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An Adaptive Strategy of Classification for Detecting Hypoglycemia using Only Two EEG Channels

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***Abstract*— Hypoglycemia is the most common but highly feared side effect of the insulin therapy for patients with Type 1 Diabetes Mellitus (T1DM). Severe episodes of hypoglycemia can lead to unconsciousness, coma, and even death. The variety of hypoglycemic symptoms arises from the activation of the autonomous central nervous system and from reduced cerebral glucose consumption. In this study, electroencephalography (EEG) signals from five T1DM patients during an overnight clamp study were measured and analyzed. By applying a method of feature extraction using Fast Fourier Transform (FFT) and classification using neural networks, we establish that hypoglycemia can be detected non-invasively using EEG signals from only two channels. This paper demonstrates that a significant advantage can be achieved by implementing adaptive training. By adapting the classifier to a previously unseen person, the classification results can be improved from 60% sensitivity and 54% specificity to 75% sensitivity and 67% specificity.**

I. Introduction

Type 1 Diabetes Mellitus (T1DM) is a form of diabetes which is caused by the loss of insulin-producing beta cells in the pancreas leading to insulin deficiency. It has been reported that intensive insulin therapy is the most efficient treatment for T1DM patients which can delay the onset and reduce the risk of acute diabetic complications like retinopathy, nephropathy and neuropathy [1]. However, it increases, by three times, the incidence of hypoglycemia among patients with T1DM over conventional therapy. Hypoglycemia is the medical term for the state produced by an abnormally low level of blood glucose. This is considered as the most common but highly severe complication for patients with T1DM and a limiting factor of the intensive insulin therapy.

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 alleviated by eating or drinking glucose-rich food. If left untreated, hypoglycemia can become severe and leads to seizures, coma, and even death. One of the most dangerous effects of hypoglycemia is hypoglycemia unawareness. This is caused by frequent episodes of hypoglycemia which can lead to changes in the response of patients' bodies. In unawareness situations, patients' bodies do not release counter-regulatory hormones which are the origin of early warning symptoms for patients like shaking, sweating, hunger, anxiety, etc. Because of the lack of warning, patients cannot realize the occurrence of hypoglycemia until it becomes severe and could lead to fatal damage. Nocturnal hypoglycemia is also especially dangerous because sleep reduces and obscures symptoms, so that an initially mild episode may become severe. It was reported previously that almost 50% of all episodes of severe hypoglycemia occur at night during sleep [4]. Because of its severity, intensive research has been devoted to the development of systems that can detect the onset of hypoglycemic episodes, and then give an alarm to provide enough time for patients and carers to take action.

The human brain depends on a continual supply of glucose and is vulnerable to any glucose deprivation. Since the electroencephalogram (EEG) is directly related to the metabolism of brain cells, hypoglycemia is shown to cause early changes in EEG that can be detected non-invasively. Previous studies have demonstrated several evidences of changes in EEG signals due to hypoglycemia [5-9]. In recent papers, we proposed methods of detecting hypoglycemic episodes using Fast Fourier Transform (FFT) and neural network [10, 11]. Those studies lead to acceptable results which show the potential ability to detect the onset of hypoglycemia from EEG signals. With the aim of developing a system that can be applied into real clinical situations, the study needs to be expanded and improved further.

The main objective of this paper is to demonstrate that by applying a properly adaptive strategy of classification, hypoglycemia can be detected efficiently using only two EEG channels. Using data of 5 T1DM children from a glucose clamp study, different EEG parameters are extracted and analyzed to find important features that significantly change under hypoglycemia conditions. The features from two EEG channels are employed as inputs for a neural network to classify patients' conditions into two states: hypoglycemia and non-hypoglycemia. The neural network is trained and tested adaptively in order to allow the classifier to customize itself to new EEG patterns from new individual users. Section II provides an overview of the methodology used for detection of hypoglycemia using EEG signals. In Section III, the development and results of the study will be mentioned and discussed. Conclusions for this study are drawn in Section IV.

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II. METHOD

A. Study

EEG signals were acquired from five adolescent patients with T1DM (between the ages of 12 and 18 years) who volunteered for the overnight hypoglycemia study at the Princess Margaret Hospital for Children in Perth, Australia. During the study, signals were continuously recorded and stored using Compumedics system with the sampling rate of 128 Hz. Accordingly to the International 10/20 system, 4 EEG electrodes (or channels) were positioned at 4 different brain positions, O1 and O2 in the occipital lobe; C3 and C4 in the central lobe, referenced to A1 with left-side positions and A2 with right-side position. There were also two electrodes placed on patients' chins to measure the electromyogram (EMG) signals and two electrodes placed near patients' eyes to measure the electrooculogram (EOG) signals. During the study, the actual blood glucose levels (BGLs) from patients were also routinely collected to be used as reference. BGLs were acquired 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, several steps of signal processing are carried out in EEGLAB [15]. First, at each blood-sampling point, an epoch of 2 minutes is selected. Each epoch is labeled as hypoglycemia or non-hypoglycemia according to the corresponding BGL. Epochs which correspond with BGL lower than 3.3mmol/l are defined as hypoglycemia. Otherwise, they are labeled as non-hypoglycemia. An IIR highpass filter with a cut-off frequency of 2Hz is applied to each epoch to get rid of low frequency artifacts. A notch filter at 50Hz is also applied to remove power noise. A visually artifact-rejecting method is used to exclude EEG segments contaminated with artifacts. Segments containing significant artifacts are discarded, based on EMG and EOG signals. Finally, from each patient, 2 sets of 40-second epochs (which are hypoglycemia and non-hypoglycemia sets) are taken.

Non-artifact 40-second EEG epochs are segmented into 5-second non-overlapping segments. By using FFT, each segment is transformed into the frequency domain which results in the power spectrum $P(f_i)$, with frequency resolution of 0.2 Hz. The power spectrum is then subdivided into 3 frequency bands: theta (θ: 3.4-7.8Hz), alpha (α : 8-13 Hz) and beta (β: 13.2-30Hz). From the power spectrum of each frequency band, different EEG parameters are estimated as follows:

Power (P): The power level within each frequency band has been shown as a common feature in EEG research. In this paper, the power level within each frequency band is estimated from the power spectrum $P(f_i)$ by using a numerical integration technique (the trapezoidal rule).

Centroid Frequency (CF): This feature can be referred to the center of gravity of the spectrum within each band. It is estimated as the frequency which subdivides the area, under the spectral curve, into identical parts.

$$CF = \frac{\sum_i f_i * P(f_i)}{\sum_i P(f_i)} \quad (1)$$

As a result, a total set of 24 EEG features (2 different kinds of feature x 4 channels x 3 frequency bands) are estimated for each epoch.

The Student's *t*-test is then applied to each feature to estimate the significance of differences between hypoglycemia and non-hypoglycemia conditions. Probability values (*p*-value) less than 0.05 are considered to be significant. The statistically significant features will be used as inputs for the classification.

C. Neural network

Artificial neural networks have been employed popularly in biomedical area as a powerful tool of classification and pattern recognition. It has been recognized that neural networks are useful for classifying complex situations. It can effectively model non-linear relationships between inputs and outputs.

In this study, a neural network with feed-forward multi-layer structure is developed and employed as a classification unit. This network consists of one input layer which includes the features extracted from EEG signals, one hidden layer and one output layer. The structure of the neural network is shown in Fig. 1. The input-output relationship of the neural network can be written as follows:

$$y = \sum_{i=1}^{S} v_i \, tan\,sig\left(\sum_{j=1}^{R} w_{ij} x_j - b_{1i} \right) - b_2 \quad (2)$$

where $w_{ij}, i = 1,2,...,S; j = 1,2,...,R$ is the weight of the link between *i*-th hidden node and the *j*-th input; v_i is the weight of the link between *i*-th hidden node and the output; b_{1i}, b_2 are the biases for the input layer and hidden layer respectively; S is the number of hidden nodes; R is the number of inputs; $tan\,sig$ is the hyperbolic tangent sigmoid transfer function of hidden layer:

$$tan\,sig(a) = \frac{e^a - e^{-a}}{e^a + e^{-a}} \quad (3)$$

The overall data are grouped into a training set, a validation set and a testing set. The developed neural network is trained by using the training set with a stopping procedure determined by the validation set. This neural network is trained by the Levenberg-Marquardt (LM) algorithm which is an effective and popular training algorithm. In brief, the LM algorithm estimates the second directional derivative of the error function, in order to direct the training process to a local minimum and find optimized network parameters (including w_{ij}; b_{1i}; v_i; b_2). The number of hidden nodes is selected as the one which give the best classification performances.

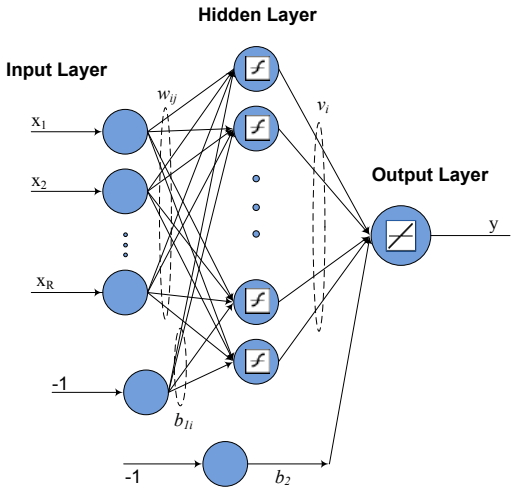

Figure 1. Neural network structure

After determining the final structure and parameters for the neural network, the Receiver Operating Characteristic (ROC) curve will be found based on the combined training and validation dataset. By definition, a ROC curve presents the tradeoff between the true positive rate versus false positive rate (equivalently, sensitivity versus 1–specificity) for different thresholds of the classifier output. In this paper, we use that characteristic to choose the output threshold which is most suitable to the application of hypoglycemia detection. The area under the ROC curve (*AuR*) is also estimated as a measure of classification performance. The higher the *AuR*, the better the classification. A random classification gives an *AuR* of 0.5, while an ideal classification gives an *AuR* of 1.

Finally, based on the derived structure as well as the output threshold of neural network, the test set will be applied to test the performance of the developed neural network. These performances are determined in terms of sensitivity and specificity of the classification results:

$$Sensitivity = \frac{TP}{TP + FN}\ ;\quad Specificity = \frac{TN}{TN + FP} \qquad (4)$$

where True Positive (*TP*) is the number of hypoglycemic episodes which are correctly classified as hypoglycemia; True Negative (*TN*) is the number of non-hypoglycemic episodes which are correctly classified as non-hypoglycemia; False Positive (*FP*) is the number of non-hypoglycemic episodes which are wrongly classified as hypoglycemia; False Negative (*FN*) is the number of hypoglycemic episodes which are wrongly classified as non-hypoglycemia.

It has been noted in our previous work that EEG patterns significantly vary from person to person, which leads to a difficulty in generalizing the system to a new user. To overcome this, in this paper, we implement a strategy of training neural network adaptively, which allows the neural network to adapt itself to each new individual user. The system is initially trained and validated with data from four patients. The resulting neural network is then further trained with a small set of data taken from the previously unseen patient. The final trained neural network is then tested with the major part of data from the same patient.

III. Results

The actual BGL profiles of five patients which were collected by the Yellow Spring Instruments during the study are shown in Fig. 2. The reference (Ref line in Fig. 2) is set at 3.3mmol/l which is used as the BGL threshold of hypoglycemia.

EEG responses from all five patients show significant changes during the hypoglycemia state against the non-hypoglycemia state. There are some slight changes in alpha power and theta power at channels O1 and O2 ($p \le 0.05$). The beta power levels at all channels except C3 do not change significantly between non-hypoglycemia and hypoglycemia states. Because these responses are not consistent in all patients, we conclude that they are caused by body movements as well as changes in sleep stages of patients during night. The study shows that the centroid alpha frequency is the most significant feature. Under hypoglycemia conditions, the centroid alpha frequency of 5 patients reduces significantly at all four channels ($p \le 0.0001$). 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, there is a power shift to the border area between alpha band and theta band in the power spectra of EEG signals.

The statistical results also indicate similarities between channels O1 and O2 in the occipital lobe; C3 and C4 in the central lobe. As a result, we establish there are no significant difference in responses between channels in left and right brain hemispheres. Therefore, to evaluate classification performance, we use data from two channels C3 and O2 which are in two different sides and area of the brain.

Based on these statistical results, centroid theta frequencies and centroid alpha frequencies from channels C3 and O2 are selected as inputs of classification. A neural network is developed with 4 input nodes (2 features × 2 channels), 1 output node and *S* hidden nodes. The desired output is set at 1 in case of hypoglycemia and –1 in case of non-hypoglycemia. *S* is varied from 4 to 10 to select the one that gives the best performance. As a result, in our application, $S = 8$ gives a best classification performance and we use it for our study.

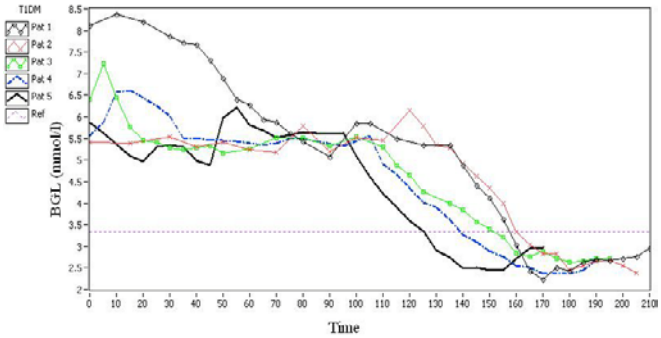

Figure 2. Actual blood glucose level profiles in 5 T1DM children

The overall data set is separated into a training set, a validation set and a testing set. The training set and validation set is formed by randomly dividing data from 4 patients. As a result, the training set consists of 127 episodes which include 54 episodes of hypoglycemia. The validation set consists of 63 episodes which include 28 episodes of hypoglycemia. After being trained, the neural network will be tested by data from one previously unseen patient. The data set from the testing patient consists of 44 episodes which include 20 episodes of hypoglycemia.

The classification results are showed in Table I. The corresponding *AuR* for the combined training/validation dataset is 0.78. The curve is plotted in Fig. 3. With this ROC curve, the threshold to distinguish between the hypoglycemia and non-hypoglycemia states is selected at the point producing sensitivity higher than 75%. At that point, the combined training and validation results of 76% sensitivity and 67% specificity are gained. These results indicate a potential ability of neural network to detect hypoglycemia from non-invasive EEG signals. To show how well these results generalize, the data from an entirely new patient are applied to neural network. This testing leads to results of 60% sensitivity and 54% specificity which are reasonable due to the patient-to-patient variability of EEG signals. In order to overcome this variability, we carry out a further training process. 20 non-hypoglycemia data points from the fifth new patient, which are not included in the testing set, are added to the training set to re-train the previously achieved neural network. After that, the testing set is then applied to this re-trained neural network. The adaptive training increases the classification results for the fifth patient up to 75% sensitivity and 67% specificity.

TABLE I. CLASSIFICATION RESULTS

Data set	Sensitivity	Specificity
Training	76%	67%
Test	60%	54%
Adaptive Training	76%	68%
Re_test	**75%**	**67%**

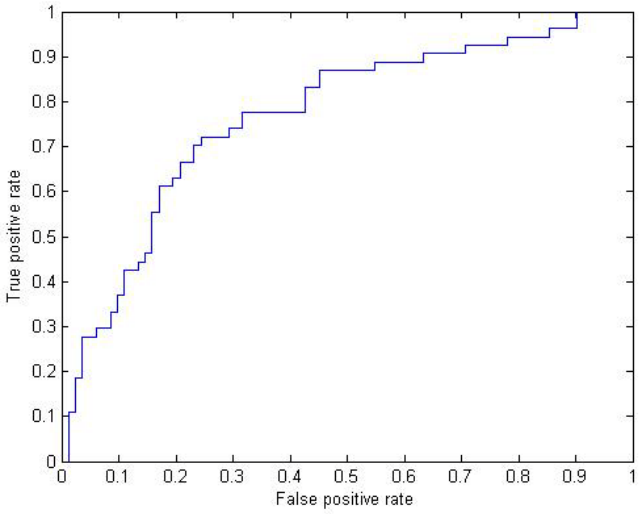

Figure 3. ROC plot

IV. CONCLUSION

In this paper, a method for early detection of hypoglycemia episodes from EEG signals is proposed. Statistical results show that theta and alpha centroid frequencies are significant to be used as inputs of detecting system. A neural network algorithm is developed for the purpose of classification. In order to increase the generalization of the developed neural network, an adaptive training is employed. This paper demonstrates that by adapting the classifier to a small data set from an entirely unseen patient, the classification performance can be enhanced markedly from 60% sensitivity and 54% specificity to 75% sensitivity and 67% specificity. The results imply that by applying partly individual training, the hypoglycemia detecting system which uses only 2 EEG channels can perform efficiently.

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