Complexity of continuous glucose monitoring data in critically ill patients: CGM devices, sensor locations and DFA methods

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Abstract

BACKGROUND: Critically ill patients often experience high levels of insulin resistance and stress-induced hyperglycemia, which may negatively impact outcomes. However, evidence surrounding the causes of negative outcomes remains inconclusive. Continuous glucose monitoring (CGM) devices allow researchers to investigate glucose complexity, using detrended fluctuation analysis (DFA), to determine whether it is associated with negative outcomes.

AIM: The aim of this study was to investigate the effects of CGM device type/calibration and CGM sensor location on results from DFA.

METHODS: This study uses CGM data from critically ill patients who were each monitored concurrently using Medtronic iPro2's on the thigh and abdomen, and a Medtronic Guardian Real-Time on the abdomen. This allowed inter-device/calibration type and inter-sensor site variation to be assessed. DFA is a technique that has previously been used to determine the complexity of CGM data in critically ill patients. Two variants of DFA, monofractal and multifractal, were used to assess the complexity of sensor glucose (SG) data, as well as the pre-calibration raw sensor current. Monofractal DFA produces a scaling exponent (H), where H is inversely related to complexity. The results of multifractal DFA are presented graphically, by the multifractal spectrum.

RESULTS: From the 10 patients recruited, 26 CGM devices produced data suitable for analysis. The values of H from abdominal iPro2 data were 0.10 [0.03 – 0.20] higher than those from Guardian Real-Time data, indicating consistently lower complexities in iPro2 data. However, repeating the analysis on the raw sensor current showed little or no difference in complexity. Sensor site had little effect on the scaling exponents in this data set. Finally, multi-fractal DFA revealed no significant associations between the multifractal spectrums and CGM device type/calibration or sensor location.

CONCLUSIONS: Monofractal DFA results are dependent on the device/calibration used to obtain CGM data, but sensor location has little impact. Future studies of glucose complexity should consider the findings presented here when designing their investigations.

Abbreviations:

BG – blood glucose

CGM – continuous glucose monitoring

FDA – Food and Drug Administration

DFA – detrended fluctuation analysis

ICU – intensive care unit

STAR – Stochastic TARgeted

SG – sensor glucose

BGA – blood gas analyser

IQR – inter-quartile range

MARD – mean absolute relative dfference

1.0 Introduction

Critically ill patients often experience high levels of insulin resistance [1-7] and stress-induced hyperglycemia, which may negatively impact outcomes [1-3, 8, 9]. The 2001 landmark study by Van den Berghe et al was the first data showing lower blood glucose (BG) levels in critically ill patients were associated with improved outcomes [9]. Many subsequent studies tried to replicate those results with some showing reduced mortality [10, 11], others failing to match the results [12-14], and many seeing no difference [15]. Since then it has been determined that that glycemic variability also plays a very important role [16-21].

With FDA approval of the first commercially available continuous glucose monitoring (CGM) device in 2004, glycaemic dynamics could be captured at a much higher resolution compared to conventional BG monitoring. More recently, CGM devices have allowed researchers to test the latest hypothesis, that glucose complexity could also be associated with mortality in critically ill patients [22, 23]. Glucose complexity, in a very simplistic view, is a measure of the 'fuzziness' of a glucose trace.

The current hypothesis is that a healthy glucose regulatory system will be highly reactive to disturbances and make many small adjustments to keep glucose concentration within a normal range [22]. Conversely, a failing glucose regulatory system will be ‘sluggish’ and the glucose profile should appear smooth with very few high frequency adjustments. To date, there have been two studies that have investigated glucose complexity in critically ill patients [22, 23]. Both studies used Detrended Fluctuation Analysis (DFA) to quantify glucose complexity, reporting an association between the results of DFA and mortality.

Outside of glycemia research, DFA has been widely used to quantify the scaling and correlation properties of other non-stationary, physiological time series. For example, DFA has been applied to inter-breath-interval of human respiration, inter-beat-interval of human heartbeat and inter-stride-interval of human stride to differentiate between healthy and pathological conditions [24-30]. The aim of this study was to extend the knowledge of glucose complexity in critically ill adults by investigating the effects of CGM device type/calibration and CGM sensor location on DFA results.

2.0 Methods

2.1 Patients

This study uses CGM data from patients admitted to the Christchurch Hospital ICU, a mixed surgical and medical ICU, between June and November 2012. Inclusion criteria for the study were an expected duration of ICU admission longer than 5 days and 2 consecutive BG measurements > 144mg/dL, indicating the need for glycaemic control using the STAR protocol [31]. STAR is a model based glycaemic control protocol that modulates insulin and nutrition to control BG concentration. Written and signed consent was obtained from the patient or next of kin if the patient was unable to consent. This study and use of data was approved by the Upper South A Regional Ethics Committee, New Zealand.

2.2 Continuous Glucose Monitoring

Each participant in the study was monitored using 3 Medtronic CGM devices (Medtronic Diabetes, Northridge, CA) for a period of up to 6 days. Two sensors were located on the patient's abdomen, one of which was connected to a Medtronic Guardian Real-Time monitor and the other connected to a Medtronic iPro2 recorder. The third sensor was located on the patient's thigh and was connected to a second Medtronic iPro2 recorder. This configuration allowed comparison of results between different devices and sensor locations within each subject. Importantly, all sensors in the study had the same Medtronic Enlite glucose sensor technology. It should be noted that these CGM devices and sensors were not designed for use in the ICU and were being used off-label in this study.

One significant difference between the Guardian and iPro2 CGM devices is the calibration algorithm. Calibration algorithms use independent calibration BG measurements to convert the raw sensor

current (I_{SIG}) into a series of sensor glucose (SG) values for the user. The iPro2 device stores the sensor signal information internally and it is retrospectively calibrated after the device has been removed from the patient. Retrospective calibration allows the calibration algorithm to use information both before and after the time point of interest to obtain an optimal calibration to each reference point. However, the Guardian CGM device displays a glucose value in real time and the calibration algorithm can only use prior data for calibration. Otherwise, all sensor technology was identical.

Calibration BG measurements were obtained by specifically trained ICU nurses at least 3 times per day, per manufacturer guidelines. A blood sample was drawn from the patients arterial line and a blood gas analyzer (BGA) was used to determine the glucose concentration. The value from the BGA was immediately entered into the Guardian Real-Time device and then recorded for retrospective calibration of the iPro2 devices. In addition to BGA measurements, glucometer BG measurements using arterial blood samples were done every 1-3 hours for glycemic control. These measurements were independent of CGM and could therefore be used to assess CGM performance.

2.3 Glucose complexity

Glucose complexity was quantified in this study using DFA, which has been widely used to quantify the scaling and correlation properties of non-stationary, physiological time series. For a self-similar time series (X), the scale invariant structure can be described by $X(ct) = c^H X(t)$, where the power law exponent (H) describes the scaling and is used to quantify complexity. In some cases, the scaling properties of a time series are associated with changes in physiology and may be useful to help better understand certain illnesses or medical conditions [26, 28].

In terms of glucose complexity, the current hypothesis is that a healthy glucose regulatory system will make many small adjustments to keep glucose concentration within a healthy range and the high complexity is characterized by a low value of H. In contrast, a failing glucose regulatory system will be 'sluggish' and appear smooth with low complexity, characterized by high values of H.

Two modes of DFA are available depending on the properties of the signal or time series. Monofractal DFA is used when the scaling properties of the time series can be quantified by a single power law exponent, which is independent of time and space. However, a limitation of monofractal DFA is that real world physiological signals often do not exhibit simple monofractal scaling behavior over the entire time period [28, 32]. In these cases, multiple scaling exponents are required to fully characterize the correlation properties of the signal and multifractal DFA should be employed.

The results of a multifractal DFA are typically displayed in a multifractal spectrum (see the supplementary file for details). The width, shape and location of the multifractal spectrum can all be used to give important information about the relationship between the time series and the physiological phenomenon being studied. This capability has been illustrated in previous studies that have used multifractal DFA to help differentiate between healthy and pathological conditions, such as heart disease [28].

An example of two spectrums produced using multifractal DFA are shown in Figure 1. The spectrum plotted with red dots was produced from a signal with monofractal scaling properties and the spectrum plotted with blue crosses was produced from a signal with multifractal scaling properties, data for both of which were provided by Ihlen [32]. Note the spectrum for the monofractal signal is very narrow compared to the multifractal signal, indicating the scaling exponents are almost

independent of time and space. Thus, a single H from monofractal DFA is sufficient to characterize the scaling and correlation properties of the signal.

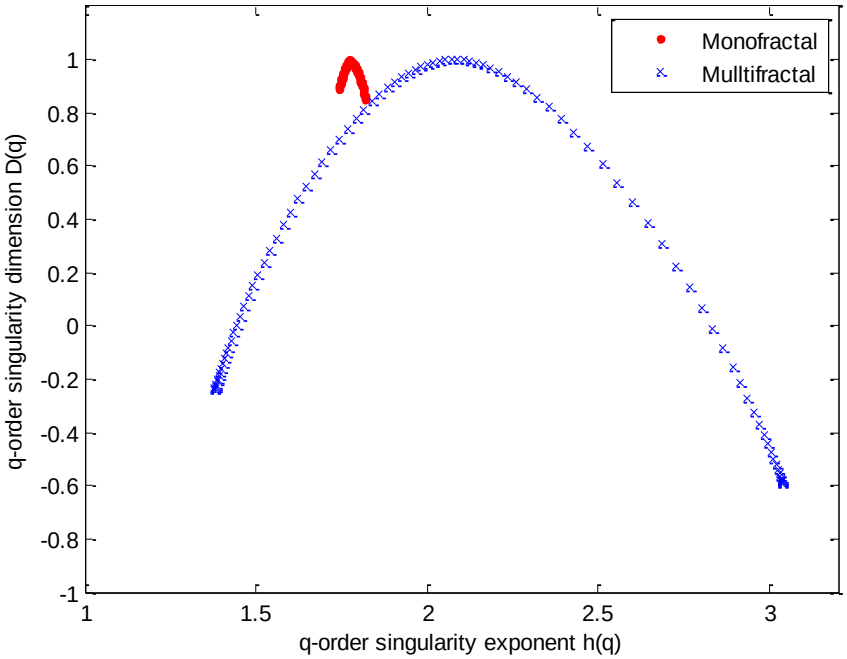

Figure 1: Example of multifractal spectrum that is produced from multifractal DFA. Note the monofractal signal produces a very narrow spectrum, indicating monofractal scaling is present and monofractal DFA is sufficient to characterize the scaling and correlation properties of the signal.

This study uses both monofractal DFA and multifractal DFA implemented in MATLAB (Mathworks, Natick, MA), based on the descriptions provided in [32, 33]. A thorough discussion of both methods can be found elsewhere (monofractal DFA [27] and multifractal DFA [33]). However, a general implementation for both methods is summarized in the supplementary file with examples.

2.4 Analysis

This study uses DFA to investigate the glucose complexity of critically ill patients who were monitored by 3 simultaneous CGM devices during their ICU stay. Specifically, it investigates:

1. Whether CGM device type/calibration or CGM sensor location affects DFA results.
2. Whether monofractal or multifractal DFA is more appropriate for CGM signals, given the use of monofractal DFA as a discriminator in [22, 23].

Each patient enrolled in the study had 3 CGM devices monitoring glucose levels for up to 6 days. The warm-up period for these devices is 1-2 hours [34, 35], but due to off-label use here the first 12 hours of SG data were excluded to ensure the devices were performing properly during the period of interest. Data sets with less than 500 SG measurements were excluded and SG data sets with less than 1000 SG measurements were analyzed with increased care to ensure robust results as this value is a recommended minimum [32]. The SG data were analyzed using both monofractal DFA and multifractal DFA to determine whether the analysis method has an impact on results.

In particular:

- Data from the two iPro2 CGM devices, one on the thigh and one on the abdomen, were compared to assess sensor location effects independent of technology.
- Data from the iPro2 on the abdomen were compared to data from the Guardian Real-Time located on the opposite side of the patient's abdomen, to assess the impact of CGM device type/calibration on DFA results.
- Analyses were repeated using the I_{SIG}, which removed any effects induced by device calibration.

Monofractal DFA results are presented in a table, as the result from each analysis is a single scaling exponent; H. Results from the multifractal DFA are presented in figures containing a plot of the

multifractal spectrum. When comparing results, similar values of H from the monofractal analysis and spectrums of similar shape/position from the multifractal analysis indicate little or no difference in the scaling properties of the time series.

Numerical results are presented as median [25^{th} – 75^{th} percentile] where applicable. The Wilcoxon signed-rank test was used to determine statistical significance when comparing inter-sensor site or inter-device type results. This test was used because the results are not independent or normally distributed.

3.0 Results

During the study period, 10 patients were recruited and consented to participate in the study. Table 1 shows the cohort demographics, as well as measures of BG control for these patients. The results show that 81% of BG measurements were within the 72 - 144mg/dL euglycemic range and no BG measurements were recorded below 54 mg/dL.

Table 1: Cohort demographics and blood glucose control results
Displayed as Median [IQR] where applicable

Demographics	
Patients	10
Age (years)	51 [39 - 64]
Sex (M/F)	5/5
APACHE II	24 [17 - 27]
APACHE III	85 [52 - 99]
SAPS II	52 [30 - 59]
Length of stay (days)	20 [10 - 33]
Outcome (L/D)	6/4
Diabetes (None/T1/T2)	10/0/0
Blood glucose control	
Time between BG (hours)	1.5 [0.9 - 2.3]
Median [IQR] BG (mg/dL)	124 [112 - 137]
Percent BG in 72 -144 mg/dL band	81%
Percent BG < 72 mg/dL	0.14%
Percent BG < 54 mg/dL	0%

SAPS - Simplified Acute Physiology Score
APACHE - Acute Physiology And Chronic Health Evaluation

Of the 30 CGM sensors used during the study, 26 sensors from 9 patients produced enough data for use in the DFA analysis. The 4 excluded data sets contained less than 500 measurements and were considered too short for analysis. Three of the excluded data sets were from a short stay patient eliminating all their CGM data, and the other excluded data set was from a sensor with adhesion issues that was dislodged early in the monitoring period.

3.1 Monofractal DFA

The results from the monofractal DFA are shown in Table 2. The top half shows the results of DFA when analyzing SG data from the CGM devices. It is important to reiterate that the Guardian and iPro2 devices use different calibration algorithms with the same sensor technology. Thus, these results include any effects of calibration on DFA results.

The *CGM device type* section shows the results when comparing CGM device type. Across the cohort, the retrospectively calibrated iPro2 reported higher scaling exponents of 1.56 [1.46 – 1.60] compared to 1.43 [1.37 - 1.48] for the Guardian Real-Time device. Furthermore, when comparing the two different abdominal devices monitoring the same individual, the H values for iPro2 data were 0.10 [0.03 – 0.11] higher than the H values for Guardian data ($p = 0.08$).

The *Sensor location* section shows the results comparing a sensor inserted in the abdomen to a sensor inserted in the thigh of the same CGM device type (iPro2). There is no significant difference in the H values for different sensor locations ($p = 0.64$). Furthermore, performance at both sites relative to independent BG measurements was similar, at 11.8% MARD (mean absolute relative difference) in the abdomen and 12.4% MARD in the thigh.

The bottom half of Table 2 shows results from a similar analysis conducted on I_{SIG}, which removes the effects of CGM device calibration. The data sets are stratified into the same groups as the top half of Table 2 based on CGM type and sensor location. When the effects of calibration are removed, the results show no significant differences between the groups, in any of the sub analyses.

Table 2: Results from monofractal DFA of SG and I_{SIG} data over cohort

Analysing calibrated SG data			
CGM device type (both in abdomen)			
	Guardian	**iPro2**	**P value**
Number of data sets	9	8	
Scaling exponent (H)	1.43 [1.37 - 1.48]	1.56 [1.46 - 1.60]	
Difference in H (iPro2 - Guardian)	0.10 [0.03 - 0.20]		0.08*
Sensor location (both iPro2)			
	Abdomen	**Thigh**	**P value**
Number of data sets	8	9	
Scaling exponent (H)	1.56 [1.46 - 1.60]	1.52 [1.50 - 1.61]	
Difference in H (Thigh - Abdomen)	0.04 [-0.06 - 0.11]		0.64*
Analysing pre-calibration ISIG data			
CGM device type (both in abdomen)			
	Guardian	**iPro2**	**P value**
Number of data sets	9	8	
Scaling exponent (H)	1.42 [1.34 - 1.52]	1.54 [1.37 - 1.60]	
Difference in H (iPro2 - Guardian)	0.06 [-0.04 - 0.10]		0.53*
Sensor location (both iPro2)			
	Abdomen	**Thigh**	**P value**
Number of data sets	8	9	
Scaling exponent (H)	1.54 [1.37 - 1.60]	1.51 [1.47 - 1.60]	
Difference in H (Thigh - Abdomen)	0.04 [-0.03 - 0.09]		0.38*

*** Wilcoxon signed Rank test**

3.2 Multifractal DFA

Monofractal DFA revealed all 26 CGM data sets have H values between 1.2 - 1.8, as shown in Table 2. Thus, for the multifractal DFA the integration step (Equation 1 in the supplementary file) was omitted and the resulting H values from the analyses were adjusted by +1 [32].

Figure 2 shows the multifractal spectrums for all SG and I_{SIG} data sets used in the analyses. The two subplots on the left side were created using SG data, comparing CGM device type (top), and sensor location (bottom). Equivalent plots on the right side of Figure 2 were created using I_{SIG} data. There

were no significant or obvious associations between sensor site or CGM device type and the shape, width or location of the multifractal spectrums.

Figure 3 shows four examples of how monofractal and multifractal DFA can give contradicting results and why the results must be interpreted with care. In all four cases, monofractal DFA of the two SG data sets resulted in the same scaling exponent. However, the multifractal DFA resulted in significantly different spectrums for each of the paired data sets. Furthermore, the width of the spectrums suggests the scaling properties of the time series are multifractal and that multifractal DFA is a more appropriate analysis technique [28, 32].

Figure 4 shows two examples of SG data from patients in this study and the subsequent results of multifractal DFA. Example 'A' shows SG data from three sensors that report similar glucose traces throughout the monitoring period, but the multifractal DFA produces three quite different multifractal spectrums. In contrast, example 'B' shows SG data from two sensors that do not track each other very well and despite the discrepancies in SG data, the multifractal DFA resulted in two multifractal spectrums that are almost identical.

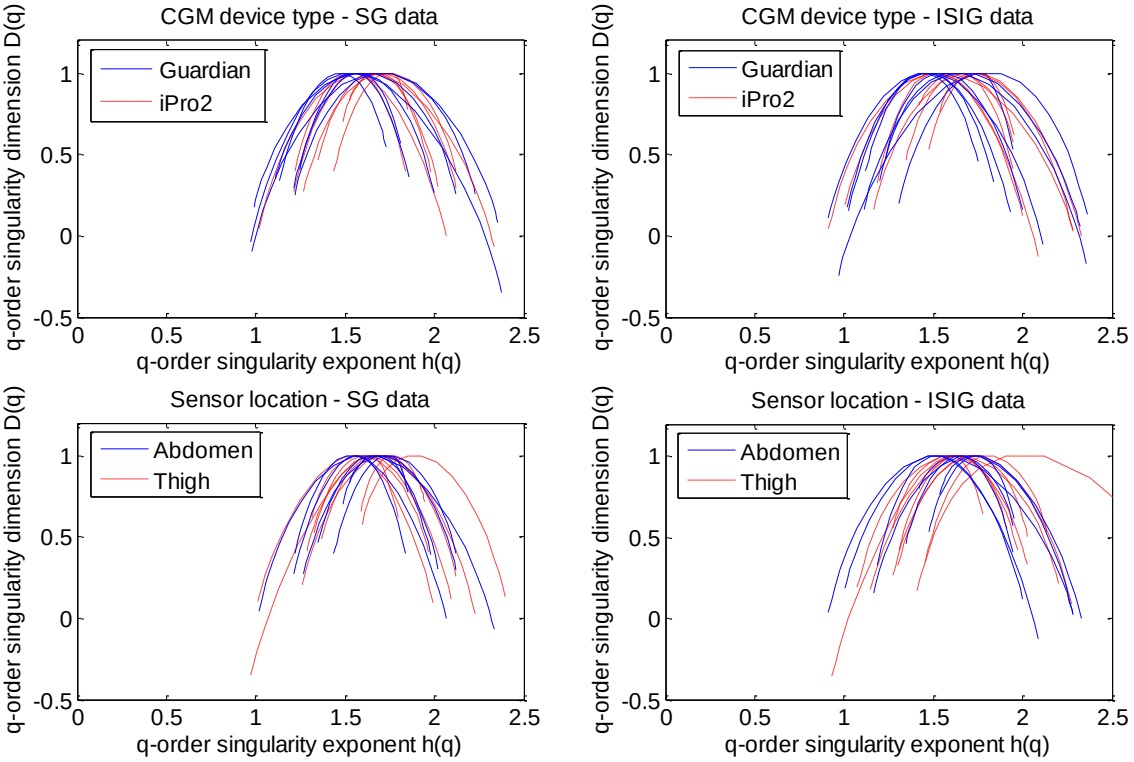

Figure 2: Multifractal spectrums comparing CGM device types and sensor locations. The plots on the left were created using SG data and the plots on the right were created using I_{SIG} data.

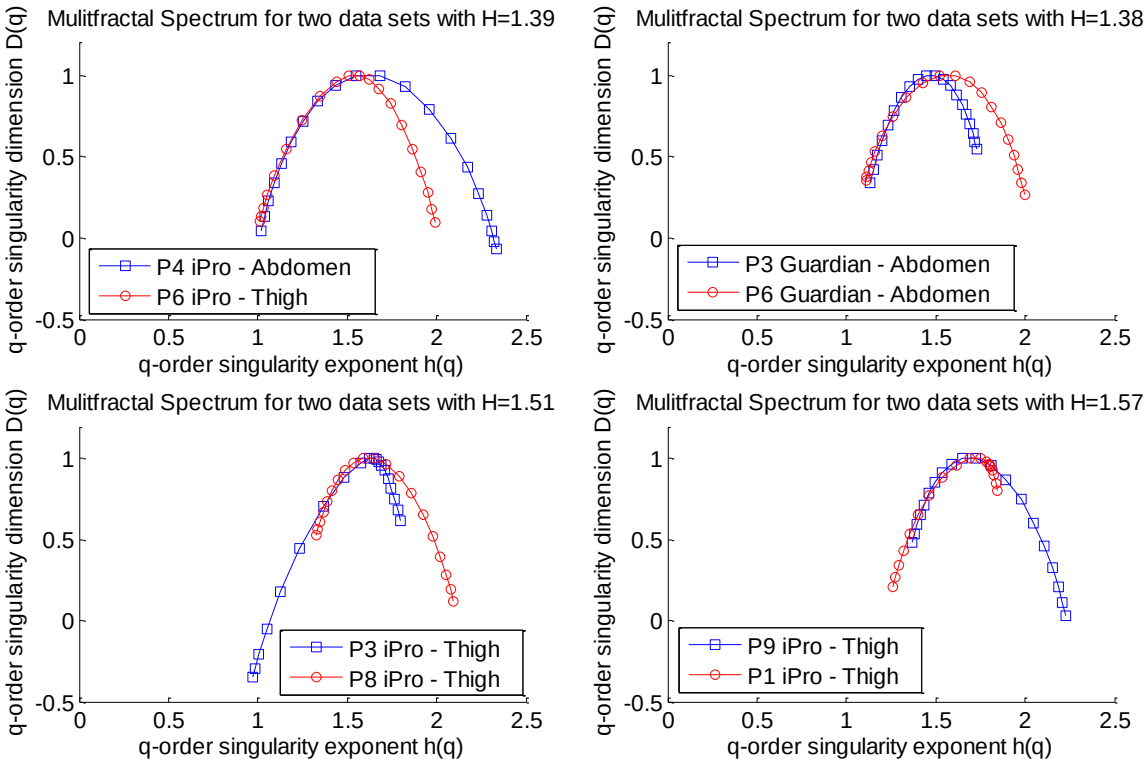

Figure 3: Multifractal Spectrum comparison for data sets that had the same scaling exponent from monofractal DFA.

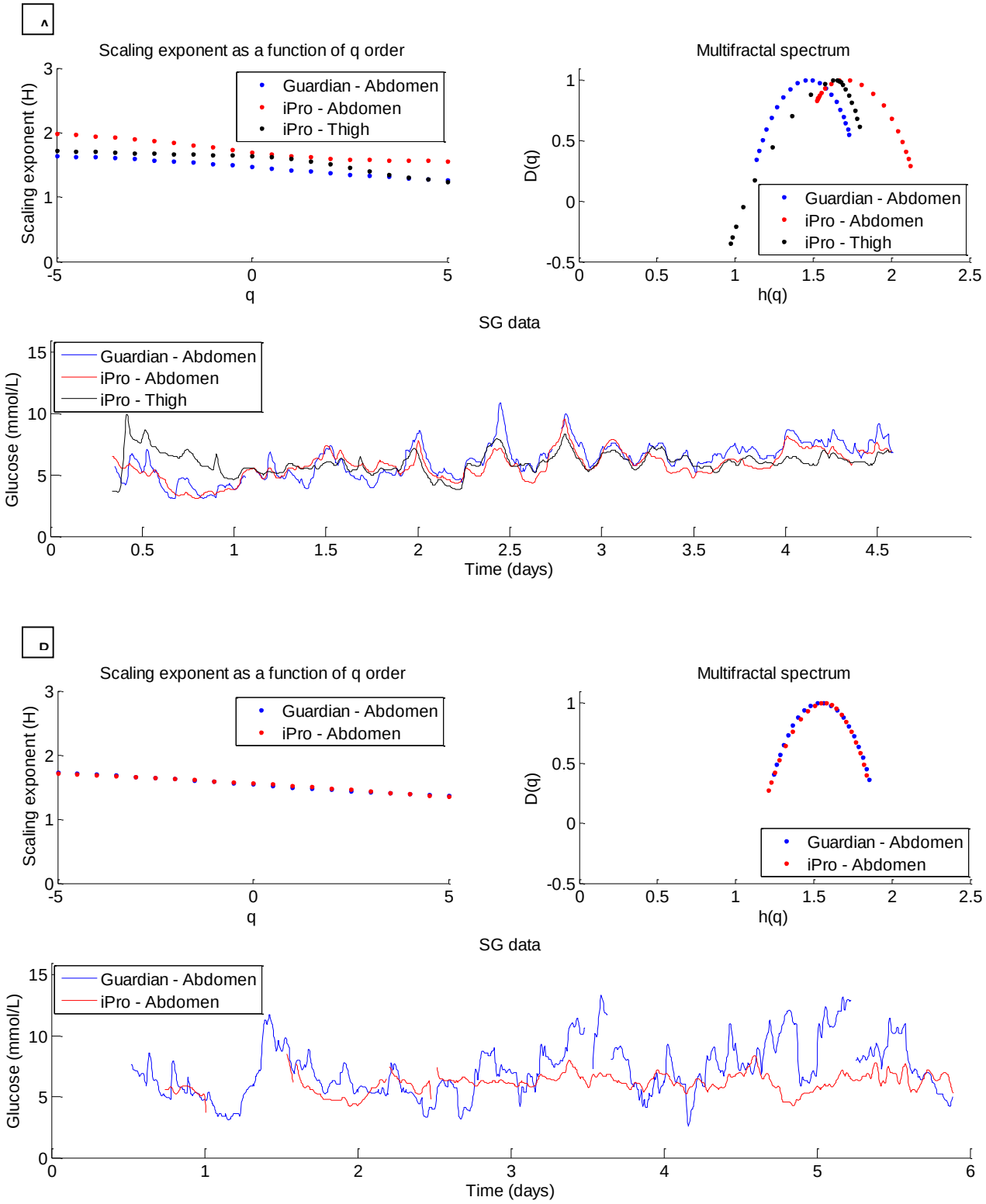

Figure 4: A) This example shows good agreement between SG data for each of the three CGMs, but the multifractal spectrums for each data set are quite different. B) This example shows average agreement between SG data for two CGMs, but the multifractal spectrums for each data set overlap.

4.0 Discussion

The aim of this study was to investigate the effects of CGM device type/calibration and CGM sensor location on DFA results in critically ill patients. Due to the configuration of CGM devices and sensor locations in this study, there was a unique opportunity to study the effects of these parameters on DFA results.

4.1 Monofractal DFA

The effects of CGM device type on monofractal DFA results revealed an important trend. The two sensors located in the patient's abdomen were identical, but one CGM device was an iPro2 and one was a Guardian Real-Time. H values from the iPro2 data were consistently higher than H values from the Guardian device. This outcome is most likely due to the calibration algorithms used to process the raw sensor data and estimate the underlying blood glucose concentration. The retrospective calibration utilized by the iPro2 device potentially has a higher degree of smoothing/filtering that leads to lower complexity of the output CGM trace. Due to privacy restrictions placed on the calibration algorithms, this could not be fully confirmed by comparing the algorithms directly. However, an analysis of the raw pre-calibration I_{SIG} data from the sensors showed no significant difference between the H values from each device. Thus, the difference in H observed when assessing SG data can be attributed to the calibration algorithm and/or potentially the CGM hardware used.

Sensor location (thigh iPro2 data vs. abdomen iPro2 data) had little effect on the scaling exponent determined through monofractal DFA and the range of H values for each sensor location were similar. Furthermore, comparing the results from two sensors monitoring the same individual showed no consistent trend of one sensor having a higher H value than the other. Repeating the analysis using the raw sensor I_{SIG} to eliminate any calibration effects gave similar results and the scaling exponent

was not dependent on location. These results suggest that CGM sensor location, at least thigh vs. abdomen, should not have a significant effect on the results of a study using monofractal DFA.

4.2 Multifractal DFA

The two previous studies of DFA in ICU patients only used monofractal DFA to assess glucose complexity [22, 23], but this study also tested multifractal DFA. Analyses of SG data using multifractal DFA in this study were unable to associate the shape, width or position of the multifractal spectrum with CGM device type or sensor location. Furthermore, overlaying all of the multifractal spectrums from all sensors in a single figure, similar to Figure 2, showed no clear trends to differentiate between CGM device types or sensor locations. The I_{SIG} results showed essentially the same results.

However, one very important finding from the multifractal DFA was the width of the multifractal spectrums. Each spectrum was spread across a wide range of exponents, which suggests the scaling of SG data is multifractal, and not monofractal, by nature. Thus, future studies that investigate glucose complexity using CGM data should test for multifractal scaling and consider multifractal DFA in their analyses.

Another interesting finding from the multifractal analysis is depicted in the subplots of Figure 3. In these four cases, monofractal DFA of both data sets produced the same H value, but their multifractal spectrums were clearly and significantly different. These differences between monofractal and multifractal results are important as they could skew the interpretation of results and lead to incorrect conclusions from studies of this nature. These results reiterate the need for a thorough analysis and highlight why care must be taken when interpreting results.

Figure 4 illustrates an important secondary observation from this study, that complexity analysis provides different information to other metrics such as mean glucose or glycaemic variability. Example 'A' shows three SG traces that track each other well and report similar overall glycaemia. Although the mean and variability of the traces are similar, their multifractal spectrums are very different, indicating each SG trace has unique scaling properties. Conversely, example 'B' shows two SG traces that have quite different dynamics and don't track each other very well, but the multifractal spectrums for each sensor show very similar scaling properties.

4.3 Limitations

There are several limitations of this study that need to be addressed. First, the data set used here contains 26 sets of CGM data from a relatively small cohort of critically ill patients, compared with the two previous studies of DFA in critically ill patients. Despite this limitation, the analysis did highlight several important aspects that should be considered in future studies including the effects of sensor location and CGM device/calibration on DFA results. Equally, the total number of sensors available for assessing the impact of calibration and location ensure novel results that are robust.

Second, the patients in this study all had stress-induced hyperglycemia due to the severity of their illness, rather than pre-existing diabetes. A similar study investigating patients with diabetes in the ICU may yield different results leading to different conclusions. Thus, the findings presented here are not necessarily generalizable to all patient types.

Third, the sensors and devices used in this study were different to those used in the two previous studies of DFA in critically ill patients. Therefore, a direct comparison between all three studies is not appropriate. The devices in those studies were no longer available when this study data was collected and a newer generation of technology was used. Thus, the study conditions that would allow an exact comparison could not be replicated. However, any potential differences due to advancing technology would, again, indicate the impact of technology on DFA assessment of physiology.

Fourth, the quality of results from DFA depends on the quality of CGM data. While an MARD of ~12% is considered good performance by current CGM device standards, it cannot be guaranteed that the device has accurately and reliably recorded only true physiological glycemic dynamics without interferences or noise. Fortunately, sensor technologies are constantly evolving and their accuracy improving. It is also possible that clinical factors, such as certain drugs and/or illnesses may have an impact on sensor performance. However, the impact of such clinical factors were mitigated in this study by strictly comparing SG data from devices monitoring the same individual, ensuring sensors were exposed to the same monitoring conditions.

5.0 Conclusion

The results of this study revealed three key findings that should be considered when analyzing glucose complexity in critically ill adults:

1. Monofractal DFA results were sensitive to the type of CGM device used to collect the glucose data, and the calibration in particular. Data from the iPro2 CGM device gave consistently higher DFA results compared to data from the Guardian Real-Time CGM device.
2. Sensor location (abdomen vs. thigh) had no significant effect on DFA results.
3. Multifractal DFA results were not always consistent with monofractal DFA results. Furthermore, the width of the multifractal spectrums suggests that multifractal DFA should be considered in future glucose complexity studies.

Further investigations of glucose complexity are required before solid conclusions can be drawn. However, this study clearly highlights where care should be taken in the design of those studies and the analysis of the results.

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Supplementary file - DFA implementation

First, the time series (x) is summed and mean subtracted using Equation S1.

$$Y(i) = \sum_{k=1}^{i}[x_k - \langle x \rangle], \quad i = 1, \ldots, N \qquad \text{Equation S1}$$

Second, the profile $Y(i)$ is divided into N_s non-overlapping segments of equal length s and the trend for each segment is approximated using a least-square fit, as shown in Figure S1 for segment sizes of 32, 64 and 128 SG measurements.

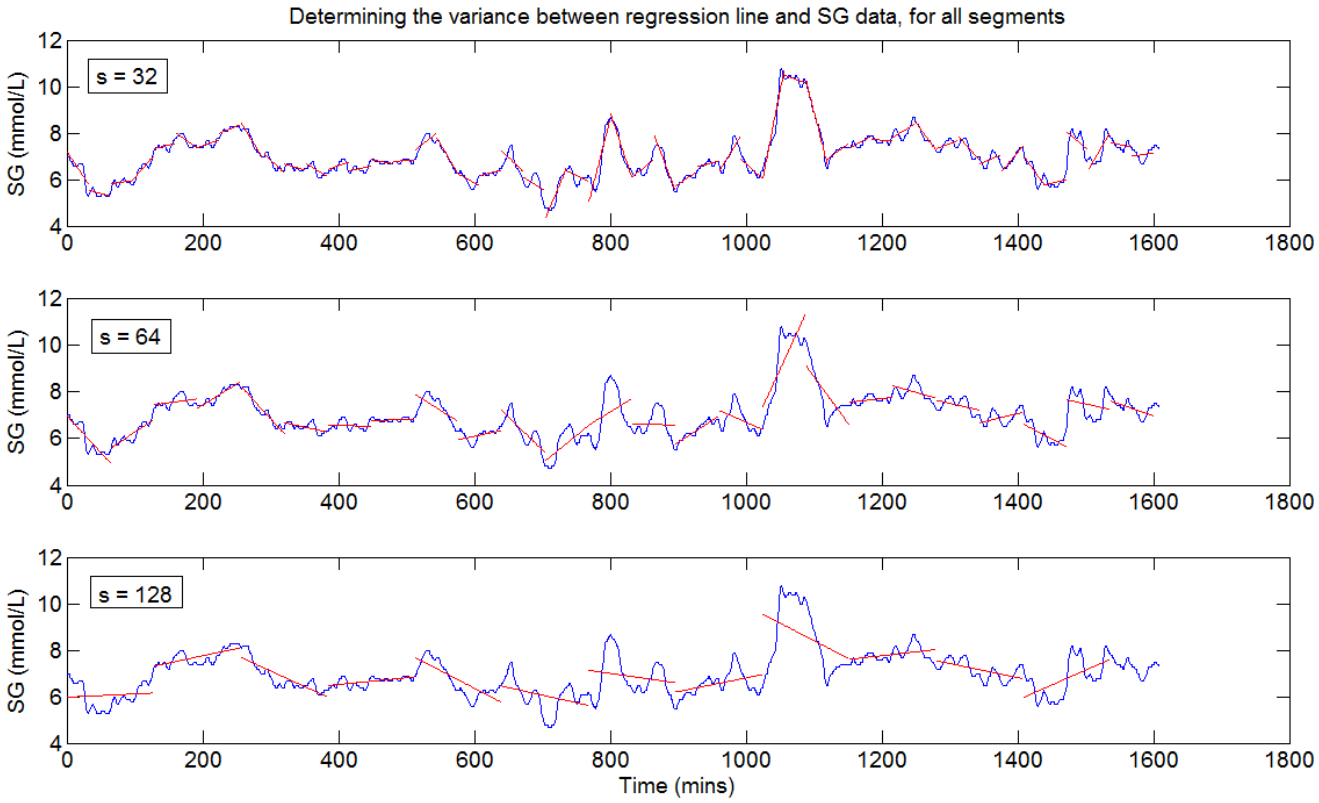

Figure S1: Three examples showing segmented SG data with linear regression lines. The segment size increases from top to bottom. The variance between each regression line and the corresponding SG data in that segment is calculated using Equation 2.

The variance between the time series and the least-square fit for each segment v is calculated using Equation S2.

$$F^2(v,s) = \frac{1}{s}\sum_{i=1}^{s}(Y[(v-1)s + i] - y_v(i))^2 \qquad \text{Equation S2}$$

Third, the *qth* order fluctuation function is calculated using equation S3, where a monofractal DFA is obtained by holding *q*=2. Essentially, Equation S3 gives a *qth* order RMS of the variances calculated using Equation S2. For positive *q*, large deviations from the fitted trend will have more influence on the fluctuation function than small deviations, and, for negative values of *q* small deviations will have a larger influence on the fluctuation function. The degree to which the fluctuation function is influenced by *q* is determined by the magnitude of *q*.

$$F_q(s) = \left\{\frac{1}{N_s}\sum_{v=1}^{N_s}[F^2(v,s)]^{q/2}\right\}^{1/q} \qquad \text{Equation S3}$$

The scaling behavior of the fluctuation functions is illustrated by analyzing a plot of log($F_q(s)$) versus log (s) for each *q*. For a scale invariant series, the relationship is linear and the slope represents the power law exponent, H, as in Figure S2 (left). For a multifractal time series, the scaling exponent will change for different values of q, as shown in Figure S2 (right).

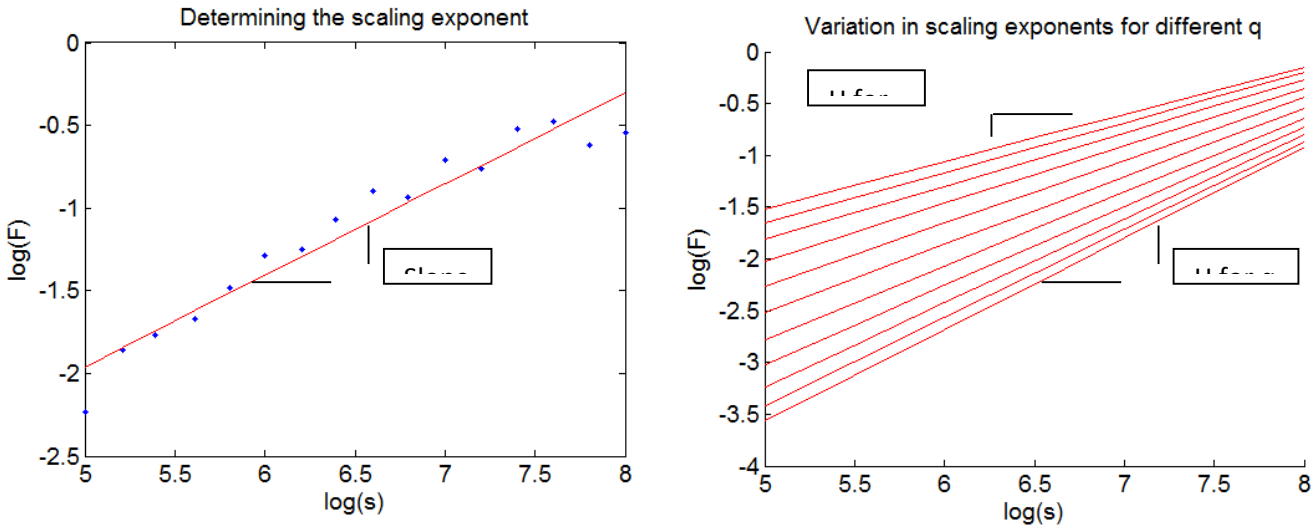

Figure S2: (left) Example plot of log(F) versus log(s) for a single value of *q*, where the slope of the linear regression line is the scaling exponent, H. (right) Example of how H changes for different values of q, for a multifractal time series

For the case of q=0, Equation S3 cannot be employed so a logarithmic averaging procedure is used instead (Equation S4).

$$F_0(s) = exp\left\{\frac{1}{2N_s}\sum_{v=1}^{N_s}\log[F^2(v,s)]\right\} \quad \text{Equation S4}$$

Multifractal DFA performs best when the signal being analyzed is noise-like rather than a random walk. To determine the type of signal a monofractal DFA can be run prior to multifractal DFA. If the power law exponent, H, is between 0.2 – 0.8 then the time series is noise-like and multifractal DFA can be run without modification. However, if H is between 1.2 – 1.8 then the time series is more like a random walk. For random walk signals, the integrating process (Equation S1) can be skipped, and +1 should be added to the power law exponents determined in the multifractal analysis [32].

To aid the interpretation of the multifractal scaling properties of a time series, the mass exponent ($\tau(q)$), q-order singularity exponent ($h(q)$) and q-order singularity dimension ($D(q)$) are calculated using Equations S5-S7.

$$\tau(q) = q.H(q) - 1 \quad \text{Equation S5}$$

$$h(q) = \tau'(q) \quad \text{Equation S6}$$

$$D(q) = q.h(q) - \tau(q) \quad \text{Equation S7}$$

A plot of $\tau(q)$ vs. q (Figure S3 - left) or $h(q)$ vs. q (Figure S3 - right) can be used to determine the degree of multifractal scaling in a time series. A plot of $D(q)$ vs. $h(q)$ displays the mulitfractal spectrum. The width, shape and location of the multifractal spectrum can all be used to give important information about the relationship between the time series and the physiological phenomenon being studied.

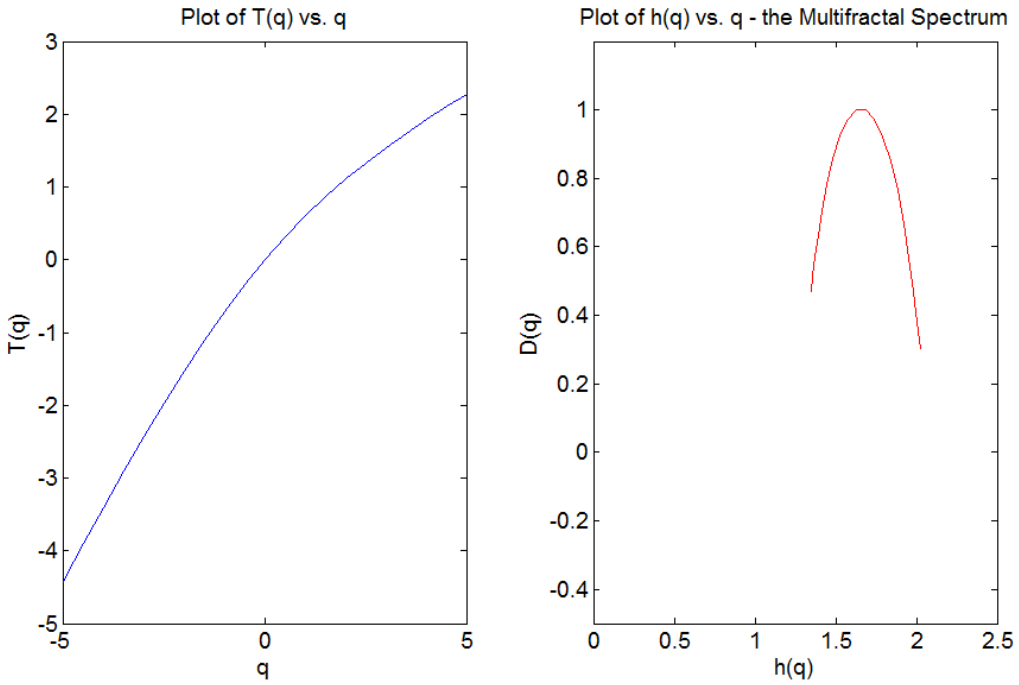

Figure S3: (left) plot of $\tau(q)$ vs. q and (right) $h(q)$ vs. q, either of which can be used to interpret the scaling properties of a multifractal time series.