

# The Effect of Hypoglycemia on Spectral Moments in EEG Epochs of Different Durations in Type 1 Diabetes Patients

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**Abstract**—The potential of using an electroencephalogram (EEG) to detect hypoglycemia in patients with type 1 diabetes (T1D) has been investigated in both time and frequency domains. Under hyperinsulinemic hypoglycemic clamp conditions, we have shown that the brain's response to hypoglycemic episodes could be described by the centroid frequency and spectral gyration radius evaluated from spectral moments of EEG signals. The aim of this paper is to investigate the effect of hypoglycemia on spectral moments in EEG epochs of different durations and to propose the optimal time window for hypoglycemia detection without using clamp protocols. The incidence of hypoglycemic episodes at night time in five T1D adolescents was analyzed from selected data of ten days of observations in this study. We found that hypoglycemia is associated with significant changes ( $P < 0.05$ ) in spectral moments of EEG segments in different lengths. Specifically, the changes were more pronounced on the occipital lobe. We used effect size as a measure to determine the best EEG epoch duration for the detection of hypoglycemic episodes. Using Bayesian neural networks, this study showed that 30 second segments provide the best detection rate of hypoglycemia. In addition, Clarke's error grid analysis confirms the correlation between hypoglycemia and EEG spectral moments of this optimal time window, with 86% of clinically acceptable estimated blood glucose values. These results confirm the potential of using EEG spectral moments to detect the occurrence of hypoglycemia.

**Index Terms**—Electroencephalogram (EEG), hypoglycemia, optimal time window, spectral moment.

## I. INTRODUCTION

**H**YPOGLYCEMIA is defined as a low blood glucose level (usually less than 3.9 mmol/L). This condition is a dangerous complication of insulin and sulphonylureas in diabetes treatment. The average T1D patient suffers thousands

of episodes of symptomatic hypoglycemia over a lifetime of diabetes [1]. The fear of hypoglycemia affects the daily routines of both patients and their carers and contributes a significant factor in the failure of achieving satisfactory glycemic targets for the patients [2]. Hypoglycemia manifests both autonomic symptoms and neuroglycopenic symptoms. Whereas some autonomic symptoms are adrenergic (palpitations, anxiety, etc.), others are cholinergic (sweating, hunger, etc.). Neuroglycopenic symptoms include seizures, loss of consciousness, and can be life-threatening [3].

Severe hypoglycemia is defined as a hypoglycemic episode having blood glucose levels less than 2.8 mmol/L and/or requiring assistance from another person for treatment to recover [4]. The brain depends on a constant supply of glucose to maintain its function. Severe hypoglycemic episodes can cause acute brain malfunction that leads to neuroglycopenic symptoms. There are three high-risk sources of severe hypoglycemia: hypoglycemia unawareness, intensive insulin therapy, and being asleep [5]. In people with diabetes, the defense mechanisms may become attenuated and cannot correct hypoglycemia naturally, leading to hypoglycemia unawareness. People with hypoglycemia unawareness have reduced symptomatic responses. Their blood glucose levels, therefore, can fall to dangerously low values in the severe range. With intensive insulin therapy, although the risk of retinopathy, nephropathy, and neuropathy is effectively reduced, patients undergoing this therapy experience a threefold increase of severe hypoglycemic episodes [4]. Nocturnal hypoglycemia is particularly dangerous because sleep may obscure autonomic counterregulatory responses. More than half of severe hypoglycemic episodes occur at night time [6].

It has been established that in clamp studies, there is a relationship between hypoglycemia and EEG recordings of the brain. In these studies, hypoglycemia was induced by a variation of insulin doses to allow blood glucose levels to follow a specific clamp profile. During hypoglycemic episodes, theta activity increased, and alpha activity decreased [7, 8]. When patients experienced hypoglycemia, EEG power spectra estimated from P4-O2 shifted from fast alpha frequencies to lower frequencies in theta and delta bands [9]. Centroid frequencies of the alpha and theta bands on the occipital lobe (O1 and O2) changed significantly when adolescents with T1D experienced hypoglycemic episodes at night time [10-13]. The significant changes in alpha centroids

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of C3-P3 electrodes were found in adult patients during hypoglycemia [14]. Besides the standard spectral features, EEG coherence and complexity were reported as potential features for detecting hypoglycemia. The influence between O1 and C4 measured by partial directed coherence decreased significantly in 19 T1D patients during hypoglycemia [15]. There was also a significant reduction in P3-C3, O1-A1A2, and O2-A1A2 complexity when T1D patients experienced a hypoglycemic state [16-18].

Without clamp protocols, changes in electrocardiogram (ECG) and EEG signals have also been observed during hypoglycemia. Associated with hypoglycemic episodes, the corrected QT interval of ECG signals increased significantly [19, 20]. The power of EEG signals was used to investigate the association between hypoglycemia and brain waves. There was coherence between interstitial blood glucose fluctuations and EEG power in all frequency bands of six channels (F3, F4, C3, C4, O1, and O2) [21]. In a study on 9 adolescents with T1D, changes in EEG power in different areas of the brain had no significant correlation with interstitial glucose concentration in the hypoglycemic range [22].

Recently, we have proposed the use of EEG spectral moments for the detection of nocturnal hypoglycemia [23]. From the data of eight patients in the hyperinsulinemic hypoglycemic clamp study, the proposed features showed a better benchmark compared to standard features. The potential of using EEG as a biomarker for hypoglycemia episodes is still in need. In contrast to autonomic symptoms, hypoglycemia associated EEG changes are not blunted during low blood glucose episodes in patients with hypoglycemia unawareness [24]. In addition, EEG signals provide a direct correlation with the fluctuation of plasma blood glucose.

Different from our previous study [23], we analyze changes in EEG spectral moments of the central and occipital areas during hypoglycemia in the current study, without using the clamp protocol. We hypothesize that these changes would be similar to what we found in the clamp conditions. Using interpolation, we match the number of hypoglycemic episodes to that of non-hypoglycemic episodes. We investigate the effect of hypoglycemia on spectral moments in EEG epochs of different durations. In this work, Cohen's  $d$  effect size is used to compare the difference of EEG spectral moments between hypoglycemic and non-hypoglycemic conditions for various segment lengths of EEG signals. The calculated effect size will be used to select the optimal time window for nocturnal hypoglycemia detection. The classification results of hypoglycemic episodes from different segment lengths are then used to validate this selection. We also assess the clinical accuracy of using EEG spectral moments for detecting hypoglycemia from the optimal time window size. The estimated blood glucose levels are compared to the actual/interpolated blood glucose levels on Clarke's error grid.

The rest of this paper is structured as follows. Section II presents the study protocol of hypoglycemia, interpolation of glucose data, and extraction of spectral moments. This section also covers the determination of the optimal EEG segment length. In Section III, we report the results of this study. This is followed by Section IV, which gives a discussion on the obtained results. Finally, the entire work is concluded in Section V.

## II. METHODOLOGY

### A. Study Protocol

This study was conducted on five adolescents with type 1 diabetes at Princess Margaret Hospital for Children (Perth Children's Hospital) in Perth, WA, Australia. Informed consent was obtained from all participants or their representatives. The participants were studied in the sleep laboratory. EEG signals were acquired continuously using the Compumedics EEG system. Participants' blood glucose levels were monitored by glucose analysis using YSI 2300 STAT sampling. To reduce the number of blood samples taken and minimize disruption to participants' sleep, a continuous glucose monitoring (CGM) device, Dexcom G4, was also used in this work.

EEG electrodes were attached on the scalp according to the international 10/20 system, with the setting of impedance less than 5 k $\Omega$  on arrival. During the study, changes in electrode impedances were recorded. The acquisition of EEG data was performed with the participants at rest in bed and during sleep. Signals from the frontal (F3 and F4), central (C3 and C4), parietal (P3 and P4), and occipital (O1 and O2) regions were acquired at a sampling rate of 512 Hz. The EEG amplifier was configured with a 0.15 to 30 Hz band-pass filter and a 16-bit analog to digital converter. Two electrocardiogram electrodes were also attached as a part of monitoring.

All participants had their CGM sensor insertion one to three days before the study day at the clinic. Two sets of observations were conducted for each participant. On one visit of the study, a cannula was inserted in a superficial vein for venous blood sampling. The participants had their usual dinner at least 2 hours prior to bed, and had their usual insulin dose given at meal time. While sensor glucose readings were recorded at each 5 minutes interval, the blood sampling period using YSI varied between 5 to 30 minutes, depending on the rate of fall when hypoglycemia is predicted. The same procedure was conducted for another visit, except the overnight insulin dose was intensified by 20% to increase the likelihood of hypoglycemia. The endpoint of the study is when two consecutive venous samples are having glucose levels of less than 2.8 mmol/L, or participants wake up requesting hypoglycemic treatment.

### B. Interpolation of Blood Glucose Levels

In this study, the blood sampling frequency was minimized to reduce disturbance to the participants. As a result, we achieved a limited number of YSI glycemic samples for the study. In addition, the number of hypoglycemic episodes was unmatched by that of non-hypoglycemic episodes. Therefore, we used interpolation to approximate the intermediate blood glucose levels. The original YSI blood glucose profile of each patient was resampled using linear piecewise interpolation. Data between YSI sampling points were represented by a linear trace. This technique of interpolation was proved to provide acceptable intermediate values of blood glucose [25].

The interpolated profiles were then compared to the CGM profiles to ensure the selected interpolated values are appropriate for use. Fig. 1 shows blood glucose levels of two representative patients estimated by the CGM, the YSI, and selected from the interpolation algorithm. For each patient, the

selected interpolated values were added to the original YSI profile in the way that the number of glycemic episodes under hypoglycemia and non-hypoglycemia became matched.

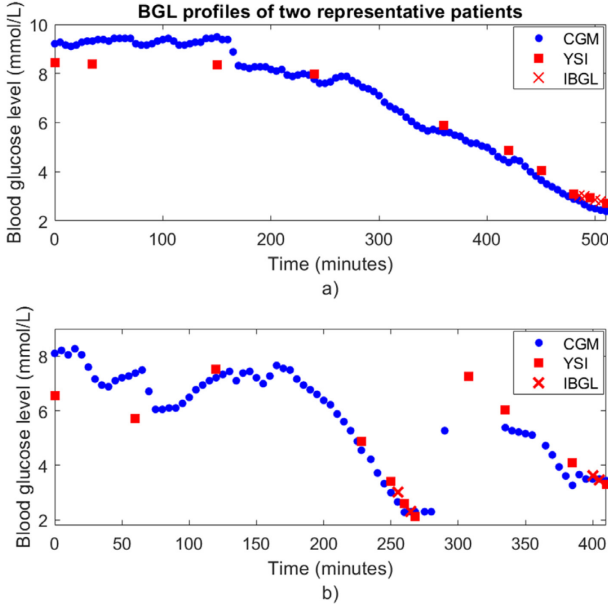


Fig. 1. Blood glucose profiles of two representative patients: a) and b), estimated by the Dexcom G4 device (CGM), the Yellow Springs Instrument device (YSI). IBGL denotes selected interpolated blood glucose levels.

### C. EEG Segmentation and Feature Extraction

EEG signals from the central and occipital areas were chosen for analysis in this study since these areas were proven to be highly responsive to hypoglycemic episodes [7, 11]. EEG epochs were then extracted at the selected blood resampling points. Choosing a proper window size for the segmentation plays a vital role in analyzing EEG signals, especially for the application of hypoglycemia detection. In this work, EEG epochs of different durations from 5 seconds to 90 seconds were investigated. These epochs were labeled as hypoglycemia (corresponding to a blood glucose level of less than 3.9 mmol/L) and non-hypoglycemia.

The EEG epochs were transformed into the frequency domain using Welch's power spectral density estimation. The analysis was carried out on four frequency bands: delta (0.25-3.75 Hz), theta (4-7.75 Hz), alpha (8-12.75 Hz), and beta (13-29.75 Hz). Features based spectral moments [23] were then calculated for each band, as shown in Table I.

Spectral moments provide quantitative information about the shape of a spectral curve in a specific frequency band. In particular, the zero-order moment of a band is the total power in that band. The ratio of the first and zero order spectral moments is named centroid frequency, which is the center of gravity of the power spectrum. The spectral gyration radius is the root mean square of the second order moment divided by the total power. This feature measures the spread of power with respect to the coordinate origin. The use of the second-order moment helps to distinguish two spectral curves that have the same center of gravity but are different in shape.

In this study, we also computed the spectral gyration radius

of mobility and complexity of EEG signals. The mobility and complexity are derived from the first and second derivatives, respectively, of the signals. Using the property of the Fourier transform, the spectral gyration radius measures of the mobility and complexity were obtained from the second, fourth, and sixth order moments without performing calculations in the time domain.

TABLE I  
SPECTRAL MOMENTS BASED FEATURE EXTRACTION

Feature	Description	Explanation
$CF$	$\frac{m_1}{m_0}$	The center of gravity of an EEG power spectrum.
$G_0$	$\sqrt{\frac{m_2}{m_0}}$	The spectral gyration radius of EEG signals.
$G_1$	$\sqrt{\frac{m_4}{m_2}}$	The spectral gyration radius of EEG mobility.
$G_2$	$\sqrt{\frac{m_6}{m_4}}$	The spectral gyration radius of EEG complexity.

The combination of centroid frequency and spectral gyration radius measures forms an EEG pattern for hypoglycemia associated EEG analysis. In this work, we used t-tests to point out the differences between EEG spectral moments during hypoglycemia and those during non-hypoglycemia. The significance levels of change in spectral features extracted from different segment lengths were then compared to investigate the effect of segmentation on hypoglycemia-induced EEG. Features having P-values of less than 0.05 are considered to be statistically significant.

### D. Optimal EEG Segment Length

Statistical results have been used to choose the optimal thresholds, electrodes, or window sizes in a lot of EEG based studies [26-28]. The power of a statistical test depends on the number of samples in the study, the effect size, and the significance criterion [29].

Effect size is a measure of separability between groups of observations. This parameter explains the practical significance of statistical results. In this study, Cohen's  $d$  effect size was used to compare the effect of different segment lengths of EEG signals. Firstly, the effect size of significant spectral features was calculated as follows:

$$d = \frac{X_1 - X_2}{\sqrt{\frac{(n_1 - 1)\sigma_1^2 + (n_2 - 1)\sigma_2^2}{n_1 + n_2 - 2}}}, \quad (1)$$

where  $X_i$  is the mean value,  $\sigma_i^2$  is the variance, and  $n_i$  is the number of samples in each group (hypoglycemia vs. non-hypoglycemia,  $i = 1, 2$ ).

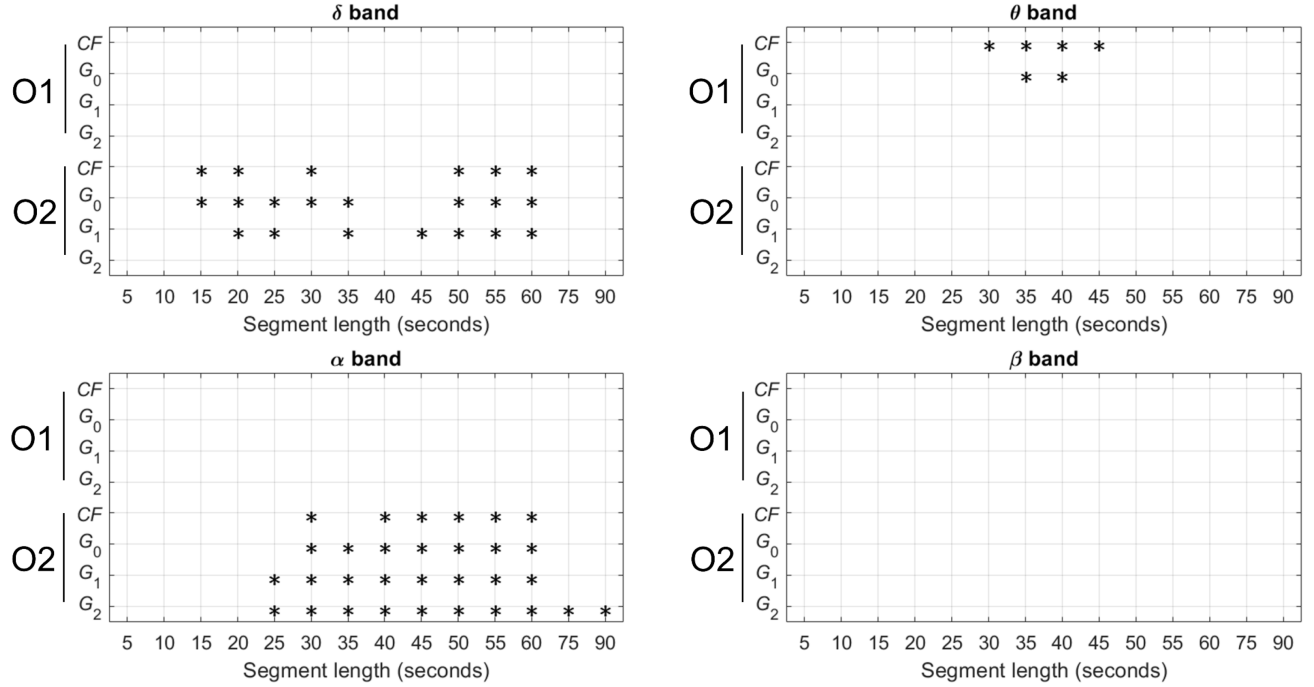


Fig. 2. Significant levels of different EEG segment lengths in the delta, theta, alpha, and beta bands of the occipital lobe. The levels of significance are marked with symbols (an asterisk \* means  $P < 0.05$ ). No significant changes were found in the beta band during hypoglycemia.

The effect size of each segment length was then computed by averaging of the effect sizes obtained from the four frequency bands. The segment length with the largest effect size would be considered as an optimal window for detecting hypoglycemic episodes.

To validate the optimal window from the effect size calculation, we compared the classification results of glycemic episodes from each segment length. In this work, Bayesian neural networks were exploited to classify glycemic episodes [23, 30].

### III. RESULTS

TABLE II  
BLOOD GLUCOSE CHARACTERISTICS OF FIVE PARTICIPANTS (MMOL/L)

Condition	Original profiles	Matched profiles
Hypoglycemia	2.97±0.48	2.97±0.48
Non-Hypoglycemia	6.94±2.67	6.87±2.66

On each visit with a 20% extra insulin dose, all five participants had hypoglycemia. Without this extra dose, only one patient experienced hypoglycemic episodes. There is a total of 21 hypoglycemic and 35 non-hypoglycemic YSI blood sampling measures in the actual glucose profiles of 5 patients. For each patient, the YSI blood glucose profile was resampled at 5 minute intervals using interpolation when required. We used Dexcom estimated blood glucose values as a reference to choose interpolated blood sampling points for matching profiles. The final data set in this study is composed of 36 hypoglycemic episodes and 36 non-hypoglycemic episodes. As shown in Table II, the matched profiles were created with minimal changes compared to the original profiles.

EEG segments in different lengths from 5 seconds to 90 seconds were extracted at the selected blood resampling points in the matched profiles. Spectral features were then computed for each segment. We found no significant changes in channel C3. Changes in channel C4 were only significant at the spectral gyration radius extracted from 60 second segments. In contrast to the central area, the most significant changes were observed on the occipital lobe. The level of significance of differences in the spectral features between hypoglycemia and non-hypoglycemia on this lobe is shown in Fig. 2. Changes in O2 spectral moments of the delta band were significant with the segment lengths from 15 seconds to 60 seconds except for 40 second segments. For the theta band, the centroid frequency and spectral gyration radius extracted from 30 second to 45 second segments changed significantly. It is worth noticing that all the spectral features of the alpha band from channel O2 were found to be significant in 30 second segments and in segments from 40 seconds to 60 seconds. For the beta band, the results show no significant changes during hypoglycemia.

The effect sizes of different EEG segment lengths are shown in Fig. 3. Three segment lengths provided the effect sizes of greater than 0.38: 30 second, 35 second, and 45 second segments. Although the highest effect size came from 35 second segments, there was little distinction between the effect size of 30 second and 35 second segments. The figure also reveals that the effect sizes computed from the other segments are less than 0.28. Notably, the sizes of differences between hypoglycemia and non-hypoglycemia obtained from 5 second and 10 second segments were zero because there were no significant changes in these segment lengths.

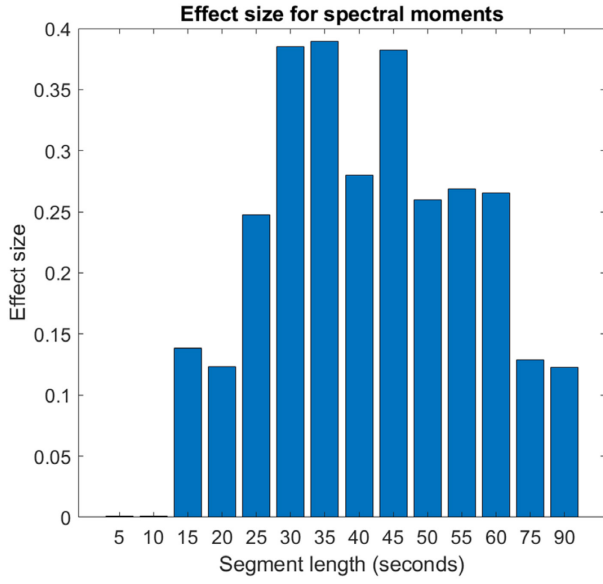


Fig. 3. Effect size for EEG spectral moments of different segment lengths. Three segment lengths provided the effect sizes of greater than 0.38: 30 second, 35 second, and 45 second segments.

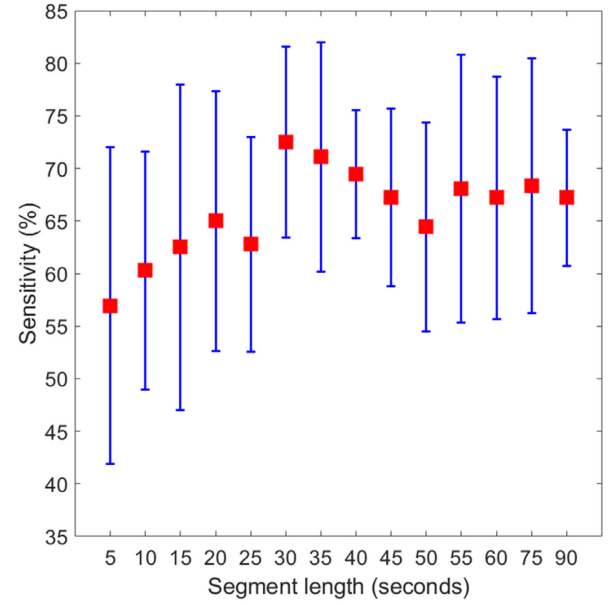


Fig. 4. Results of sensitivity of different EEG segment lengths. The 30 second segment provided the best sensitivity.

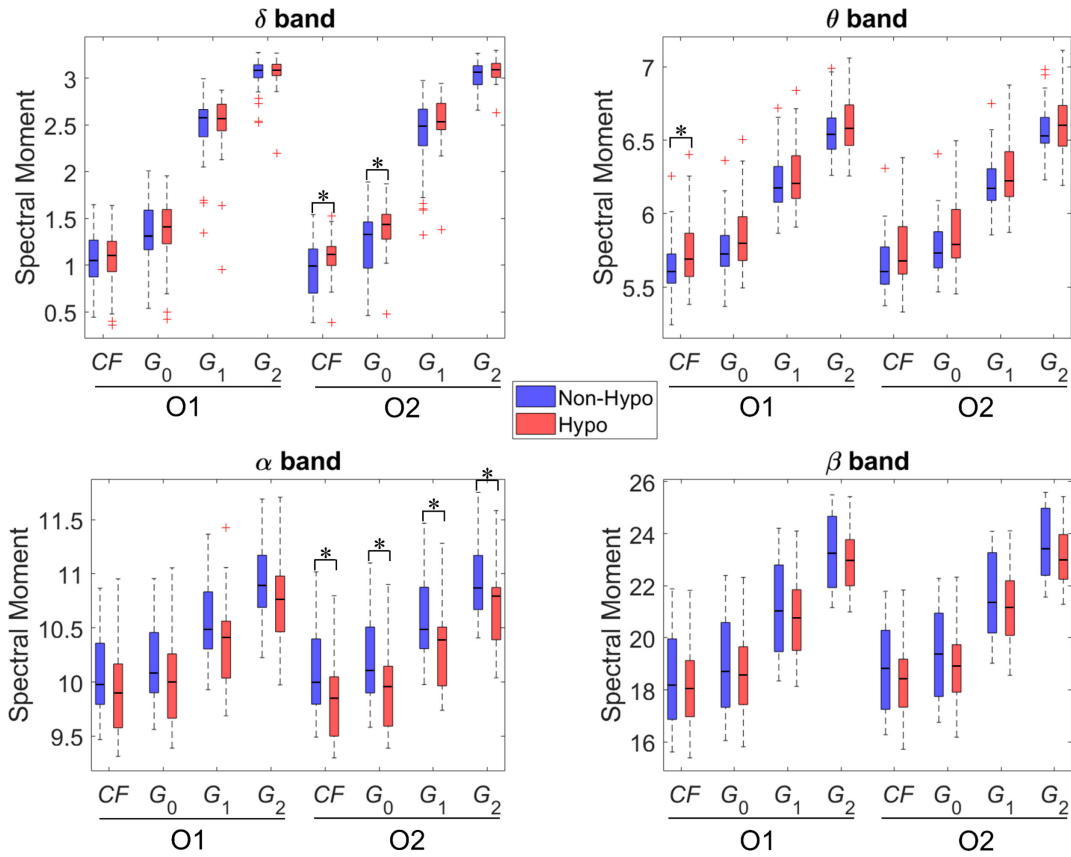


Fig. 5. Changes in spectral moments of the delta, theta, alpha, and beta bands on the occipital lobe. Boxplots represent the values of spectral features computed from 30 second EEG segments during hypoglycemia (red) and non-hypoglycemia (blue). The level of significance is presented by asterisks (\* means  $P < 0.05$ ).

The results of the effect size calculation suggest that 30 second or 35 second EEG segments should provide the best detection rate for an EEG based hypoglycemia detection system. To validate this, we compared the classification results of glycemc episodes from all observed segment lengths. Bayesian neural networks were used as classifiers for this purpose.

From four frequency bands of the four channels, the feature extraction algorithm results in 64-element input vectors for the networks. Tangent functions were used for the network hidden layer, and sigmoid functions were employed to activate the network output layer. From the resampled blood glucose profiles, the data set corresponding to each segment length of five patients is composed of 36 hypoglycemic vectors and 36 non-hypoglycemic vectors. 50% of the data were used as the training set, and the other 50% were used as the test set. The training and testing phases were repeated in 20 repetitions for each segment length using the algorithm described in our previous study [23]. In the training stage, specificity was kept at 50% to maximize the value of sensitivity and to find the cut-off value for the output of the classifier. The results of the sensitivity of the test set obtained from different lengths of EEG segments are presented in Fig. 4. This figure shows that 30 second EEG segments provide the best average sensitivity of  $72.50 \pm 9.10\%$ . For 35 second segments, the average sensitivity stops at  $71.11 \pm 10.90\%$ .

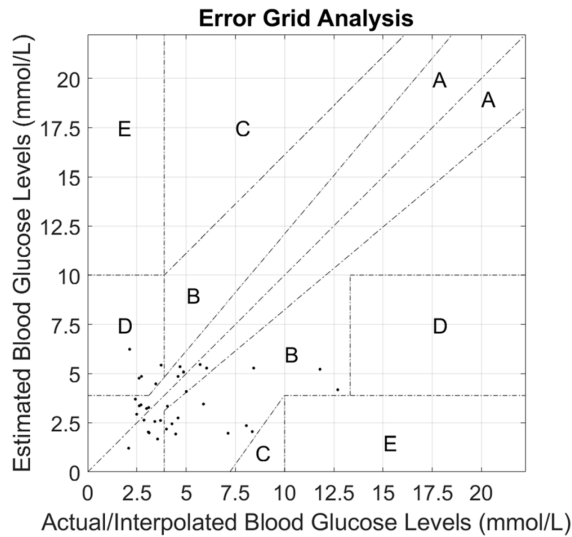


Fig. 6. Clarke's error grid analysis for evaluating the correlation between estimated blood glucose values and actual/interpolated blood glucose levels.

TABLE III  
DISTRIBUTION OF POINTS ON THE ERROR GRID

Zone	Number of points	Percentage (%)
A	20	55
B	11	31
C	0	0
D	5	14
E	0	0

In comparison with the results of the effect size computation, classification results showed that the optimal length of EEG segments for hypoglycemia detection using spectral moments is 30 seconds. Fig. 5 presents changes in spectral moments of EEG signals on the occipital lobe using this segment length. Data in this figure reveal that during hypoglycemic episodes, the delta centroid and spectral gyration radius increased significantly on channel O2. For the theta band, the centroid frequency went upward significantly on channel O1. By contrast, all spectral features of the alpha band decreased significantly at O2. The figure shows a reduction in the values of all beta spectral features, but no significance was found for this band.

We designed a Bayesian neural network to estimate blood glucose levels using the extracted EEG features of 30 second segments. The one-node output of this network was activated by a linear function. The training and testing schemes were set to maximize the sensitivity, as described in [31]. Using the hypoglycemic threshold of 3.9 mmol/L, the optimal neural network resulted in a sensitivity of 72% and a specificity of 50% for the test set. The clinical accuracy of the estimated blood glucose values was assessed by Clarke's analysis. The results of this error grid analysis are shown in Fig. 6 and Table III. The grid was created using resampled blood glucose levels and estimated values. The table shows that 86% of estimated blood glucose levels are clinically acceptable. In particular, there are 20 points (55%) in zone A and 11 points (31%) in zone B. However, 14% of the estimated values are potentially not acceptable.

#### IV. DISCUSSION

Previous publications have established that there are significant correlations between hypoglycemia and EEG signals [13, 15, 17, 32]. However, these studies were conducted under hyperinsulinemic hypoglycemic clamp conditions. Hypoglycemia associated EEG changes have to date been poorly investigated in the setting of non-clamp conditions. The first aim of the current work was to investigate the effect of hypoglycemia on spectral moments in EEG epochs of different durations in five T1D patients. Fourteen epoch durations were used for the observation. The second aim of this work was to propose the optimal time window for the detection of hypoglycemia.

Linearly interpolated blood glucose levels were proved to enhance results for glycemc control performance [25]. In our study, the use of interpolation helped to increase the number of glycemc samples. In particular, we exploited linear interpolation to resample YSI blood glucose profiles. The matched profiles were created from the actual YSI profiles and the selected interpolated values. Compared to the excessive use of interpolated blood glucose values in our previous study [33], the intermediate blood values in the current study were chosen with a reference from CGM measures to ensure there are appropriate values resulting in the matched profiles.

Since EEG signals are non-stationary, the selection of the epoch duration may affect the assessment of how hypoglycemia induces the electrical activity of neurons in the brain. In our previous study [23], we extracted spectral

moments from 20 second EEG segments for analyses. Different EEG segment lengths were used in other hypoglycemia-related studies, such as 2 seconds [22], 4 seconds [17], 5 seconds [34], and 10 seconds [14]. To the best of our knowledge, there has been no quantification of which length of EEG segments provides the best performance for a hypoglycemia detection system. From the balanced profiles, hypoglycemia associated EEG changes were investigated using different segment lengths of EEG signals in the present study. Significant changes in EEG spectral features were observed during the occurrence of hypoglycemia. This study shows that 30 second segments can provide the best detection rate for a hypoglycemia detection system using EEG spectral moments. With the finding of the optimal length, our study, therefore, has proposed an optimal detection rate defined within 30 seconds of YSI measured/interpolated blood glucose values. This time delay is reasonable, compared to CGM devices. For instance, the detection rate of the Dexcom G6 is defined within 15 minutes of YSI measures [35].

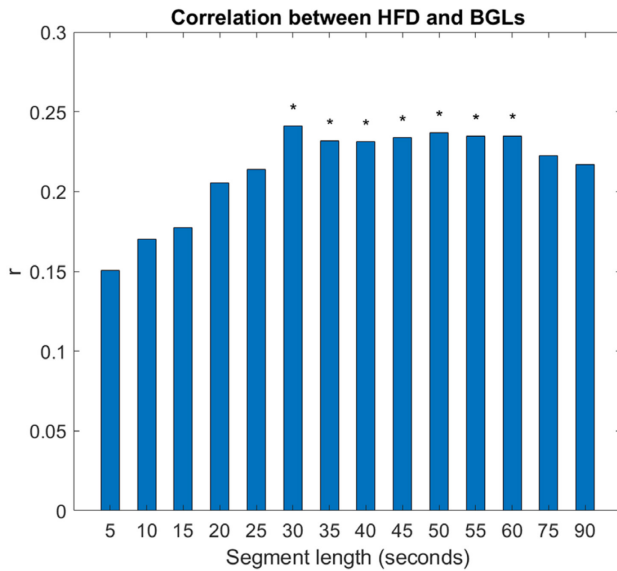


Fig. 7. Correlation between the Higuchi fractal dimension (HFD) and blood glucose levels in EEG segments of different lengths from channel O2. 30 second segments provide the highest correlation of 0.24.

We also analyzed changes in EEG signals' complexity using the Higuchi fractal dimension [36]. The Higuchi measure of fractal dimension has been used to detect EEG changes induced by hypoglycemia [17]. This algorithm has the computational cost of  $O(n)$ , which is the same as the calculation of spectral moments [23]. In the present study, the fractal dimension was computed for EEG epochs in different durations (5 seconds to 90 seconds) with the setting of  $k_{max}=6$  [17, 37]. During the occurrence of hypoglycemia, a decrease in the Higuchi fractal dimension of channel O2 was found statistically significant ( $P<0.05$ ) in segments from 30 seconds to 60 seconds. It is noticeable that the values extracted from the other channels (C3, C4, and O1) had no significant changes. The correlation between O2 fractal dimension and blood glucose levels is presented in Fig. 7. Data in this figure

shows that the fractal dimension extracted from 30 second segments provides the highest correlation ( $r=0.24$ ,  $P<0.05$ ) to blood glucose levels. Furthermore, the effect size for the Higuchi fractal dimension from channel O2 was also largest (0.52) at the epoch duration of 30 seconds. These findings confirm the potential of this segment length of EEG signals in discriminating glycemic conditions in T1D patients.

The trend of changes in theta and alpha bands during the occurrence of hypoglycemia in the current study are consistent with the previous clamp studies [10, 11, 13, 23, 24]. When blood glucose levels went lower than 3.9 mmol/L, alpha centroids decreased, and theta centroids increased, both significantly. Fig. 2 shows that during hypoglycemia, significant changes in the theta band are at O1, whereas it is O2 for the alpha band. To achieve a robust conclusion about the relationship between frequency bands and probe positions, a larger number of T1D patients is required. In the present study, although the beta band showed a reduction in its centroid, no significance was found.

It can be questioned whether sleep patterns would interfere with hypoglycemic patterns. There have been few studies investigating this concern. Hypoglycemia was detected in all sleep stages except for the REM sleep in a clamp study of 10 adult participants [32]. In another clamp study on prepubertal children [38], changes in the delta band were found significant during hypoglycemia at sleep stages N1, N2, and N3. However, the brain also produced more delta waves during the stage of deep sleep [39]. Therefore, delta features should not be used as an independent measure to detect hypoglycemia.

Our study is the first study using the effect size to select a proper EEG segment length for hypoglycemia detection. There are three levels in the benchmark of the effect size: small ( $d=0.2$ ), medium ( $d=0.5$ ), and large ( $d=0.8$ ) [40]. However, it is suggested that these values should not be interpreted rigidly [41]. Using a threshold of 0.2, the use of the effect size for electrode and feature selection resulted in competitive accuracy for emotion recognition using EEG signals [27]. In our study, five lengths of EEG segments (from 25 seconds to 60 seconds) had effect sizes of greater than 0.2. Among these, 35 second segments provided the largest effect size. In spite of having the second-largest effect size of 0.39, 30 second segments produced the best sensitivity.

As reported in [17, 42] and from the use of Higuchi fractal dimension in this study, during hypoglycemia, the EEG signal is more regular and less complex than that during euglycemia. In the frequency domain, a significant reduction of the alpha centroid was observed when patients experienced hypoglycemic states. This slowing of alpha waves during hypoglycemia corresponds to a decrease in vigilance [43, 44]. In addition, hypoglycemia-associated EEG changes are not affected by an antecedent episode of hypoglycemia in both hypoglycemia aware and unaware T1D patients [14]. This is an important neurological interpretation, as it would indicate the robustness of detecting hypoglycemic states using EEG changes in T1D patients.

There are limitations to the current study. Firstly, the number of participants is still limited. Secondly, we have not observed the long-term stability of hypoglycemia associated EEG spectral moments. We were not able to engage the young patients for several occasions over a long period of time due to



the complications associated with hypoglycemia episodes. Thirdly, although participants' blood glucose levels were not clamped to follow a target profile, their usual overnight insulin doses were intensified by 20%. This approach increases the incidence of hypoglycemia in T1D patients during the studies but may not reflect clinical hypoglycemia in their daily life. Finally, around 22% of blood glucose levels in the final data were taken from intermediate values using the linear interpolation algorithm.

## V. CONCLUSION

The study on five T1D patients in this paper shows that the occurrence of hypoglycemia induced significant changes in spectral moments of EEG signals in different segment lengths. The occipital area was more responsive to hypoglycemia compared to the central area. Using Cohen's  $d$  effect size, the present study reveals that the best EEG segment length, which provides the most significant difference between hypoglycemia and non-hypoglycemia, is 30 seconds. Statistical analyses were validated by classification results using Bayesian neural networks. The observation on the optimal segment length showed that hypoglycemia resulted in an increase of theta spectral moments ( $P < 0.05$ ) and a reduction in alpha spectral moments ( $P < 0.05$ ). A decrease in beta spectral moments was also observed. However, no significance was found from this band.

In this study, only EEG channels from the central and occipital regions were investigated. The results from these channels provide optimism for a design of real-time wearable devices in which the limited number of electrodes is required for easy implementation in daily use. Future developments of the current work will be related to the optimization of the present algorithm in a broader pool of participants.

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