alarm threshold	3		
Average gradient at threshold (mg/dl·min)	< 0		
Alarm threshold (mg/dl)	50	60	70
Hypo detection time cohort (min)	-15 [-25, -5]	-40 [-75, -25]	-75 [-110, -45]
Hypo detection time patient median (min)	-10 [-26, -10]	-40 [-69, -25]	-75 [-105, -41]
BG level at alarm (mg/dl)	44 [41, 46]	50 [44, 53]	55 [52, 62]
false alarms	-1 [-1, -1]	-1 [-1, 6]	7 [-1, 13]

[a] Data are median (IQR). A negative value in false alarms indicates that no alarm was triggered.

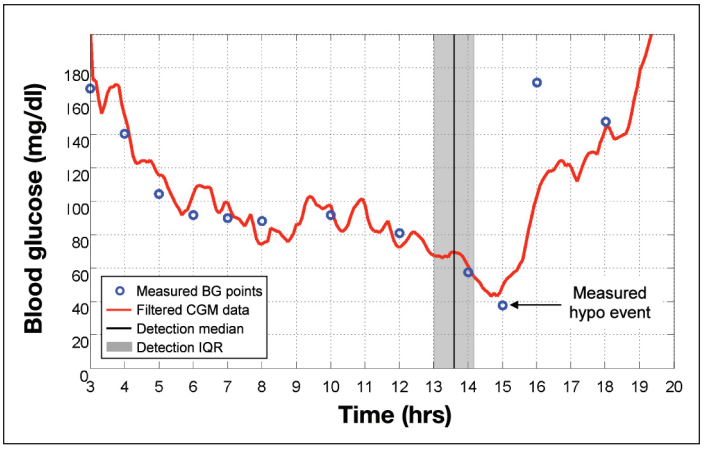

Figure 2. An indication of early hypoglycemic detection provided by CGM sensors for one patient showing the median (IQR) for detection over all 700 Monte Carlo runs. Measured data (circles) and one example of filtered CGM data (line) are shown for context.

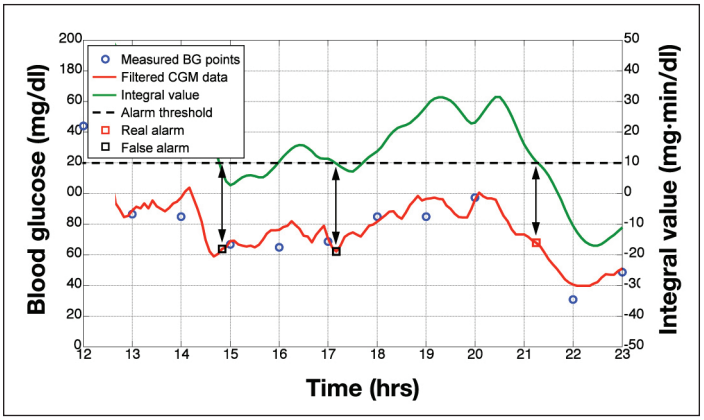

Figure 3. An illustration of false alarms triggered during a simulation.

Performance

Results of this study showed that using CGM sensors for early hypoglycemic event detection in an ICU can be very effective. Depending on the design of the filter and alarm algorithm, reliably detecting hypoglycemic events 1–2 hours before they would normally have been picked up is quite feasible, allowing very early intervention. Early detection and intervention may reduce or eliminate both the events themselves and thus any harm caused by these episodes.

Filtering the raw CGM output with the median filter/LMS fit provides better results than using a more common FIR filter (results not shown). Raw, noisy CGM data had a MAPE of 17.4%—the median/LMS filter reduced this to 9.3% for this cohort. To provide a comparison with "standard" filtering methods, a ninth-order, low-pass FIR filter designed using the window method resulted in a MAPE of 13.7%, which is much higher than this filtering approach for the same data.

Using an integration-based algorithm to trigger the alarm is much more effective than a simple consecutive value-based or derivative-based method. The residual postfiltering noise is still enough to trigger multiple false alarms with a high threshold or to prevent any alarms at all with a lower threshold when simply using filtered BG values to trigger the alarm. **Table 3** illustrated this point, particularly with an alarm threshold of 60 mg/dl. No alarms were triggered in more than 50% of the simulations with this threshold value, but in 25% of simulations there were six or more false alarms triggered, as the IQR 75th percentile is 6 in **Table 3** for some cases. Derivative-based algorithms were not considered in this study as they are known to be highly susceptible to noise, whereas integrals filter noise much like a basic FIR or other digital filter. The integral-based algorithm is thus more robust to noise and therefore provides a much more reliable alarm.

Sensor error due to bias has not been modeled in this research, as it is a calibration issue rather than strictly noise. However, if present and positive (BG actually lower than measured), bias would reduce the lead time for hypoglycemic detection. If negative bias was present (BG actually higher than measured), the detection lead time would be improved; however, the number of false positive detections may also increase. The potential presence of sensor bias therefore necessitates careful calibration of the device and tuning of the detection algorithm to ensure good performance.

Tuning the integral algorithm to optimize the performance involves adjusting the window length and the alarm threshold parameters. There is a trade-off with integral window length, where long windows provide a more reliable alarm, but with less advance warning than shorter windows. With a long window, the integral takes longer to fall below the threshold once the blood glucose starts dropping. This trade-off also explains why a lower alarm threshold parameter is more reliable, but provides less warning than a higher value.

Selecting optimal values for window length and alarm threshold would ideally be done over a larger set of patients than used in this proof of concept analysis. This study has a number of limitations; however, the method presented can be readily generalized to ICU populations. This performance would justify a pilot clinical trial, not only to validate the detection algorithm, but also the assumptions behind the simulated noise.

Limitations

Clinical. The small number of patients in this study (seven) may mean that the results are not representative of the overall population behavior. Repeating the study with a larger cohort would provide a more statistically powerful result. However, in the Christchurch ICU, all patients receiving insulin are on the SPRINT glycemic control protocol and therefore very unlikely to suffer a serious hypoglycemic event (~4% of patients or less), making it difficult to recruit a large cohort. Data from a different study might alleviate this issue for *in silico* studies or a pilot clinical trial should be developed.

A further limitation is that only hypoglycemic episodes at or below 40 mg/dl were investigated in this research. The SPRINT protocol controls patients between 72 and 108 mg/dl[11,25] without significant prejudice toward lower values in this range. Hence, examining a higher hypoglycemic level (e.g., moderate hypoglycemia <60 mg/dl) is infeasible, as getting closer to the target band results in more false alarms. Uncontrolled or poorly controlled patients may permit the investigation of CGM hypoglycemic detection performance on less severe episodes.

Finally, although the virtual patient simulation method is clinically well validated,[25,34,43–45] this *in silico* study needs to be confirmed with clinical testing. The actual blood glucose sequences used were model based, derived from one to two hourly clinical measurements with added noise, not real CGM output data. Testing and

validation of the findings in a clinical setting, particularly the noise model, will confirm the results.

Signal Processing. Signal processing and noise model limitations of this study were that we only considered a conservative noise model and simple filtering methods and ignored calibration drift or bias. We assumed nonbiased, random-independent noise based on reported data.

Continuous glucose monitor sensor error consisted of a bias due to calibration drift with random or quasi-random noise superimposed on top. Calibration drift due to sensor degradation over time was not considered in this study. Without correction, calibration drift will show up as though the actual BG measurements were higher or lower in a relatively consistent manner as the sensor gain drifts.[40] This drift would cause the alarm to trigger early (possibly falsely) or late. However, such calibration drift is very much a function of the frequency and quality of calibration measurements, which can likely be controlled more readily in a critical care setting.

The random component of noise modeled in this study was assumed to be independent and normally distributed. The assumption of independent errors may not model the actual CGM sensor noise perfectly, but with no reported time-series data available in the literature (to the authors' knowledge), a more comprehensive model was not possible.

The Gaussian noise model employed was conservative (MAPE = 17.4% for this cohort), as it was based on data from a 2004 study[28] and there have been significant advances in emerging CGM sensor hardware and software since that time. Improved sensor noise characteristics, combined with more advanced filtering techniques, would result in a much cleaner CGM data stream and hence more reliable alarms. However, the higher noise levels used thus provide a conservative test of the approach.

This study only investigated simple median/LMS and FIR filters. More advanced filtering techniques, such as adaptive filtering and Kalman filtering, have been shown to produce very good results.[39,40] Kalman filtering can also be used to correct for calibration drift,[40] which was not studied in this case. However, it is difficult to compare performance here as all studies have used different data with different noise or error distributions from the sensors.

Analysis Method. It should be noted that this proof of concept study examined only hypoglycemic events. Thus, there were no opportunities to examine "false positive" alarms. The false alarms here occurred significantly before or, in some cases, after the hypoglycemic event. The false alarms here are thus more representative of a lack of robustness.

However, as seen in **Figure 3**, moderate hypoglycemia, which is corrected before the severe hypoglycemic event, can still trigger a false alarm if the thresholds are not optimized perfectly—an effort that may be nearly impossible given the variety of patient behaviors that can be encountered. That said, a trigger at this level is still clinically useful and definitely not spurious with regard to treating. Thus, another view of **Figure 3** would be that these false alarms, if not frequent, may be earlier precursors of hypoglycemic dynamics in the patient's response to the intervention, which could potentially be used to moderate care.

Summary. Finally, while these are significant limitations, this article focused on proof of concept for a novel integration-based method of hypoglycemia detection. The primary goal was to develop a method for accurate, reliable alarms with good warning that account for realistic or greater sensor noise that was also readily generalizable to similar sensors. Thus, the larger noise used is a conservative test, and application to cases with lesser noise will provide better results. The main comparison to other alarm methods should then be in terms of relative performance presented here. Overall, the good result with suboptimal filtering and a conservative noise model only serves to show that the method is feasible and deserves further investigation.

Finally, examining the SPRINT and prior pilot trial results, hypoglycemia could have been avoided without using CGM if measurements were made every 30 minutes (48/day). However, this rate potentially is invasive to the patient and far too burdensome for regular practice in a clinical ICU environment. Hence, CGM offers the opportunity to observe trends semi-invasively and to reduce clinical burden, while also increasing potential safety by mitigating the trade-off between the burden of more frequent measurement and the safety and TGC outcomes that it can provide. In SPRINT, even one to two hourly measurements yielded only 10 events over eight patients (2%), a majority of which were due to clinical errors. As a result, the methods presented here are thus about reducing a potentially small number of events to zero, as well as mitigating the clinical burden of frequent measurement.

Conclusions

This article developed and analyzed, *in silico*, a hypoglycemia alarm detection method for application with CGM sensors in critical care or, potentially, other hospital patients. While the results remain to be verified in a pilot clinical trial, the overall method appears robust and accurate to conservatively large sensor noise. The main conclusions and outcomes drawn include the following:

- A median filter with LMS smoothing was presented and shown to be robust at removing significant sensor noise with minimal lag compared to standard FIR filters and similar to reported results for more advanced filters.
- An integral-based method was developed and seen to provide robust hypoglycemia detection with significant lead time before the event to enable intervention. The number of false alarms was very low, and performance was better than the simple use of thresholds using the integral approach.
- The results presented justify a pilot clinical trial of the methods.

Finally, the methods presented are readily generalizable to other hypoglycemic levels or control protocols.

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References:

1. Capes SE, Hunt D, Malmberg K, Gerstein HC. Stress hyperglycaemia and increased risk of death after myocardial infarction in patients with and without diabetes: a systematic overview. Lancet. 2000;355(9206):773-8.
2. Finney SJ, Zekveld C, Elia A, Evans TW. Glucose control and mortality in critically ill patients. JAMA. 2003;290(15):2041-7.
3. Krinsley JS. Association between hyperglycemia and increased hospital mortality in a heterogeneous population of critically ill patients. Mayo Clin Proc. 2003;78(12):1471-8.
4. McCowen KC, Malhotra A, Bistrian BR. Stress-induced hyperglycemia. Crit Care Clin. 2001;17(1):107-24.
5. Mizock BA. Alterations in fuel metabolism in critical illness: hyperglycaemia. Best Pract Res Clin Endocrinol Metab. 2001;15(4):533-51.
6. Umpierrez GE, Isaacs SD, Bazargan N, You X, Thaler LM, Kitabchi AE. Hyperglycemia: an independent marker of in-hospital mortality in patients with undiagnosed diabetes. J Clin Endocrinol Metab. 2002;87(3):978-82.
7. Van den Berghe G, Wouters P, Weekers F, Verwaest C, Bruyninckx F, Schetz M, Vlasselaers D, Ferdinande P, Lauwers P, Bouillon R. Intensive insulin therapy in the critically ill patients. N Engl J Med. 2001;345(19):1359-67.
8. Bistrian BR. Hyperglycemia and infection: which is the chicken and which is the egg? JPEN J Parenter Enteral Nutr. 2001;25(4):180-1.
9. Van den Berghe G, Wilmer A, Hermans G, Meersseman W, Wouters PJ, Milants I, Van Wijngaerden E, Bobbaers H, Bouillon R. Intensive insulin therapy in the medical ICU. N Engl J Med. 2006;354(5):449-61.
10. Krinsley JS. Effect of an intensive glucose management protocol on the mortality of critically ill adult patients. Mayo Clin Proc. 2004;79(8):992-1000.
11. Chase JG, Shaw G, Le Compte A, Lonergan T, Willacy M, Wong XW, Lin J, Lotz T, Lee D, Hann C. Implementation and evaluation of the SPRINT protocol for tight glycaemic control in critically ill patients: a clinical practice change. Crit Care. 2008;12(2):R49.
12. Mackenzie I, Ingle S, Zaidi S, Buczaski S. Tight glycaemic control: a survey of intensive care practice in large English hospitals. Intensive Care Med. 2005;31(8):1136.
13. Schultz MJ, Spronk PE, Moeniralam HS. Tight glycaemic control: a survey of intensive care practice in the Netherlands. Intensive Care Med. 2006;32(4):618-9.
14. Gale SC, Gracias VH. Glycemic control needs a standard reference point. Crit Care Med. 2006;34(6):1856-7.
15. Diringer MN. Improved outcome with aggressive treatment of hyperglycemia: hype or hope? Neurology. 2005;64(8):1330-1.
16. Bland DK, Fankhanel Y, Langford E, Lee M, Lee SW, Maloney C, Rogers M, Zimmerman G. Intensive versus modified conventional control of blood glucose level in medical intensive care patients: a pilot study. Am J Crit Care. 2005;14(5):370-6.
17. Meijering S, Corstjens AM, Tulleken JE, Meertens JH, Zijlstra JG, Ligtenberg JJ. Towards a feasible algorithm for tight glycaemic control in critically ill patients: a systematic review of the literature. Crit Care. 2006;10(1):R19.
18. Finfer S, Chittock DR, Su SY, Blair D, Foster D, Dhingra V, Bellomo R, Cook D, Dodek P, Henderson WR Hébert PC, Heritier S, Heyland DK, McArthur C, McDonald E, Mitchell I, Myburgh JA, Norton R, Potter J, Robinson BG, Ronco JJ. Intensive versus conventional glucose control in critically ill patients. N Engl J Med. 2009;360(13):1283-97.
19. Chase J, Shaw GM, Wong XW, Lotz T, Lin J, Hann CE. Model-based glycaemic control in critical care--a review of the state of the possible. Biomed Signal Process Control. 2006;1(1):3-21.

20. Griesdale DE, de Souza RJ, van Dam RM, Heyland DK, Cook DJ, Malhotra A, Dhaliwal R, Henderson WR, Chittock DR, Finfer S, Talmor D. Intensive insulin therapy and mortality among critically ill patients: a meta-analysis including NICE-SUGAR study data. CMAJ. 2009;180(8):821-7.
21. Chase J, Andreassen S, Jensen K, Shaw G. The impact of human factors on clinical protocol performance: a proposed assessment framework and case examples. J Diabetes Sci Technol. 2008;2(3):409-16.
22. Bhatia A, Cadman B, Mackenzie I. Hypoglycemia and cardiac arrest in a critically ill patient on strict glycemic control. Anesth Analg. 2006;102(2):549-51.
23. Clayton SB, Mazur JE, Condren S, Hermayer KL, Strange C. Evaluation of an intensive insulin protocol for septic patients in a medical intensive care unit. Crit Care Med. 2006;34(12):2974-8.
24. Braithwaite SS, Edkins R, Macgregor KL, Sredzienski ES, Houston M, Zarzaur B, Rich PB, Benedetto B, Rutherford EJ. Performance of a dose-defining insulin infusion protocol among trauma service intensive care unit admissions. Diabetes Technol Ther. 2006;8(4):476-88.
25. Lonergan T, LeCompte A, Willacy M, Chase JG, Shaw GM, Wong XW, Lotz T, Lin J, Hann CE. A simple insulin-nutrition protocol for tight glycemic control in critical illness: development and protocol comparison. Diabetes Technol Ther. 2006;8(2):191-206.
26. Krinsley JS. Glycemic variability: a strong independent predictor of mortality in critically ill patients. Crit Care Med. 2008;36(11):3008-13.
27. Egi M, Bellomo R, Stachowski E, French CJ, Hart G. Variability of blood glucose concentration and short-term mortality in critically ill patients. Anesthesiology. 2006;105(2):244-252.
28. Goldberg PA, Siegel MD, Russell RR, Sherwin RS, Halickman JI, Cooper DA, Dziura JD, Inzucchi SE. Experience with the continuous glucose monitoring system in a medical intensive care unit. Diabetes Technol Ther. 2004:6(3):339-47.
29. Klonoff DC. Continuous glucose monitoring: roadmap for 21st century diabetes therapy. Diabetes Care. 2005;28(5):1231-9.
30. Klonoff DC. A review of continuous glucose monitoring technology. Diabetes Technol Ther. 2005;7(5):770-5.
31. Chee F, Fernando T, van Heerden PV. Closed-loop glucose control in critically ill patients using continuous glucose monitoring system (CGMS) in real time. IEEE Trans Inf Technol Biomed. 2003;7(1):43-53.
32. Chee F, Fernando TL, Savkin AV, van Heeden V. Expert PID control system for blood glucose control in critically ill patients. IEEE Trans Inf Technol Biomed. 2003;7(4):419-25.
33. Clarke WL, Anderson S, Farhy L, Breton M, Gonder-Frederick L, Cox D, Kovatchev B. Evaluating the clinical accuracy of two continuous glucose sensors using continuous glucose-error grid analysis. Diabetes Care. 2005;28(10):2412-7.
34. Chase JG, Shaw GM, Lotz T, LeCompte A, Wong J, Lin J, Lonergan T, Willacy M, Hann CE. Model-based insulin and nutrition administration for tight glycaemic control in critical care. Curr Drug Deliv. 2007;4(4):283-96.
35. Lin J, Lee D, Chase JG, Shaw GM, Le Compte A, Lotz T, Wong J, Lonergan T, Hann CE. Stochastic modelling of insulin sensitivity and adaptive glycemic control for critical care. Comput Methods Programs Biomed. 2008;89(2):141-52.
36. Pitas I, Venetsanopoulos AN. Nonlinear digital filters: principles and applications. Boston: Kluwer Academic; 1990.
37. Chase JG, Chen H, Sirisena H, Shaw GM, Wong XW, Hann CE, Le Compte AJ, Lin J, Lotz T. Hierarchical real-time filtering for continuous glucose sensor data. J Diabetes Sci Technol. 2007;1(2):A21.
38. Chase JG, Hann CE, Jackson M, Lin J, Lotz T, Wong XW, Shaw GM. Integral-based filtering of continuous glucose sensor measurements for glycaemic control in critical care. Comput Methods Programs Biomed. 2006;82(3):238-47.
39. Knobbe EJ, Buckingham B. The extended Kalman filter for continuous glucose monitoring. Diabetes Technol Ther. 2005;7(1):15-27.
40. Kuure-Kinsey M, Palerm CC, Bequette BW. A dual-rate Kalman filter for continuous glucose monitoring. Conf Proc IEEE Eng Med Biol Soc. 2006;1:63-6.
41. Ifeachor EC, Jervis BW. Digital signal processing: a practical approach. Harlow: Addison-Wesley; 1993.
42. Chee F, Fernando T, van Heerden PV. Closed-loop glucose control in critically ill patients using continuous glucose monitoring system (CGMS) in real time. IEEE Trans Inf Technol Biomed. 2003;7(1):43-53.
43. Lonergan T, Compte AL, Willacy M, Chase JG, Shaw GM, Hann CE, Lotz T, Lin J, Wong XW. A pilot study of the SPRINT protocol for tight glycemic control in critically Ill patients. Diabetes Technol Ther. 2006;8(4):449-62.
44. Chase JG, Shaw GM, Lin J, Doran CV, Hann C, Lotz T, Wake GC, Broughton B. Targeted glycemic reduction in critical care using closed-loop control. Diabetes Technol Ther. 2005;7(2):274-82.
45. Wong XW, Singh-Levett I, Hollingsworth LJ, Shaw GM, Hann CE, Lotz T, Lin J, Wong OS, Chase JG. A novel, model-based insulin and nutrition delivery controller for glycemic regulation in critically ill patients. Diabetes Technol Ther. 2006;8(2):174-90.