Identification of hypoglycemic states for patients with T1DM using various parameters derived from EEG signals

Lien B. Nguyen, Steve Ling, *Member, IEEE*, Timothy W. Jones and Hung T. Nguyen, *Senior Member, IEEE*

***Abstract*—For patients with Type 1 Diabetes Mellitus, hypoglycemia is a very common but dangerous complication which can lead to unconsciousness, coma and even death. The variety of hypoglycemia symptoms is originated from the inadequate supply of glucose to the brain. In this study, we explored the connection between hypoglycemia episodes and the electrical activity of neurons within the brain or EEG signals. By analyzing EEG signals from a clinical study of five children with T1DM, associated with hypoglycemia at night, we found that under hypoglycemia conditions, some EEG parameters changed significantly. Based on these results, we proposed a method of detecting hypoglycemic episodes using EEG signals, including a feed-forward multi-layer neural network algorithm for classifying. The classification results are 72% sensitivity and 55% specificity when using the signals from 2 electrodes C3 and O2. We also used signals from different channels to see the contribution of each to performance of classifying. The results of the study show the potentiality of our method and will be improved and developed in the near future.**

I. Introduction

According to the Diabetes Control and Complications Trial Research Group [1], intensive insulin therapy is an effective treatment for Type 1 diabetes mellitus (T1DM) patients which can significantly delay the appearance as well as reduce the risk of acute diabetic complications like retinopathy, nephropathy and neuropathy. However, it also increases threefold the incidence of hypoglycemia among T1DM patients over conventional therapy. Hypoglycemia which is the medical term of the state of low blood glucose level (BGL) is the most dangerous complication for individuals with T1DM and an important barrier which limits the application of glycemic control therapies for diabetes patients.

Hypoglycemia can produce a variety of symptoms, from mild to severe episodes [2, 3]. Mild hypoglycemia causes sweating, nervousness, heart plumping, confusion, anxiety, etc. It can be fixed by eating or drinking glucose-rich food. If left untreated, hypoglycemia can become severe and lead to seizures, coma, and even death. Hypoglycemia reduces the quality of life for patients as well as carers by causing chronic anxiety about future potential hypoglycemic episodes [4].

One of the most dangerous effects of hypoglycemia is hypoglycemia unawareness. This effect is caused because frequent episodes of hypoglycemia can cause to changes in the response of patients' bodies. In unawareness situations, patients' bodies do not release the hormone epinephrine which is the origin of early warnings signs for patients like sweating, hunger, anxiety [3, 5]. Because of no signs, patients normally cannot realize the occurrence of hypoglycemia until it becomes severe and could lead to fatal damage. Nocturnal hypoglycemia is especially fearful for T1DM patients as sleep can make the symptoms unclear. Because of its severity, a large number of studies have been conducted to develop a system that can detect hypoglycemic episodes and give an alarm in time for patients with T1DM.

Currently there are some devices using different techniques to detect hypoglycemia available in the market. Some of them require gradually taking patients' blood samples to determine the blood glucose level. This method can give relatively exact information about hypoglycemia state. However, taking blood is uncomfortable for patients and continuous monitoring is very inconvenient, especially during night. Obviously, non-invasive technique is the best solution for these disadvantages.

Recently, we have successfully developed an effective and sensitive system to monitor hypoglycemia non-invasively using physiological parameters like heart rate, skin impedance and ECG parameters [6, 7]. However, although hypoglycemia can produce a large number of symptoms, like sweating or increased cardiac output, the principal problems arise from an inadequate supply of glucose, which is the primary metabolic fuel to the brain [5]. Since the electroencephalogram (EEG) signal is directly related to the metabolism of brain cells, hypoglycemia is believed to cause early changes in EEG that can be non-invasively detected.

Previous studies have attempted to find out EEG changes caused by hypoglycemia [8-10]. Nevertheless, most of them stopped at pointing out some spontaneous changes during hypoglycemic episodes as well as permanent changes after hypoglycemia without proposing a method of detecting hypoglycemia in real-time.

The recent study developed a portable apparatus to record EEG and a methodology using digital signal processing and artificial neural network to detect hypoglycemia [11]. This

Lien B. Nguyen, Steve Ling and Hung T. Nguyen are with the Centre for Health Technologies, Faculty of Engineering and Information Technology, University of Technology, Sydney, Broadway, NSW 2007, Australia, (e-mail: BichLien.Nguyen@student.uts.edu.au; Steve.Ling@uts.edu.au; Hung.Nguyen@uts.edu.au).

Timothy W. Jones is with Princess Margaret Hospital, Subiaco, Perth, WA 6008, Australia (e-mail: tim.jones@health.wa.gov.au).

study led to the result of 49.2% accuracy, 76% sensitivity and 32.5% specificity when the neural network was trained and validated with different subject groups. In a recent study, EEG was used as the physiological parameters to detect hypoglycemia [12]. Although this study has produced a real-time system that can detect hypoglycemia, it used implanted electrodes to record EEG signals. Recently, we proposed a Bayesian neural network algorithm for the detection of hypoglycemia using EEG signals and surface EEG electrodes [13].

In this study, we aim to explore the effects of nocturnal hypoglycemia on different EEG parameters as well as the responses from different positions of the brain. We then propose a method including spectral analysis using Fast Fourier Transform (FFT) and classification using neural network to detect hypoglycemia from EEG signals. Section II provides an overview of the methodology used in our study. Results of the study will be mentioned in Section III. Section IV provides a conclusion for this study and gives some suggestions to improve the results in future studies.

II. METHODS

A. Study

Five T1DM adolescents (between the ages of 12 and 18 year old) volunteered for the overnight hypoglycemia study at the Princess Margaret Hospital for Children in Perth, Australia. During the study, EEG signals were continuously recorded and stored using a Compumedics system with the sampling rate of 128 Hz. The EEG electrodes were positioned at O1, O2, C3 and C4 according to the international 10/20 system, referenced to Cz. We also placed 2 electrodes at patient's chin to acquire the electro-myogram (EMG) signal and 2 electrodes near patients's eyes to measure the electro-oculogram (EOG) signal. The actual blood glucose levels (BGL) were routinely collected to be used as reference using Yellow Spring Instruments with the general sampling period of 5 minutes. Data were collected with the approval of the Women's and Children's Health Service, Department of Health, Government of Western Australia, and with informed consent.

B. Feature extraction

After finalizing the signal acquiring step, signal processing was carried out using EEGLAB [14]. In EEGLAB, EEG signals from patients were filtered using an IIR highpass filter with a cut-off frequency of 2 Hz to get rid of low frequency artifacts and a notch filter at 50Hz to remove power noise. The data after pre-processing which consist of two phases (normal and hypoglycemia) was segmented into 5-second epochs. A visual artifact rejection method was used to exclude epochs contaminated with artifacts. Segments containing significant artifacts were dicarded based on EMG and EOG signals. Finally, the non-artifact signals were transformed into the frequency domain using Fast Fourier Transform (FFT). This transformation resulted in the power spectral density *P(f)* which then was subdivided into 3 frequency bands: theta (θ: 3.5-7.5Hz), alpha (α: 8-13 Hz) and beta (β: 13.5-30Hz).

The final extracted feature set includes 6 parameters at each electrode position or channel. The power level within each band at each channel is calculated using a numerical integration technique (the trapezoidal rule). The centroid frequency is defined as the center gravity of each frequency band which subdivides the area under the spectral curve into two identical parts.

The Student's *t*-test was then applied to every feature to estimate the differences between pre-hypoglycemic and hypoglycemic conditions. Probability values less than 0.05 were considered to be significant. The statistically significant features will be used as inputs for the classification. Moreover, in our study, we also explored the differences between electrode positions to find out whether the responses to hypoglycemia of different channels are similar or not.

C. Classification

Artificial neural networks [15, 16] have been employed popularly in biomedical area as a powerful tool of classification and pattern recognition. It has been recognized that the use of neural networks is a very successful method in classifying complex situations in which neural networks can model non-linear relationships between inputs and outputs effectively.

In this study, for classification purposes, we developed a neural network with the feed-forward multi-layer structure. This neural network was trained using the Levenberg-Marquardt algorithm which is a popular and effective training algorithm for feed-forward neural network. It consists of one input layer which includes the features extracted from EEG signals, one hidden layer and one output layer. The output layer has one node which indicates the state of hypoglycemia or non-hypoglycemia. In our study, the BGL threshold for defining hypoglycemia state is set at 3.3mmol/l. We used 30 data points from each patient for comparison and classification, corresponding to the 5-minute duration of each blood glucose assessment point. At each blood sampling point, a 30-second non-artifact signal fragment was used and divided into six 5-second epochs for the feature extraction. The overall data were grouped into a training set, a validation set and a test set. The final neural network was obtained from the training set with a stopping procedure determined by the validation set. The test set was then used to test the generalization of the derived neural network.

III. RESULTS

The responses of five patients show significant changes during the hypoglycemia state against pre-hypoglycemia state. The actual BGL profiles used in the study are shown in Fig. 1.

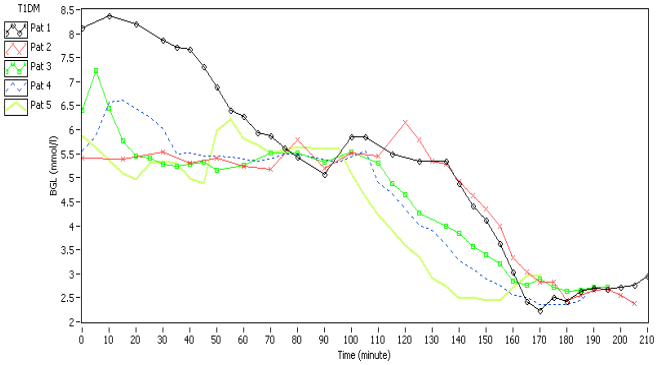

Fig. 1. Actual blood glucose level profiles in 5 T1DM children

Statistical results at each channel are presented in Tables I-IV. Significant features are reported in bold. Because the power levels are very different between patients, an appropriate normalization strategy was used to reduce the variability of this feature and to enable group comparison. To do this, we normalize each patient's power levels against their corresponding values at time zero. There are some slight changes in alpha power and theta power at channel O1 and O2. The beta power levels at all channels except C3 do not change significantly between normal and hypoglycemia states. Because these responses are not consistent with all patients, possibly they are caused by the changes in sleep stages of patients during night. The study shows that the centroid alpha frequency is the most significant feature. Under hypoglycemic conditions, the centroid alpha frequency of 5 patients reduces significantly at all four channels ($p \leq 0.0001$). The results also show an increase in centroid theta frequency at all channels ($p = 0.026$ at O2, 0.007 at C3 and 0.006 at C4). There is no significant change in the centroid beta frequency across all four channels ($p = 0.037$ at channel C3 and $p > 0.05$ at others). These results demonstrate that during the hypoglycemia onset, possibly there is a power shift to the border area between alpha band and theta band in the power spectra of EEG signals. This can be an important sign that will be explored more in future studies to find other features that can enhance the performance of our method.

Based on these statistical results, we choose the most significant features to use as inputs of classification. The final set has 8 features including the centroid theta frequency, the centroid alpha frequency at each channel. A neural network is developed using these features as inputs.

TABLE I
CHANGES UNDER HYPOGLYCEMIA CONDITION – CHANNEL C3

Feature	Normal State	Hypoglycemia State	*p*-value
Power θ	**1.5435 ± 0.7411**	**1.4107 ± 0.6309**	***p* = 0.01**
Power α	0.8802 ± 0.3596	0.8510 ± 0.3147	$p = 0.242$
Power β	**0.7694 ± 0.1965**	**0.8284 ± 0.4013**	***p* = 0.011**
CF θ	**5.2347 ± 0.2304**	**5.2800 ± 0.2323**	***p* = 0.007**
CF α	**10.2910 ± 0.3107**	**10.1531 ± 0.3415**	***p* ≤ 0.0001**
CF β	**19.8080 ± 0.7664**	**19.9430 ± 0.8253**	***p* = 0.037**

TABLE II
CHANGES UNDER HYPOGLYCEMIA CONDITION – CHANNEL C4

Feature	Normal State	Hypoglycemia State	*p*-value
Power θ	1.3392 ± 0.7256	1.3177 ± 0.7793	$p = 0.691$
Power α	1.1012 ± 0.4812	1.0982 ± 0.4117	$p = 0.928$
Power β	0.8907 ± 0.2827	0.9305 ± 0.3601	$p = 0.078$
CF θ	**5.2318 ± 0.2128**	**5.2757 ± 0.2377**	***p* = 0.006**
CF α	**10.2688 ± 0.3136**	**10.1619 ± 0.3221**	***p* ≤ 0.0001**
CF β	20.0541 ± 0.8664	20.1644 ± 0.8197	$p=0.074$

TABLE III
CHANGES UNDER HYPOGLYCEMIA CONDITION – CHANNEL O1

Feature	Normal State	Hypoglycemia State	*p*-value
Power θ	**1.6606 ± 0.9692**	**1.5098 ± 0.8384**	***p* = 0.025**
Power α	**0.7080 ± 0.4129**	**0.7950 ± 0.5205**	***p* = 0.008**
Power β	0.7866 ± 0.3459	0.8348 ± 0.4015	$p = 0.069$
CF θ	5.2586 ± 0.2260	5.2897± 0.2375	$p = 0.095$
CF α	**10.2369 ± 0.3046**	**10.0835± 0.3160**	***p* ≤ 0.0001**
CF β	19.8029 ± 0.8032	19.8078± 0.7550	$p = 0.932$

TABLE IV
CHANGES UNDER HYPOGLYCEMIA CONDITION – CHANNEL O2

Feature	Normal State	Hypoglycemia State	*p*-value
Power θ	**1.6249± 0.9068**	**1.4449 ± 0.7043**	***p* = 0.003**
Power α	**0.7717 ± 0.3769**	**0.8838 ± 0.4971**	***p* ≤ 0.001**
Power β	0.7659 ± 0.3246	0.8081 ± 0.3617	$p = 0.084$
CF θ	**5.2592 ± 0.2077**	**5.2948 ± 0.2433**	***p* = 0.026**
CF α	**10.2110 ± 0.2929**	**10.0883 ± 0.3224**	***p* ≤ 0.0001**
CF β	19.7804 ± 0.7880	19.7957 ± 0.6643	$p = 0.779$

The overall data were grouped into a training set, a validation set and a test set, with ratio of 2:1:2 patients. The corresponding Receive Operating Characteristic (ROC) Curve for the combined training/validation dataset is shown in Fig. 2. Based on this ROC curve, the most suitable cut-off point is selected as the threshold to distinguish between the hypoglycemia and normal states. To make the comparison between cases easier, we choose the point that gives the result of 70% sensitivity for the training/validation set. After training, the test set is used to find the sensitivity and specificity of the neural network. All results are reported in Table V. The reported number of hidden nodes is selected as the one that gives best classification results.

In this study, we also aim to find out how the responses of different channels contribute to the performance of classification. To do this, we develop different neural networks with inputs corresponding to data from only one EEG channel or from two EEG channels separately. For the consideration of the results from two EEG channels, we evaluate the results from various two channels at different sides and different areas of the brain (C3 and O2, C4 and O1).

TABLE V
CLASSIFICATION RESULTS

Inputs	Number of Hidden node	ROC area	Cut-off point	Sensitivity (%)	Specificity (%)
O1,O2,C3,C4	8	0.72	-0.3537	70	55
O1	10	0.64	-0.3370	74	49
O2	7	0.69	-0.3494	70	51
C3	7	0.66	-0.3343	78	37
C4	8	0.61	-0.3422	75	36
O2,C3	9	0.71	-0.3133	72	55
O1,C4	9	0.68	-0.4072	71	47

The classification using data from all four channels results in a sensitivity of 70% and specificity of 55% which indicate a potential ability of detecting hypoglycemia. With this result, it is proved that the centroid theta frequency and centroid alpha frequency are two important features in hypoglycemia detection. When using the features of one channel only, the classification results are very similar between O1 and O2 as well as C3 and C4. The results are better at O1 and O2 against those at C3 and C4. Hypoglycemia classifications using data from the two EEG channels with electrodes positioned at O2, C3 yield the best result with 72% sensitivity and 55% specificity. These results demonstrate that neural network algorithms can be developed to provide good detection of hypoglycemic episodes using only two EEG channels or even one EEG channel. With the final aim of developing a real-time EEG system to detect early detection of hypoglycemic episodes in patients with diabetes, reducing the number of features as well as electrodes is very important for effective real-time implementation.

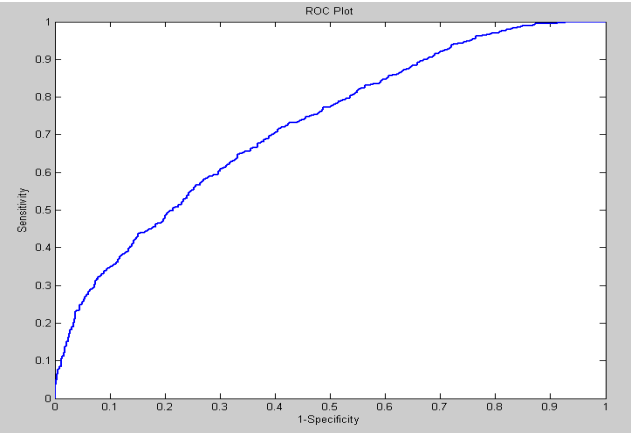

Fig. 2. ROC Plot

IV. CONCLUSION

In this paper, we explored the changes of EEG parameters associated with hypoglycemia in T1DM patients. A neural network algorithm was developed to detect hypoglycemic episodes based on EEG signals. With classification resuls of 72% sensitivity and 55% specificity derived from two channels C3 and O2, we have shown that hypoglycemia can be detected non-invasively and effectively using EEG signals. However, the overall accuracy including both sensitivity and specificity would need to be improved. To do this, a post-classification stage which involves some effective trending strategies could be developed. In the future, with the applications of more advanced computational intelligence algorithms, the results could be improved significantly.

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