Classification of Hypoglycemic Episodes for Type 1 Diabetes Mellitus based on Neural Networks

K.Y. Chan, S.H. Ling *Member IEEE*, T.S. Dillon, Fellow *IEEE*, and H.T. Nguyen, *Sr. Member IEEE*

Abstract— **Hypoglycemia is dangerous for Type 1 diabetes mellitus (T1DM) patients. Based on the physiological parameters, we have developed a classification unit with hybridizing the approaches of neural networks and genetic algorithm to identify the presences of hypoglycemic episodes for TIDM patients. The proposed classification unit is built and is validated by using the real T1DM patients' data sets collected from Department of Health, Government of Western Australia. Experimental results show that the proposed neural network based classification unit can achieve more accurate results on both trained and unseen T1DM patients' data sets compared with those developed based on the commonly used classification methods for medical diagnosis including statistical regression, fuzzy regression and genetic programming.**

I. Introduction

Episodes of hypoglycemia for Type 1 diabetes mellitus (T1DM) are common for children and have serious side effect in insulin therapy or even death [9, 10, 23, 30]. Therefore it is important to monitor the blood glucose levels of T1DM all the time. Based on the physiological parameters including heart rate and QT interval of ECG signal, the glucose levels of the T1DM can be determined and thus the episodes of hypoglycemia can be diagnosed [14]. Development of a model in relating between the physiological parameters and the episodes of hypoglycemia is the main objective of this paper.

Statistical regression [25] is commonly used to develop such classification models for various medical diagnoses [6, 7, 5] but the models developed by the method are accurate over the range of the patients' data in which they are developed. Therefore it can only be applied if the patients' data is distributed according to the developed regression model, and the correlation between dependent and independent variables does not exist. If the patients' data is irregular, the developed regression models have unnaturally too wide possibility range. Another method, genetic programming [13] is another commonly used method to generate classification models for diagnosis purposes for examples [27, 29]. In this approach, genetic operations are used to generate structures of classification models with nonlinear terms in polynomial forms, and then the least squares algorithm is used to determine the contribution of each nonlinear term of the model classification. However, it is unavoidable that patients' data involves uncertainty, due to fuzziness of measures. Therefore the genetic programming together with the least square algorithm may not yield the best classification models for diagnosis purposes, since it does not consider the fuzziness of uncertainty in measures.

Recently neural fuzzy networks have been applied on modeling and classification based on patients' data for medical diagnosis purposes in [22, 26, 16, 17]. The fuzzy neural network model is constructed by distributing input and output relationships to the weights connecting neurons. The error value is limited to a reasonable level via sample training and used for modification of each weight value to acquire the final weight value for connection between neurons. The model of the system is constructed with these weight values. This approach is especially suitable for the construction of highly nonlinear models, and also fuzzy rules which contain certain information of the developed models can be generated [18]. However, comparing with traditional neural networks, more parameters need to be determined from the fuzzy neural networks, because not only parameters of the weights connecting neurons need to be determined but also the parameters inside the fuzzy rules needed to be determined. Therefore larger memory, more computational time and learning data are required than the ones required to develop neural networks. Even fuzzy rules which represent curtain information from the models can be generated, the domains of inputs and outputs represented by the fuzzy rules are all fuzzy. Medical doctors may find it difficult to make diagnosis decisions based on those fuzzy rules.

Neural networks [24] have been used to develop classification models for medical diagnosis purposes. The advantages of using neural network approaches in diagnosis are their generalization ability in addressing both the nonlinear and fuzzy nature of the patients' data. Neural networks have been applied in building diagnosis models for various diagnoses [1, 20, 13, 4, 28, 8], these diagnosis models have the capability to transform the nonlinear or fuzzy patients' data into simplified black-box structures. In this paper, a neural network based classification unit is proposed to perform diagnosis of hypoglycemic episodes in T1DM patients. The neural network based classification unit is used for determining hypoglycemic episodes in T1DM

K.Y. Chan is with the Digital Ecosystems and Business Intelligence Institute, Curtin University of Technology, WA, Australia (phone: 61-8-9266 9269; fax: 61-8-9266 7548; e-mail: Kit.Chan@curtin.edu.au).

S.H. Ling is with the Centre for Health Technologies, Faculty of Engineering and IT, University of Technology Sydney, Ultimo, NSW, Australia. (e-mail: Steve.Ling@uts.edu.au).

T.S. Dillon is with the Digital Ecosystems and Business Intelligence Institute, Curtin University of Technology, WA, Australia (e-mail: tharam.dillon@ cbs.curtin.edu.au).

H.T. Nguyen is with the Centre for Health Technologies, Faculty of Engineering and IT, University of Technology Sydney, Ultimo, NSW, Australia. (e-mail: Hung.Nguyen@uts.edu.au).

patients using the specified physiological parameters. Based on a set of training data collected from TIDM patients, a neural network based classification unit was developed by a genetic algorithm, which has a multi-objective fitness function with two goals. It maximizes the number of TIDM patients with hypoglycemic episodes diagnosed correctly with hypoglycemic episodes, and the number of TIDM patients in normal conditions diagnosed correctly in normal conditions. At the same time, it also minimizes the number of TIDM patients with hypoglycemic episodes diagnosed wrongly under normal conditions and the number of TIDM patients under normal conditions wrongly diagnosed with hypoglycemic episodes. The neural network based classification unit was validated by a set of testing data, and satisfactory results can be found.

This paper is organized as follows: in Section II, a detailed description of applying the genetic algorithm in generating the proposed neural network based classification unit is introduced. Results and evaluations of the proposed neural network based classification unit for hypoglycaemic episodes diagnosis purposes are presented in Section III. A conclusion is given in Section IV.

II. METHOD

A. Neural Network based classification unit

Diagnosis of hypoglycaemic episodes is essential for T1DM patients especially at night, largely because episodes of hypoglycemia are common while usual insulin preparations do not adequately mimic the normal patterns of endogenous insulin secretion [30]. Based on the medical doctors' experiences [14], the blood glucose levels of T1DM, *y*, which indicate whether the patients are hypoglycemia, are significantly related to several physiological parameters of which the three most significant ones have been identified as follows:

- rates of changes of heart rates, x_1;
- corrected QT interval of electrocardiogram signal, x_2;
- rates of changes of corrected QT interval, x_3;

Hypoglycemic episodes are defined as those in which the patient's blood glucose level, $y < 3.33$ mmol/l (60mg/dl) [9, 10]. The neural network based classification unit, which is trained by a genetic algorithm based on a set of patients' data, is proposed to determine whether the patient is hypoglycemia based on the three physiological parameters. A three-layer feed-forward neural network was used to indicate whether the patient is hypoglycemia or not in relation to the three patient's physiological parameters, rate of change of heart rate, x_1, corrected QT interval of electrocardiogram signal, x_2 and rate of change of corrected QT interval, x_3. Its structure is shown in Fig. 1. It consists of an input layer including the three physiological parameters x_1, x_2 and x_3 which are fed in, and the output layer which produces the indication of hypoglycemia z = 0 or 1. The patient is in normal condition with z=0 if the glucose level *y* of the patient is higher than 3.3 mmol/l. Otherwise, they are in hypoglycemia with z=1 if the glucose level *y* of the patient is lower than 3.3 mmol/l. The hidden layer links the physiological parameters and the indication of hypoglycemia together and allows for complex, nonlinear interactions between the three physiological parameters to produce the indication of hypoglycemia.

Referring to Fig. 1 in the appendix, the input-output relationship of the proposed three-layer neural networks for the glucose level *y* can be written as follows:

$$y = \sum_{j=1}^{n_h} w_j \log sig\left[\sum_{i=1}^{3}\left(v_{ij}x_i - b_1\right)\right] - b_1 \qquad (1)$$

where n_h denotes the number of the hidden nodes; w_j, j=1, 2, …, n_h, denotes the weight of the link between the *j*-th hidden node and the output; v_{ij}, i=1,2,3 and j=1, 2, …, n_h, denotes the weight between the *i*-th input and the *j*-th hidden node; b_j and *b*, denote the biases for the *j*-th hidden nodes and output nodes respectively; log*sig*(.) denotes the logarithmic sigmoid function:

$$\log sig(\alpha) = \frac{1}{1+e^{-\alpha}}, \qquad \alpha \in \Re. \qquad (2)$$

To develop the neural network based classification unit for the estimation of hypoglycemia, values of the neural network parameters (i.e. w_j, v_{ij}, b_j and *b* with i=1, 2, 3 and j=1, 2, …, n_h) and the number of hidden-nodes (i.e. n_h) used in the hidden layer need to be determined. These two settings not only affect the convergence of neural networks, but also affect the accuracy of the estimation of the neural network. Here a genetic algorithm is introduced to determine the neural network parameters. The neural network architecture are 3-n_h-1, denoted as NNA_{n_k}, where n_h is the number of hidden nodes. First the neural network architecture, NNA_{n_k}, is selected and then a neural network is constructed according to the neural network architecture. After that, the neural network parameters (i.e.: w_j, v_{ij}, b_j and *b* with i=1, 2, 3 and j=1, 2, …, n_h) are searched by a genetic algorithm, and finally the trained error of the developed neural network is calculated.

B. Trained with genetic algorithm

To optimize the neural network parameters of the neural network, a genetic algorithm [11, 21] is used. The genetic algorithm first generates a population of strings, represented by the parameters of the neural network with an architecture NNA_{n_k} randomly. The strings are expressed as $\left[w_j, v_{ij}, b_j, b\right]$ where $-1 \ge w_j, v_{ij}, b_j, b \ge 1$, i=1,2,3 and j=1,2,…, n_h. The length of the strings is equal to the total number of neural network parameters, which is $n_h + 3n_h + n_h + 1 = 5n_h + 1$. Then the fitness of each string is evaluated by a fitness function which is defined as:

$$fitness = \lambda\varsigma + (1-\lambda)\kappa \quad (3)$$

where ς and κ are the sensitivity and the specificity of the T1DM problem represented by the string respectively, and $\lambda \in [0\ 1]$ is a constant value to control the importance of the sensitivity and specificity. λ is set at 0.52 in this application. ς and κ are defined as follows:

$$\varsigma = \frac{N_{TP}}{N_{TP} + N_{FN}}, \quad (4)$$

$$\kappa = \frac{N_{TN}}{N_{TN} + N_{FP}}, \quad (5)$$

where N_{TP} is number of true positives which implies positive T1DM patients correctly diagnosed as positive; N_{FN} is number of false negatives which implies the positive T1DM patients wrongly diagnosed as negative; N_{FP} is number of false positives which implies negative T1DM patients wrongly diagnosed as positive; and N_{TN} is number of true negatives which implies negative T1DM patients correctly diagnosed as negative [2]. The objective of the genetic algorithm is to maximize both ς and κ. The population of strings is evolved and improved iteratively by the evolution operation, crossover and mutation, until a termination condition is met. In genetic algorithms, there can be many possible termination conditions. Here the termination condition is met when a string with $\varsigma > 0.75$ and $\kappa > 0.5$, which satisfies the requirement of the diagnosis, is found.

III. Results and Discussion

A. T1DM's data

The data is collected from 16 T1DM patients at 14.6±1.5 years of age who volunteered to carry out the 10-hour overnight hypoglycemia study at the Princess Margaret Hospital for Children in Perth, Western Australia, Australia. Each T1DM patient was monitored overnight for the natural occurrence of nocturnal hypoglycemia. We measured the required physiological parameters, while the actual blood glucose levels were measured by a Yellow Spring Instrument. The actual blood glucose profiles for 16 T1DM children [31-32] are shown in Fig 2.

The responses of the 16 T1DM patients exhibited significant changes during the hypoglycemia phase against the non-hypoglycemia phase. The sampling period is around 5 minutes and 35-40 data was collected from each patient. 320 training data sets regarding to the blood glucose level y, rate of change of heart rate x_1, QT interval x_2 and rate of change of QT interval x_3 are used for developing the proposed neural network based classification unit, and 100 testing data sets were used for validating the developed proposed neural network based classification unit.

B. Classification

The following parameter settings suggested by (Schaffer et al. 1989) were implemented on the genetic algorithm to train the neural network based classification unit (NN-GA) discussed in Section II:

- Crossover operation: Intermediate crossover operation [21];
- Crossover rate = 0.8;
- Mutation operation: Gaussian perturbation mutation operation [21];
- Mutation rate $= 1/(5n_h + 1)$, where $5n_h + 1$ is the number of variables of a string and n_h is the number of hidden nodes on the neural network;
- Number of generations = 1000;
- Population size = 500.

As a comparison, the neural network (NN) based classification unit has also been trained with a Levenberg Marquardt (LM) algorithm [14, 18] called NN-LM, which is a popular training algorithm for feed-forward neural networks. Table I shows the mean training errors in terms of sensitivity and specificity of the trained neural networks corresponding to the six different neural network architectures which are 3-5-1, 3-8-1, 3-10-1, 3-12-1, and 3-15-1. As the genetic algorithm (GA) is a stochastic algorithm, different neural networks could be found with different runs. Also the neural networks searched by the LM algorithm are different with different initial searching points set in the algorithm. Therefore both the GA and the LM were run for 30 times, and their average results among the 30 runs were recorded in Table I. It can be found from Table I that the neural network with 10 hidden nodes is the best among the ones found by both GA and the LM, which can achieve the largest fitness. The sensitivity and the specificity of the optimized neural network architecture 3-10-1 with the best mean fitness found by the GA are 0.7930 and 0.6053 respectively which is considered to be a satisfactory result in which the sensitivity is larger than 0.75 and the specificity is larger than 0.5. However, the ones found by the LM are 0.1614 and 0.9913 which is not satisfactory, as the sensitivity is smaller than 0.75 and the specificity is smaller than 0.5.

Apart from using the neural network approaches, four commonly used approaches for generating explicit models are used:

a) Statistical Regression (SR) [25], which is a common modeling approach to develop empirical models in linear polynomial forms.
b) Fuzzy Regression (FR) [28], which can generate empirical models in fuzzy linear polynomial forms and the fuzziness of experimental data can be addressed.
c) Genetic Programming (GP) [15], which can generate empirical models in nonlinear polynomial forms. In the GP, the structures of the polynomials are generated by the evolutionary operations, and the coefficients of the polynomials are determined by the least square method. The following parameters with reference to [19] were used in the GP: population size =100; probability of crossover = 0.5; probability of mutation= 0.5.
d) Genetic Programming based Fuzzy Regression (GP-FR) [3], which can generate empirical models in fuzzy nonlinear polynomial forms and can address fuzziness of experimental data. In the GP-FR, the structures of the fuzzy polynomials are generated by the evolutionary operations, and the fuzzy coefficients of the polynomials

are determined by the fuzzy regression method. The parameters used in the GP-FR were identified to the ones used in the GP.

TABLE I
NEURAL NETWORK CONFIGURATION AND TRAINING ERROR PRODUCED BY THE GENETIC ALGORITHM AND THE LEVENBERG MARQUARDT ALGORITHM.

*CO-NN	Mean sensitivity		Mean specificity		Mean fitness	
	NN-GA	NN-LM	NN-GA	NN-LM	NN-GA	NN-LM
3-5-1	0.6837	0.1111	0.6063	0.9948	0.6450	0.6032
3-8-1	0.6940	0.1466	0.6016	0.9917	0.6478	0.5692
3-10-1	0.7930	0.1614	0.6053	0.9913	0.6991	0.5763
3-12-1	0.8178	0.1450	0.5654	0.9846	0.6916	0.5298
3-15-1	0.8183	0.1984	0.5605	0.9834	0.6894	0.6113

(*Configuration Of the Neural Networks)

TABLE II
TRAINING RESULTS OF THE SIX METHODS, SR, FR, GP, GP-FR, NN-LM AND NN-GA.

	Mean sensitivity and specificity		Maximum sensitive		Maximum specificity	
	Sen.	Spec.	Sen.	Spec.	Sen.	Spec.
SR	0	1	0	1	0	1
FR	0	1	0	1	0	1
GP	0.0990	0.9978	0.1005	1.0398	0.1322	1.1537
GP-FR	0.0833	1.0990	0.1377	1.0774	0.1006	1.0177
NN-LM (3-10-1)	0.1984	0.9834	0.4921	0.9922	0.2381	1.0000
NN-GA (3-10-1)	0.7930	0.6053	0.9048	0.5175	0.7302	0.7549

TABLE III
VALIDATION RESULTS OF THE SIX METHODS, SR, FR, GP, GP-FR, NN-LM AND NN-GA.

	Mean sensitivity and specificity		Maximum sensitive		Maximum specificity	
	Sen.	Spec.	Sen.	Spec.	Sen.	Spec.
SR	0	1	0	1	0	1
FR	0	1	0	1	0	1
GP	0.0893	0.8996	0.0275	0.9374	0.0290	1.0401
GP-FR	0.0744	0.9816	0.0337	0.9623	0.0005	0.9090
NN-LM (3-10-1)	0.1443	0.7646	0.3826	0.7715	0.1851	0.7775
NN-GA (3-10-1)	0.7557	0.5768	0.8623	0.4932	0.6959	0.7194

The four algorithms were implemented with Matlab programming software. As both GP and GP-FR are stochastic algorithms, different results can be found with different runs. Therefore both GP and GP-FR were run for 30 times, and their average results among the 30 runs were recorded. The mean sensitivities, the mean specificities, the maximum sensitivities among the 30 runs and the maximum specificities among the 30 runs of the six algorithms, SR, FR, GP, GP-FR, NN-GA (with the neural network configuration 3-10-1) and NN-LM (with the neural network configuration 3-10-1) among the 30 runs are summarized in Table II.

It can be found from Table II that the four approaches, SR, FR, GP and GP-FR achieved good specificities but poor sensitivities. NN-LM is better than the four approaches. Only the proposed NN-GA can achieve satisfactory results in both sensitivities and specificities in which the sensitivities are larger than 0.75 and the specificities are larger than 0.5. Also validation tests were carried out to evaluate the six approaches based on a set of testing data. Table 3 shows that the NN-GA can achieve satisfactory validation results in which the mean sensitivity is larger than 0.75 and the mean specificity is larger than 0.5, while the other five methods cannot achieve satisfactory results. The overall performance regarding to the maximum sensitive and the maximum specificity of the NN-GA are also better than the other five methods

IV. CONCLUSION

In this paper, a neural network based classification unit is developed to determine the presence of hypoglycemic episodes based on the TIDM patients' physiological parameters, rate of change of heart rate, corrected QT interval of electrocardiogram signal and rate of change of corrected QT interval. It was developed based on T1DM patients' 420 data sets which were collected from 16 T1DM patients by using the genetic algorithm. 320 data sets were used to develop the neural network based classification unit and 100 data sets were used to validate its performance. It was found that the sensitivity and specificity were found as 79.30% and 60.53% respectively which are considered to be reasonable and are better than the ones found by the commonly used methods, statistical regression, genetic programming and fuzzy regression.

However, the neural network based classification unit only has the capability to transform the nonlinear or fuzzy patients' data into simplified black-box structures in which no explicit knowledge or information can observed. Because of the black-box nature of neural networks, some medical doctors may feel uncomfortable to use neural networks for diagnosis purposes even through the approaches may achieve better accuracy diagnosis than the other explicit modeling methods like classical statistical methods or genetic programming. This could also pose serious issues of one has to provide justification for one's decision based on the implicit output of the neural network. In the future, we will investigate methodologies in extracting explicit information from the neural networks, so that the decision basis is explicit.

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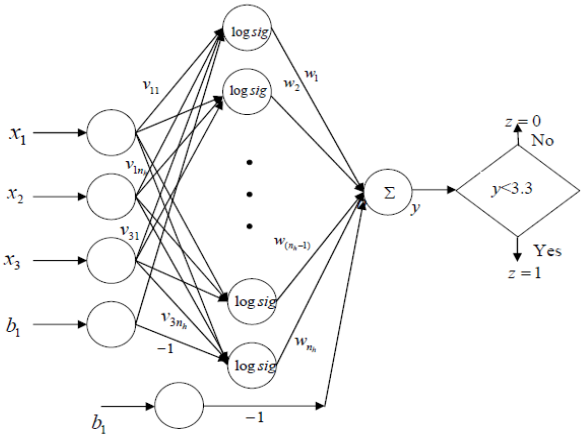

Fig. 1 Structure of the neural network based classification unit.

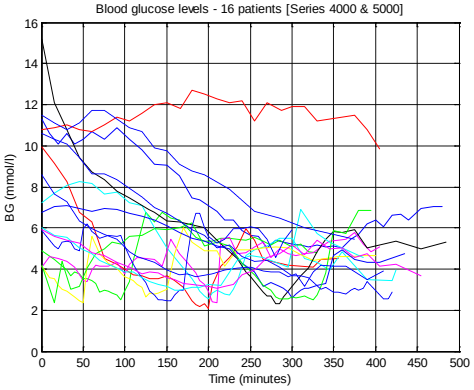

Fig. 2. Blood glucose level profiles in the 16 T1DM patients.