34th Annual International Conference of the IEEE EMBS
San Diego, California USA, 28 August - 1 September, 2012

Intelligent Detection of Hypoglycemic Episodes in Children with Type 1 Diabetes using Adaptive Neural-Fuzzy Inference System*

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Abstract— **Hypoglycemia, or low blood glucose, is the most common complication experienced by Type 1 diabetes mellitus (T1DM) patients. It is dangerous and can result in unconsciousness, seizures and even death. The most common physiological parameter to be effected from hypoglycemic reaction are heart rate (HR) and correct QT interval (QTc) of the electrocardiogram (ECG) signal. Based on physiological parameters, an intelligent diagnostics system, using the hybrid approach of adaptive neural fuzzy inference system (ANFIS), is developed to recognize the presence of hypoglycemia. The proposed ANFIS is characterized by adaptive neural network capabilities and the fuzzy inference system. To optimize the membership functions and adaptive network parameters, a global learning optimization algorithm called hybrid particle swarm optimization with wavelet mutation (HPSOWM) is used. For clinical study, 15 children with Type 1 diabetes volunteered for an overnight study. All the real data sets are collected from the Department of Health, Government of Western Australia. Several experiments were conducted with 5 patients each, for a training set (184 data points), a validation set (192 data points) and a testing set (153 data points), which are randomly selected. The effectiveness of the proposed detection method is found to be satisfactory by giving better sensitivity, 79.09% and acceptable specificity, 51.82%.**

I. INTRODUCTION

Hypoglycemia is the medical term for a state produced by a lower level of blood glucose. It is a common and serious side effect of insulin therapy in patients with diabetes. The risk of hypoglycemia is mainly developed in diabetes patients who have been treated with insulin while it is less likely to occur in non-insulin-dependent patients who have taken sugar-lowering medicine for diabetes [1].

It is particularly dangerous because sleep reduces and may obscure autonomic counter-regulatory responses. The risk of hypoglycemia is high at night, with at least 50 % of severe hypoglycemia episodes occurring during at night time [2]. In [3], it has been reported that the severe hypoglycaemic episodes are defined in those whose blood glucose levels are $(< 3.3mmgol/L)$, thus the patients are advised to take necessary treatment. When the initial symptoms of hypoglycemia occur [4], the patient can then recognize these in ensuing episodes.

In order to measure blood glucose concentration, a limited number of non-invasive blood glucose monitoring systems are currently available in the market, but each of them has their own drawbacks in functioning, cost, reliability and obtrusiveness. Intensive research has been devoted to the development of hypoglycemia alarms exploiting principles that range from detecting changes in the electroencephalogram (ECG) or skin conductance by the use of glucose sensors [5]. Though real-time continuous glucose monitoring systems (CGMS) have been developed [6], they are not available to offer as commercial devices due to lack of sensitivity and low efficiency in detecting unrecognized hypoglycemia.

During hypoglycemia, the most profound psychological changes are caused by activation of the sympathetic nervous systems. Among them, the strongest responses are sweating and increased cardiac output [7]. Here, the change in cardiac output is mostly related to an increase in heart rate and stroke volume. The possibility of hypoglycemia induced arrhythmias and experimental hypoglycemia is associated with the prolongation of QT interval [8]. Based on the the physiological parameters collected by a continuous non-invasive monitoring system [9], the aim is to develop an effective hypoglycemia detection system with the use of advanced computational techniques.

For detection and classification of ECG and EEG [10], several algorithms have been developed by using neural network classifiers [11], fuzzy system [12] and support vector machine [13]. By the use of Lyapunov exponent, ECG features are extracted and an adaptive neuro fuzzy inference system is presented for classification [14]. In addition, an ECG classification task is performed by the fuzzy hybrid neural network which uses an FCM algorithm and MLP as the final classifier [15]. Though satisfactory results are found by the use of fuzzy hybrid neural network, the shortcomings of MLP still exist.

To overcome the shortcomings encountered in neural networks, an adaptive neural fuzzy inference system (ANFIS) [16] is presented in this paper in order to detect the status of hypoglycemic episodes. It is a class of adaptive networks in which its structure is organized by the integration of a traditional fuzzy system into a conventional feedforward multi-layer neural network. The membership function parameters are extracted from a data set, learns to recognize features in the data set and adjusts the system parameters according

*The authors would like to thank Dr. Nejhdeh Ghevondian, and Assoc. Prof. Timothy Jones for their contribution. This works was supported by a grant from Juvenile Diabetes Research Foundation.

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to a given error criterion. The parameters of ANFIS such as fuzzy membership functions and coefficients of the linear functions, are trained by the use of hybrid particle swarm optimization with wavelet mutation (HPSOWM).

The organization of this chapter is as follows: in Section II, an ANFIS and its training procedures by the use of hybrid particle swarm optimization with wavelet mutation (HPSOWM) is introduced. To show the effectiveness of our proposed methods, the results of early detection of nocturnal hypoglycaemia episodes in T1DM are discussed in Section III and a conclusion is drawn in Section IV.

II. METHODS

To recognize the status of hypoglycemic episodes in T1DM, an evolved ANFIS model Fig. 2 is developed by the use of physiological parameters of ECG signal Fig. 1 which is composed of a P wave which represents atrial depolarization while a QRS complex and a T wave represents ventricular depolarization and rapid change of repolarization of ventricles.

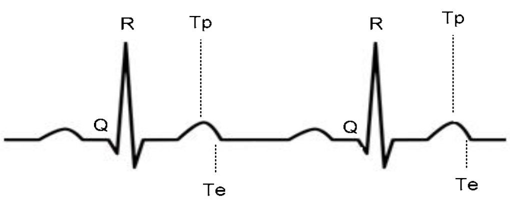

Fig. 1. ECG Signal

For patient with Type1 and Type2 diabetes, the possibility of hypoglycemia is mainly effected by prolongation of QT intervals (starting from the point of Q wave to at the end of T wave) and its correlation to heart rate carried out by Bazett's formula $QT_c = QT/RR$ [17] . Not only does QT_c interval prolongation have a significant impact on hypoglycemia, but an increase in heart rate (HR) may also influence the status of hypoglycemia [18]. Studies on the natural occurrence of hypoglycemia with an increase in heart rate, $(1.033 \pm 0.242\, vs.\, 1.082 \pm 0.298,\, P < 0.06)$ and corrected QT intervals, $(1.031 \pm 0.086\; vs.\; 1.060 \pm 0.084,\; P < 0.01)$ have been successfully carried out in [19].

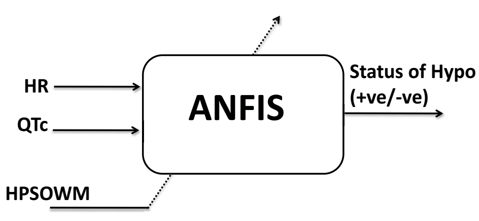

Fig. 2. HPSOWM based adaptive fuzzy inference system

With these changes in physiological parameters, an adaptive neuro-fuzzy inference system (ANFIS) is developed for early detection of hypoglycemic episodes in this application. The proposed ANFIS model with two inputs (heart rate (HR) and corrected QT interval (QT_c)), and one output system (hypoglycemia status (h)) is presented in Fig. 2. In the proposed system, HPSOWM is used to find the optimal parameters and membership function of ANFIS.

A. Adaptive Neuro Fuzzy Inference System (ANFIS)

The adaptive neuro fuzzy inference system (ANFIS) [20] is one of an hybrid neuro fuzzy network having a similar structure with a multilayer feedforwrad neural network apart from signal flow direction between nodes and no weights association with the links. An adaptive network, as the name implies, is the network structure consisting of directional links, and adaptive nodes with output depending on the variable parameters pertaining that node. Its architecture consists of five layers in which the first and fourth layers are employed with square indicator adaptive nodes whose parameters are duly updated with each subsequent iterations. The rest of the layers, second, third and fourth layers are associated with fixed nodes which use a circle indicator, devoid of any parameters.

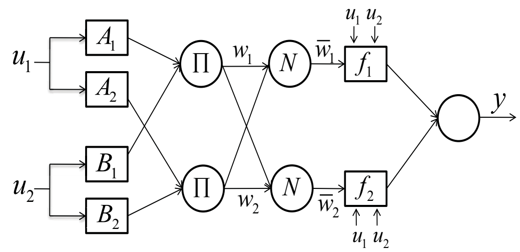

Fig. 3. Structure of Adaptive Neuro Fuzzy Inference System

For simplicity, the ANFIS in Fig. 2 can be viewed as fuzzy logic system with two inputs, u_1 and u_2 and one output, y whose if-then rules with fuzzy membership functions are generated in the following form:

Rule1: If (u_1 is A_1) and (u_2 is B_1) then ($f_1 = p_1x + q_1y + r_1$)

Rule2: If (u_1 is A_2) and (u_2 is B_2) then ($f_2 = p_2x + q_2y + r_2$)

where A_i and B_i are the fuzzy sets, f_i are the outputs within the fuzzy region specified by the fuzzy rule, and p_i, q_i and r_i are the adaptive parameters which are determined during the training process. The fuzzification process is carried out by the use of a bell shape membership function 1 in the first layer. Every node in that layer is adaptive and the output is the fuzzy membership grade of the inputs which is given by the bell shape membership function:

$$\mu_{A_i}(u_1) = e^{-(u_1 - c_i)^2 / \sigma_i}, \quad i = 1,2 \tag{1}$$

where c_i and σ_i are the parameters of fuzzy membership function. After processing multiplication, normalization and defuzzification process in the second, third, and fourth layers, the overall output y is obtained by summation of all incoming signals as follows:

$$y = \sum_{i=1}^{2} \bar{w}_i f_i = \sum_{i=1}^{2} w_i f_i / (w_1 + w_2), \quad i = 1,2 \tag{2}$$

where $\bar{w}_i$ is normalized firing strength between Layer3 and Layer4, $f_i = p_i x + q_i x + r_i$ is the function of first order polynomial with three modifiable parameters, p_i, q_i and r_i.

In this application, the status of hypoglycemia h is positive when the output y is positive which is defined as follows:

$$h = \begin{cases} +1, & y \geq 0 \\ -1 & y < 0 \end{cases} \quad (3)$$

B. Hybrid Particle Swarm Optimization with Wavelet Mutation (HPSOWM)

In HPSOWM, a swarm $X(t)$ is constituted with the number of particles. Each particle $\mathbf{x}^p(t) \in X(t)$ contains κ elements $x_j^p(t)$ at the t-th iteration, where $p = 1,2,...,\theta$ and $j = 1,2,...,\kappa$; θ denotes the number of particles in the swarm and κ is the dimension of a particle. First, the particles of the swarm are initialized and then evaluated by a defined fitness function. The objective of HPSOWM is to minimize the fitness function (cost function) $f(X(t))$ of particles iteratively. The position $x_j^p(t)$ and velocity $v_j^p(t)$ used in HPSOWM [21] are given as follows:

$$\begin{aligned} x_j^p(t) &= x_j^p(t-1) + v_j^p(t) \\ v_j^p(t) &= k.\left(w.v_j^p(t-1) + \varphi_1 r_1\right).\left(\tilde{x}_j - x_j^p(t-1)\right) \\ &+ \varphi_2 r_2 \left(\hat{x}_j - x_j^p(t-1)\right) \end{aligned} \quad (4)$$

where$\tilde{x}^p = \left[\tilde{x}_1^p, \tilde{x}_2^p, \ldots, \tilde{x}_k^p\right]$ and $\hat{\mathbf{x}} = [\ \hat{x_1}\ \ \hat{x_2}\ \ ,...\hat{x_\kappa}\ ]$, $j = 1,2,...,\kappa$. The best previous position of a particle is recorded and represented as $\tilde{x}$; the position of the best particle among all the particles is represented as $\hat{x}$; w is an inertia weight factor; r_1 and r_2 are acceleration constants which return a uniform random number in the range of [0,1]; w is inertia weight factor and k is a constriction factor.

$$\bar{x}_j^p(t) = \begin{cases} x_j^p(t) + \sigma \times \left(\rho_{\max}^j - x_j^p(t)\right) & ,\sigma > 0 \\ x_j^p(t) + \sigma \times \left(x_j^p(t) - \rho_{\min}^j\right) & ,\sigma < 0 \end{cases} \quad (5)$$

where $j \in 1,2,\ldots,\kappa$ and κ denotes the dimension of particles. The value of σ is governed by Morlet wavelet function in [21].

C. Fitness Function and Training

To determine the performance of proposed detection system, Sensitivity, (ξ) and Specificity, (η) [22] are introduced:

$$Sensitivity\ \ (\xi) = \frac{N_{TP}}{N_{TP} + N_{FN}} \quad (6)$$

$$Specificity\ \ (\eta) = \frac{N_{TN}}{N_{TN} + N_{FP}} \quad (7)$$

where N_{TP} is defined as number of true positive, N_{FN} is number of false negative, N_{FP} is number of false positive, and N_{TN} is number of true negative. The values of these are within 0 to 1

In clinical study, the sensitivity is more important than the specificity because it mainly represents the performance of classifier. The higher sensitivity represents the better performance of the detection system. The objective of the proposed detection system is to maximize fitness function $f(\xi,\eta)$ which is equivalent to maximization of the sensitivity and the specificity. The parameter $\eta_{\max}$ in (8) is used to fix the region of specificity from 0 to 1 in order to find the optimal sensitivity in the specified region.

In order to analyze the performance of the proposed detection system, the fitness function is defined in (8) with upper limit of specificity, $\eta_{\max}$.

$$f(\xi,\eta) = \xi + \frac{\eta_{\max} - \eta}{\eta_{\max}} \quad (8)$$

For a given set of particle $\mathbf{x}$, HPSOWM evaluates the fitness value of each particle at each iteration and searches for the optimum network parameters.

III. RESULT AND DISCUSSION

To study the natural occurrence of nocturnal hypoglycemia, 15 children with T1DM are monitored for 10-hours overnight at the Princess Margaret Hospital for Children in Perth, Western Australia, Australia. The required physiological parameters are measured by the use of the non-invasive monitoring system, while the actual blood glucose levels (BGL) are collected as reference using Yellow Spring Instruments. The main parameters which are used for the detection of hypoglycemia are the heart rate (HR) and corrected QT (QTc). The response from the 15 children with T1DM [23] exhibit significant changes during their hypoglycemia phase in contrast to the non-hypoglycemia phase.

The overall data set consist of both hypoglycemia data part and non-hypoglycemia data part and organized into a training set (5 patients with 184 data points), a validation set (5 patients with 192 data points) and a testing set (5 patients with 153 data points) which are randomly selected. To tackle the problem of T1DM, the hypoglycemia episodes (BGL $\leq 3.3 mmol/l$) are detected by the use of hybrid PSO based ANFIS.

The clinical results for hypoglycemia detection with different methods are tabulated in Table I - II. For comparison purpose, fuzzy inference system (FIS), wavelet neural network (WNN), feedforward neural network (FWNN) and multiple regession (MR) are analyzed. The average (mean) testing result of proposed ANFIS with 2 inputs is satisfactorily found by giving the sensitivity and specificity of (77.44% and 51.73%). It can also be seen in Table II that the performance of ANFIS is better than other classifiers by giving the best testing sensitivity, 79.09% and acceptable specificity 51.82%.

In this study, γ analysis is defined as $\gamma = \theta\xi + (1-\theta)\eta$ (θ varies $0.1 \rightarrow 1$) for evaluation of the proposed system performance. Since the minimum requirement of a hypoglycemia detection system is 60 % of sensitivity and 40 % of specificity , θ is set to 0.6 in this analysis. As can be seen in Table I and II, in terms of γ analysis, the proposed ANFIS performs better than other classifiers by giving the γ value of 67.16% (mean) and 65.12% (best). Thus, the proposed detection system gives satisfactory results with higher accuracy.

TABLE I

MEAN VALE OF TRAINING VALIDATION AND TESTING RESULTS: SET MAXIMUM SPECIFICITY, $\eta_{\max}$= 40%

$\eta_{\max}$			ANFIS	WNN	FWNN
40%	Training (%)	Sen(ξ)	90.61	84.12	83.64
		Spec(η)	40.40	40.63	40.50
		γ	70.53	66.72	66.38
	Validation (%)	Sen(ξ)	90.94	80.44	79.07
		spec(η)	41.81	40.94	41.38
		γ	71.28	64.64	63.99
	Testing (%)	Sen(ξ)	**77.44**	71.39	68.84
		Spec(η)	**51.73**	44.37	48.34
		γ	**67.16**	60.58	60.64

TABLE II

BEST TESTING RESULT FOR HYPOGLYCEMIA DETECTION WITH NEURAL AND FUZZY CLASSIFIERS

Methods	Sensitivity (ξ)	Specificity (η)	γ
ANFIS	**79.09 %**	**51.82%**	**68.18%**
FRM ([23])	75.00%	50.00%	65.00%
WNN	74.42%	48.18%	63.92%
FWNN	69.77%	49.09%	61.50%
MR	65.12%	57.27%	61.98%

IV. CONCLUSIONS

For detection of the hypoglycemic episodes for diabetes patients an intelligent diagnostic system using they hybrid approach of adaptive neural-fuzzy inference system (ANFIS) has been developed. The above results indicate that hypoglycemic episodes in T1DM children can be detected non-invasively and effectively by the use of real time physiological parameters of ECG signal. To optimize the membership functions and adaptive parameters of ANFIS, a hybrid particle swarm optimization with wavelet mutation is presented. The performance evaluation is done in comparison with other classifiers (FRM, WNN, FWNN and MR). The improvement in sensitivity and specificity is satisfactorily found at 79.09% and 51.82%. In short, the proposed intelligent system can detect episodes of hypoglycemia effectively and efficiently .

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