FUZZY INFERENCE SYSTEM AND
MULTIPLE REGRESSION FOR DETECTION
OF HYPOGLYCEMIA

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ABSTRACT

Hypoglycemia or low blood glucose oftenly occurs with patients that take insulin therapy for diabetes. Hypoglycemia is serious and causes unconsciousness, seizures or even death. The proposed system uses ECG signal for the detection of hypoglycemia. To find the presence of the hypoglycaemic episodes the system uses heart rate(HR),corrected QT interval, change of HR and change of corrected QT interval of the ECG signal. The system is developed using multiple regression with fuzzy inference system(FIS). Genetic algorithm and particle swarm optimization is used to optimize the parameters of FIS and multiple regression. Fuzzy Inference System is used to estimate the hypo level based on the physiological parameters. The physiological parameters are heart rate and corrected QT interval. Multiple regression is used to fine tune the performance of the hypoglycemic detection based on the estimated hypo level and the change of the HR and corrected QT interval. Neural network with particle swarm optimization is also used to find the presence of hypoglycemia. Finally the performance of both systems are compared.

KEYWORDS

Fuzzy inference system (FIS), hypoglycemia, multiple regression, genetic algorithm, neural network, particle swarm optimization.
1. INTRODUCTION

Hypoglycemia is a condition that occurs when your blood sugar (glucose) is too low. Hypoglycemia can result in unconsciousness, seizures or even death, are common and can cause serious side effect in insulin therapy[1]. Hypoglycemic episodes are suggested as those in which the patient had blood glucose (BG) levels less than 3.3 mmol/l (60 mg/dl) [2].

Hypoglycemia develops when rates of glucose entry into the systemic circulation are reduced relative to glucose uptake by tissues. It is usually corrected naturally by the combination of a number of defense mechanisms. Initially, a decrease in insulin secretion in response to declining blood glucose levels occurs. As glucose levels continue to fall, a number of redundant glucose counter-regulatory factors are sequentially activated at specific thresholds to ensure sufficient glucose uptake to the brain and other central nervous system tissue metabolism [3].

In patients with Type 1 diabetes mellitus (T1DM) undergoing intensive insulin therapy, falling plasma glucose concentrations often do not elicit counter-regulatory responses at normal glycemic thresholds, allowing glucose levels to drop to dangerously low values. After many years of type 1 diabetes, the glucagon's secretory response to hypoglycemia could become deficient. Additionally, warning symptoms may be lost in some cases, and the episode may lead to serious acute reactions known as hypoglycemia unawareness. Studies in T1DM patients have demonstrated that as few as two episodes of antecedent hypoglycemia can blunt responses to subsequent hypoglycemia [4].

Symptoms of hypoglycemia arise from the activation of the autonomous central nervous systems (autonomic symptoms) and from reduced cerebral glucose consumption (neuroglycopenic symptoms), some of the latter being potentially life threatening. Autonomic symptoms (e.g., tachycardia, palpitations, shakiness, sweating) are activated before neuroglycopenic symptoms (e.g., reduced concentration, blurred vision, dizziness). Autonomic symptoms may provide the initial indication of the presence of hypoglycemia and allow the patient to recognize and correct the ensuing episode.

Nocturnal hypoglycemia is particularly dangerous because sleep reduces and may obscure autonomic counter-regulatory responses so that an initially mild episode may become severe. The risk of severe hypoglycemia is high at night, with at least 50% of all severe episodes occurring during that time [5]. Deficient glucose counter-regulation may also lead to severe hypoglycemia even with modest insulin elevations. Regulation of nocturnal glycemia is further complicated by the dawn phenomenon. This is a consequence of nocturnal changes in insulin sensitivity secondary to growth hormone secretion: a decrease in insulin requirements approximately between midnight and 5 A.M. followed by an increase in requirements between 5 and 8 A.M.

In this paper, we develop a fuzzy inference system with multiple regression for the detection of hypoglycemia episodes using physiological parameters such as heart rate, corrected QT interval, change of heart rate and change of QT interval. Section II provides an overview of the method used for non-invasive detection of hypoglycemia. Section III presents the development and results of an optimized fuzzy inference system used for the identification of hypoglycemic episodes. Section IV provides a conclusion for this study.
2. METHODS

A study of the system proposed by Steve S.H. Ling and Hung T. Nguyen [13] is carried out by applying it to hypoglycemia detection. To realize the detection of hypoglycemic episodes in patients, multiple regression with fuzzy inference system (FIS) is developed as shown in Fig. 1. The inputs are the HR, corrected QT interval of the ECG signal (QTc), change of HR (ΔHR), and the change of corrected QT interval (ΔQTc); and the output is the binary level of hypoglycemia (low level represents hypo and high level represents nonhypo).

The ECG parameters that will be investigated in this research involve the parameters in depolarization and repolarization stages of electrocardiography. The concern points are Q point, R peak, T wave peak, and T wave end, as can be seen in Fig. 2. The peak of T wave is searched in the section of 300 ms after R peak. In this section, the maximum peak is defined as the peak of T wave. Q point is searched in the section of 120 ms in left side of R peak. The Q point is found by investigating the sequential gradients of negative–negative–positive/zero–positive/zero from the right side[6]. These concerned points are used to obtain the ECG parameters that are used for inputs in the hypoglycemia detection. QT is interval between Q and Tp points. QTc is QT/√(RR) in which RR is the interval between R peaks. HR is 60/RR.

Based on the linear correction analysis, HR and QTc have a medium correlation with hypoglycemia, and the ΔHR and ΔQTc have a slight correlation with hypoglycemia. With the result of correction analysis, the hypoglycemic episodes detector system is combined with two subsystems and, namely, FIS and multiple regression model are proposed.

2.1 Fuzzy Inference System

Referring to Fig. 1, the FIS is used to realize the approximated correlation between the physiological parameters (HR and QTc) and hypoindex (υ). Due to the highly correlation of the input HR and QTc, FIS plays a main role to approximate the correlation between the physiological parameters (HR and QTc) and the approximated hypoindex (υ) by using a set of υ determined fuzzy rules[7]. The index υ is in the range of 0–1. Larger value of υ is implied that the possibility of hypoglycemia is higher. The fuzzy detection system consists of three components: fuzzification, inferencing, and defuzzification.
2.1.1. Fuzzification:

The first step is to take the inputs, and determine the degree of membership they belong to each of the appropriate fuzzy sets. The membership function is defined as:

\[ \mu_{NB}(z) = \frac{1}{1 + \left(\frac{z - m_k}{s_k}\right)^2} \]  \hspace{1cm} (1) \]

where \( z(t) = [HR(t) \text{ QT}(t)] \) in which \( z(t) \) denotes the nonfuzzy input, \( k = 1, 2, \ldots \) in which \( n_d \) denotes the number of membership functions, \( t = 1, 2, \ldots, n_a \) in which \( n_a \) denotes the number of input–output data pairs, and parameters \( m_k \) and \( s_k \) are the mean value and the standard deviation of the member function, respectively. If the input value is less than the minimum of the mean value or higher than the maximum of mean value, the degree of membership is set to 1.

2.1.2. Inferencing

The task of the inferencing process is to map the fuzzified inputs to the rule base, and to produce a fuzzified output for each rule. The fuzzy if-then rules in the rule base are of the following format:

Rule \( r \) : IF HR(t) is \( \mathbb{N}_{HR}^k \) (HR(t)) AND QT(t) is \( \mathbb{N}_{QT}^k \) (QT(t)) THEN u(t) is \( w_r \)

(2)

where \( \mathbb{N}_{HR}^k \) and \( \mathbb{N}_{QT}^k \) are fuzzy terms, \( \gamma = 1, 2, \ldots, n_r \) in which \( n_r \) denotes the number of rules and is equal to \( \left( n_a \right)^{n_{in}} \) here \( n_{in} = 2 \) is the number of inputs of the FIS. Aggregation is then used to obtain the output of each rule \( \gamma \) as a fuzzy value. The output for each rule is defined as:

\[ \mu_r = \left( \mu_{\mathbb{N}_{HR}^k}^r \left( HR(t) \right) \right) \times \left( \mu_{\mathbb{N}_{QT}^k}^r \left( QT(t) \right) \right) \]

(3)

\[ r=1,2,\ldots, n_r \]
2.1.3. Defuzzification

Defuzzification is the process of translating the outputs of the fuzzy rules into a value. The output of the defuzzification process is given by:

\[ u(t) = \frac{\sum R_z \cdot w_{rz} \cdot \mu_{rz}}{\sum \mu_{rz}} \]  

(4)

where \( \mu_{rz} \in [0, 1] \) is the fuzzy singleton in Rule \( r \).

2.2. Multiple Regression Model

Multiple regression model that is used to classify the presence of hypoglycemia based on the approximated \( \nu \), \( \Delta HR \), and \( \Delta QTc \). This model is used to fine-tune the hypoglycemic detection performance due to the slight correction of \( \Delta HR \) and \( \Delta QTc \). The advantages of the regression model are the simple structure and few parameters are needed [8].

A multiple regression model is introduced to find the relationship between the system’s inputs and the presence of hypoglycemic episodes. Referring to Fig. 1, the inputs are: 1) \( \nu \) that is estimated by the FIS; 2) change of HR (\( \Delta HR \)); and 3) the change of corrected QT interval (\( \Delta QTc \)). \( \Delta HR \) and \( \Delta QTc \) are used to fine-tune the performance of the system. In general, multiple regression model procedures will be estimated as the following form:

\[ Y_i = \beta_\nu + \beta_1 X_i + \beta_2 X_i^2 + \ldots + \beta_n X_i^n \]  

(5)

where the \( Y_i \) is the output to represent the binary status of hypoglycemia. When \( Y_i \geq 0 \), which represents positive (sick), and appositively, when \( Y_i < 0 \), which represents negative (healthy). \( X_i \) is the inputs of the system, i.e., \( X_i = [\nu, \Delta HR, \Delta QTc] \), \( i = 1, 2, \ldots, n \); \( \beta \) denotes the parameters of the regression model; and \( \eta \) denotes the number of order.

2.3 Genetic Algorithm

To optimize the fuzzy membership functions and rules (the values of \( m, \zeta \) and \( w \)), the Genetic Algorithm (GA) is used. The GA process is shown in Fig. 3. First, a population of chromosomes \( P \) is generated. Each chromosome \( p_i \) contains a set of genes \( p_{ij} \), where \( i = 1, 2, \ldots, n_p \), \( j = 1, 2, \ldots, n_g \). \( n_p \) and \( n_g \) denote the population size (number of chromosomes) and the number of genes respectively. Second, the chromosomes are evaluated by a defined fitness function \( f(p_i) \). The form of the fitness function depends on the application. The better chromosomes are those returning higher fitness values in this process. Third, some of the chromosomes are selected to undergo genetic operations for reproduction by the method of normalized geometric ranking [9]. It is a selection based on a non-stationary penalty function which is a function of the generation number. As the number of generation increases, the penalty increases that puts more and more selective pressure on the GA to find the feasible solution. In general, a higher-rank chromosome will have a higher chance to be selected. Fourth, the genetic operation of crossover is performed.

The crossover operation is mainly for exchanging information from the two parents, chromosomes \( p_1 \) and \( p_2 \), obtained in the selection process with a defined probability of crossover \( \mu_c \). This probability gives an expected number of chromosomes that undergo the crossover. In this paper, Blend-\( \alpha \) [10] is used as the operation of crossover, which has a good searching ability and can handle multimodal and separability problem effectively. For the Blend-\( \alpha \) crossover, the resulting offspring is chosen randomly from the interval \([X^i_j, X^2_j]\) following the uniform distribution, where
and gives an expected number of genes that undergo the mutation. After the crossover operation, the mutation operation follows. The mutation operation is to change the genes of the chromosomes in the population such that the features inherited from their parents can be changed. A probability of mutation $\mu m$ is defined to govern the operation and gives an expected number of genes that undergo the mutation.

$$X_j^i = \min(p_{1j}, p_{2j}) - \alpha d_j$$

$$X_j^i = \min(p_{1j}, p_{2j}) + \alpha d_j$$

(6)

where $d_j = |p_{1j} - p_{2j}|$, $p_{1j}$ and $p_{2j}$ are the jth elements of $p1$ and $p2$, respectively, and $\alpha$ is a positive constant.

**2.3.1 Tune the Parameters of FIS Using GA**

GA is employed to optimize the fuzzy rules by finding out the best parameters $m_{HR}^k$, $m_{QT}^k$, and $w_r$ of the FIS. GA is used to learn the input output relationship of HR, QTc interval and hypo index value. The input output relationship is described by

$$v^d(t) = g(z^d(t)),$$

$$z^d(t) = [HR^d(t) \quad QT^d(t)]$$

(7)

where $z^d(t)$ and $v^d(t)$ are the given physiological inputs and the desired hypoindex output of an nonlinear function $g(\cdot)$, respectively. When BG levels are less than 3.3 mol/l, $v^d(t)$ will set to 1, otherwise, set to 0. Referring to (5) of the GA, the fitness function is defined as
The objective is to maximize the fitness function of (8) (minimize the mean square error between the desired \( v^d(t) \) and the \( v(t) \) from FIS using the GA by setting the chromosome to be \( [m_{HR}^k, \sigma_{HR}^k, m_{QT}^k, \sigma_{QT}^k, w_j] \) for all \( j, k \). After the training, an optimized FIS is found.

### 2.3.2 Tune the Parameters of Multiple Regression Using GA

The objective of the multiple regression model is to detect the hypoglycemic episodes accurately based on the output of trained FIS, ΔHR, and ΔQTc. To measure the performance of the biomedical classification test, sensitivity and specificity are introduced [11]. The sensitivity measures the proportion of actual positives that are correctly identified and the specificity measures the proportion of negatives that are correctly identified. The definitions of the sensitivity (\( \varsigma \)) and the specificity (\( \kappa \)) are given as follows:

\[
\varsigma = \frac{N_{TP}}{N_{TP} + N_{FN}} \quad \text{(9)}
\]

\[
\kappa = \frac{N_{TN}}{N_{TN} + N_{FP}} \quad \text{(10)}
\]

where \( N_{TP} \) is the number of true positives that means the sick people are correctly diagnosed as sick; \( N_{FN} \) is the number of false negatives that means the sick people are wrongly diagnosed as healthy; \( N_{FP} \) is the number of false positives that means the healthy people wrongly diagnosed as sick; and \( N_{TN} \) is the number of true negatives that means the healthy people are correctly diagnosed as healthy.

The objective of the system is to maximize the sensitivity and the specificity; thus, the fitness function is defined as follow:

\[
fitness = \lambda \varsigma + (1 - \lambda)\kappa + \rho \quad \text{(11)}
\]

\[
\rho = \begin{cases} 
1 & \text{if } \varsigma \geq 0.7 \text{ and } \kappa \geq 0.5 \\
0 & \text{otherwise}
\end{cases}
\]

where \( \rho \) is a penalty value. This penalty function gives a force to the optimization method to meet the target \( \lambda \in [0, 1] \) is a constant value to control a balance of the sensitivity \( \varsigma \) and specificity \( \kappa \). A larger value of the \( \lambda \) gives a strong force to the system to maximize the sensitivity; however, it will reduce the performance of the specificity in optimization.

### 2.4 Neural Networks And Particle Swarm Optimization

To realize the detection of hypoglycemic episodes, a neural network (NN) with 2 inputs and 1 output system is developed based up on the system proposed by Steve Phyo Phyo San, Sai Ho Ling and Hung T. Nguyen [14]. PSO based neural network for hypoglycemic detection is shown in the figure 4.
The two inputs are the psychological input: the heart rate (HR) and the corrected QT interval (QTc) of electrocardiogram (ECG) signal while the output is the presence of hypoglycemia (h) in which +1 represents hypoglycemia and −1 is non-hypoglycemia. In this proposed system, the weights of Neural Network are optimized by PSO [12].

### 2.4.1 Neural Network

The system proposes a bayesian neural network. Bayesian neural networks were firstly introduced by MacKay as a practical and powerful means to improve the generalisation of neural networks. A Bayesian neural network has the following main benefits:

- Its network training adjusts weight decay parameters automatically to optimal values for the best generalization. The adjustment is done during training, so the computational intensive search for the weight decay parameters is no longer required.
- The evidence for each model can be estimated using the Bayesian framework. During training, networks converge to different local minima and networks with different network architectures and can be compared and ranked according to the evidence. The evidence can be used as a stop criterion.
- As no separate validation set is required, more data can be used for training.

Bayesian learning of multi-layer perception neural networks is performed by considering Gaussian probability distributions of the weights which can give the best generalization [15]. In particular, the weights w in network X are adjusted to their most probable values given the training data D. Specifically, the posterior distribution of the weights can be computed using Bayes’ rule as follows:

$$ p(w|D,X) = \frac{p(D|w,X)p(w|X)}{p(D|X)} $$  \hspace{1cm} (12)

where $p(D|w,X)$ is the likelihood function, which contains information about the weights from observations and the prior distribution $p(w|X)$ contains information about the weights from background knowledge. The denominator, $p(D|X)$, is known as the evidence for network X.

### 2.4.2 Particle Swarm Optimization

Particle swarm optimization (PSO) is a computational method that optimizes a problem by iteratively trying to improve a candidate solution with regard to a given measure of quality. PSO optimizes a problem by having a population of candidate solutions, here dubbed particles, and
moving these particles around in the search-space according to simple mathematical formulae over the particle's position and velocity. Each particle's movement is influenced by its local best known position and is also guided toward the best known positions in the search-space, which are updated as better positions are found by other particles. This is expected to move the swarm toward the best solutions[12].

PSO is initialized with a group of random particles (solutions) and then searches for optima by updating generations. In every iteration, each particle is updated by following two "best" values. The first one is the best solution (fitness) it has achieved so far. (The fitness value is also stored.) This value is called pbest. Another "best" value that is tracked by the particle swarm optimizer is the best value, obtained so far by any particle in the population. This best value is a global best and called gbest. When a particle takes part of the population as its topological neighbors, the best value is a local best and is called lbest.

![Figure 5: Basic steps in PSO](image)

3. Results And Discussion

The detection of hypoglycemic episodes (BG<=3.3 mmol/l) by using these variables is based on a GA-based multiple regression with FIS developed from the obtained clinical data. In effect, it estimates the presence of hypoglycemia at sample period \( k \) based on the basic of the data at sampling period \( k \) and the previous data at sampling period \( k-1 \). In general, the sampling
period is 5 min. By using regression analysis, the correlation coefficients for the hypoglycemia status and each physiological inputs (HR, QTc, ΔHR, and ΔQTc) are given and the correlation coefficients are −0.1988, −0.1224, −0.0050, and −0.0055, respectively. Values close to −1 suggest that the data have a negative linear relationship. Moreover, values equal to 0 suggest that there is no linear relationship between the data. It can be seen that HR and QTc have a medium correlation with hypoglycemia, and the ΔHR and ΔQTc have a slight correlation with hypoglycemia.

There are two steps to develop the proposed multiple regression with FIS to T1DM problem. The first step is to determine the optimized fuzzy rules and membership function of the FIS to approximate the relationship between the inputs HR, QTc, and υ. Once the optimized FIS is developed, the second step is to develop a multiple regression model to detect the hypoglycemia with the inputs υ, ΔHR, and ΔQTc.

In the FIS, the number of the membership function is set to 5 ($m_k = 5$); thus, the total number of fuzzy rules $n_r$ is equal to 25. Referring to (10), the fitness function of the GA for tuning the parameters $[m_{HR}^k, m_{QT}^k, w^k, m_{VT}^k]_g$ of FIS is defined, where $k = 1, 2, \ldots, 5$ and $γ = 1, 2, \ldots, 25$.

After the training process, the tabulated fuzzy rule are shown in Figs. 3. There are five fuzzy terms, namely, VL (very low), L (low), M (middle), H (high), and VH (very high). The value of the fuzzy singleton $w_r$ for different fuzzy terms is optimized and shown in Fig. 3, and higher value that represents the presence of hypo is “VH.” With these set of parameters, 25 fuzzy if-then rules are developed. Give one rule as an example: IF HR(t) is VH AND QT(t) is “VH,” THEN $υ(t)$ is “VH” (or $w_r = 0.9807$).

<table>
<thead>
<tr>
<th>HR</th>
<th>VL</th>
<th>L</th>
<th>M</th>
<th>H</th>
<th>VH</th>
</tr>
</thead>
<tbody>
<tr>
<td>VL</td>
<td>0.0177</td>
<td>0.2433</td>
<td>0.3733</td>
<td>0.5600</td>
<td>0.5581</td>
</tr>
<tr>
<td>L</td>
<td>0.0805</td>
<td>0.3045</td>
<td>0.1749</td>
<td>0.4465</td>
<td>0.5718</td>
</tr>
<tr>
<td>M</td>
<td>0.1192</td>
<td>0.4433</td>
<td>0.6938</td>
<td>0.8495</td>
<td>0.6853</td>
</tr>
<tr>
<td>H</td>
<td>0.2044</td>
<td>0.4157</td>
<td>0.9764</td>
<td>0.9854</td>
<td>0.7058</td>
</tr>
<tr>
<td>VH</td>
<td>0.2592</td>
<td>0.3308</td>
<td>0.9910</td>
<td>0.9126</td>
<td>0.9807</td>
</tr>
</tbody>
</table>

Table 1. Fuzzy rule table fuzzy.

Once an optimized FIS is developed, a multiple regression is used to fine-tune the hypoglycemic detection performance with the inputs of ΔHR and ΔQTc. For comparison and analysis purpose, first order (liner), second order and third order of the multiple regression model are used. According to (5), $η$ is set to 1−3, respectively.

The figure 6 illustrates ECG signal for a hypoglycemic person for 5 minutes. The heart rate is calculated from the ECG signal using the formula $60/RR$ where RR is the interval between R peaks of the signal. The corrected QTc value is calculated using the formula $QT/√RR$ where QT is the interval between the Q and Tp points. After calculating the heart rate and corrected QT interval value membership function value of each are calculated. The membership value lies between 0 and 1. After finding the membership function value of each heart rate and corrected QTc interval inference rule is applied. The rule is ‘If HR(t) is VH and QTc(t) is VH then $w_r = 0.9807$’. Based on the fuzzy rule table shown in the table 1 inferring rule value for the heart and corrected QTc interval are calculated. Based on the inferring rule and membership function value defuzzified value is calculated. This value is called as hypo index value. After calculating the hypo index value multiple regression in done based up on (5). All these results are shown in the figure 7. The result shows that it is a hypoglycemic person.
The overall data set consisted of a training set and a testing set with five patients. For these, the whole data set that included both hypoglycemia data part and nonhypoglycemia data part. By using GA, that is used to find the optimized fuzzy rules and membership functions and the model parameters of the multiple regression model, the basic settings of the parameters of the GA are shown as follows:

1) Population size \( np = 5 \).
2) Probability of crossover \( \mu_c = 0.8 \)
3) Probability of mutation \( \mu_m = 0.1 \).
4) Number of iteration \( T = 10 \) for FIS tuning

Once an optimized FIS is developed, a multiple regression is used to fine-tune the hypoglycemic detection performance with the inputs of \( \Delta HR \) and \( \Delta QTc \). To train the regression model, we use
GA to maximize the sensitivity (9) and specificity (10) by setting the chromosome to be $[\beta_0 \beta_1 \ldots \beta_\eta ]$. In this study, five testing patients are used. The system gives a sensitivity of 80% and specificity of 72.5%.

For neural network system, the dataset consist of a training set and a testing set. For these, the whole data set that included both hypoglycemia data part and nonhypoglycemia data part. The comparision results of sensitivity and specificity of FIS and neural system is shown below.

![Fig 8 Sensitivity Of FIS and Neural Network System](image)

![Fig 7 Specificity Of FIS and Neural Network System](image)

4. CONCLUSIONS

In this paper, multiple regression with FIS detection algorithm is developed to recognize the presence of hypoglycemic episodes. The aforementioned results indicate that hypoglycemic episodes in TIDM children can be detected noninvasively, continuously, and effectively from the real-time physiological responses. A multiple regression with FIS is proposed to detect the presence of hypoglycemic episodes. To optimize the fuzzy rules and the regression model, genetic algorithm is used. Also a system with neural network and particle swarm optimization is proposed to find out the presence of hypoglycemia. Finally the performance of the both the
system are compared. In the future, a neuro fuzzy system can be developed to detect hypoglycemia.

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