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Ventricular Repolarization Variability for Hypoglycemia Detection

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Abstract—**Hypoglycemia is the most acute and common complication of Type 1 diabetes and is a limiting factor in a glycemic management of diabetes. In this paper, two main contributions are presented; firstly, ventricular repolarization variabilities are introduced for hypoglycemia detection, and secondly, a swarm-based support vector machine (SVM) algorithm with the inputs of the repolarization variabilities is developed to detect hypoglycemia. By using the algorithm and including several repolarization variabilities as inputs, the best hypoglycemia detection performance is found with sensitivity and specificity of 82.14% and 60.19%, respectively.**

I. Introduction

HYPOGLYCEMIA is the most common complication of type 1 diabetes [1] and can result death in diabetic patients [2], [3]. It can be dangerous in which patients with diabetes might not recognize early the hypoglycemic symptoms while plasma glucose decreases to very low level [4]. Therefore, hypoglycemia detection is crucial and, until recently, hypoglycemia detection systems are being still developed to obtain adequate performance [5-7].

This paper provides our main contribution through introducing ventricular repolarization variabilities and a swarm-based support vector machine (SVM) algorithm for hypoglycemia detection system. We have developed a hybrid particle swarm optimization (PSO) based SVM model for detection of hypoglycaemic episodes with inputs of repolarization variabilities.

Ventricular repolarization variability is a physiological phenomenon where the duration of ventricular repolarization varies from beat-to-beat. Recent studies showed an increase of QT variability in relation to a variety of disease conditions, such as ventricular tachycardia or fibrillation [8], dilated cardiomyopathy [9] and myocardial Ischemia [10]. The process relating to beat-to-beat fluctuation of repolarization is likely mediated by stochastic behavior of ion channels [11].

Ventricular repolarization in hypoglycemia was widely studied in which hypoglycaemia results in prolonged corrected-QT (QT_c) intervals [12-14]. The association of heart rate in hypoglycemia was also investigated in which hypoglycaemia was found to increase heart rate [15]. Moreover, hypoglycemia detection techniques, such as neural networks and fuzzy systems, were developed using repolarization as input [16-18]. On the other hand, repolarization variability has not yet been widely studied for hypoglycemia detection. Thus, this paper will develop a new hypoglycemia detection strategy by using ventricular repolarization variabilities as inputs and employing a novel swarm-based SVM technique.

The new detection strategy uses repolarization variabilities in the form of repolarization variability indexes. One of the repolarization variability indexes is *QTe* interval variability indexes (*QTeVI*) as described in the following formulation [19],

$$QTeVI = \left(log_{10} \frac{QTe_v / QTe_m^{\,2}}{HR_v / HR_m^{\,2}} \right), \quad (1)$$

where QTe_v and QTe_m are the variance and mean of *QTe*, respectively. *QTe* is the time interval from the Q point to the end of T-wave. HR_v and HR_m are the variance and mean of heart rate, respectively. The other repolarization variability indexes are *TpTeVI*, *ToTpVI* and *RTpVI* having similar formulation with *QTeVI* in (1), by replacing *QTe* with *TpTe*, *ToTp* and *RTp*. *TpTe* is the time interval from the peak to the end of T-wave; *ToTp* is the time interval from the beginning to the end of T-wave; and *RTp* the time interval from the R peak to the peak of T-wave.

The new hypglycemia detection algorithm is based on a swarm-based SVM technique. SVM has proved to yield good performance for classification in various applications [20] and showed the ability to generalize well, even with a small size sample [21]. In this study, particle swarm optimization (PSO) [22] is used to optimize the SVM parameters. SVM parameter selection using PSO has been applied for applications, such as engineering industry process [23].

The rest of this paper is organized as follow. Section II describes the hypoglycemia detection method which is based on a swarm-based SVM technique. Section III presents the results and discussion, and section IV is the conclusion.

II. Methodology

To realize the hypoglycemia detection system, a swarm-based SVM with input of repolarization variabilities is developed. The system with four inputs and one output is described in Fig. 1. The inputs are *QTeVI*, *TpTeVI*, *ToTeVI* and *RTpVI*. The output is a binary state which involves hypoglycemia (+1) or non-hypoglycemia (-1). The base of

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the system is SVM-RBF, which is SVM applying radial basis function (RBF). Optimal values of the SVM-RBF parameters are obtained using PSO.

A. SVM-RBF

The detailed description of SVM is available in [24],[25]. Essentially, a SVM searches an optimal hyperplane to classify two class data $\{\mathbf{x}_k, z_k\}$, where $\mathbf{x}_k \in R^m$ is an m dimensional space and the associated z_k is class label, -1 or +1. The optimal hyperplane can be defined by $\mathbf{w}\cdot\mathbf{x}+b=0$, where $\mathbf{w}$ is hyperplane perpendicular vector and $|b| / \| \mathbf{w}^2 \|$ is the distance of the hyperplane to the origin. The optimal hyperplane maximizes distance between two hyperplanes; $\mathbf{w}\cdot\mathbf{x}+b=+1$ and $\mathbf{w}\cdot\mathbf{x}+b=-1$.

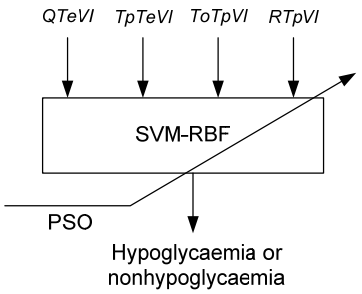

Fig. 1. Hypoglycemia detection system with inputs of the repolarization variabilities.

The hyperplane is determined by minimizing

$$C\sum \xi_k + \tfrac{1}{2}\|\mathbf{w}\|^2 , \tag{2}$$

where C, called SVM soft margin parameter, is a constant for controlling the tradeoff between complexity and proportion of nonseparable points. ξ_k is nonnegative slack variable. The minimization is subjected to

$$z_k(\mathbf{w}\cdot\mathbf{x}+b) \geq 1-\xi_k . \tag{3}$$

This optimization is solved by introducing the Lagrange multiplier α_k for its dual optimization model. Using the optimal solution of α_k^* and b^*, the class prediction for any test vector $\mathbf{x} \in R^m$ is given by

$$sign(\sum \alpha_k^* z_k(\mathbf{x}_k, \mathbf{x}) + b^*) . \tag{4}$$

The data is mapped to higher dimensional feature so that this class prediction formulation can be used to separate nonlinear data. By introducing this mapping, the nonlinear SVM classifier has the following form,

$$sign(\sum \alpha_k^* z_k K(\mathbf{x}_k, \mathbf{x}) + b^*) , \tag{5}$$

where $K(\boldsymbol{x}_k, \boldsymbol{x})$ is the mapping using kernel function. In this paper, the following radial basis function (RBF) kernel function is used,

$$K(\mathbf{x}_k, \mathbf{x}) = exp\left(-\gamma \|\mathbf{x}_k - \mathbf{x}\|^2\right) , \tag{6}$$

where γ is a constant and the determination of its value is discussed in the next section.

Facing to the imbalance data of this work, in which the data number in one class is far more than in another class, the modification on (2) is performed by

$$w_{-1}C \sum_{k:y_k=-1} \xi_k + w_1 C \sum_{k:y_k=+1} \xi_k + \tfrac{1}{2}\|\mathbf{w}\|^2 , \tag{7}$$

where w_{-1} and w_1, which are different error weights, are used to penalize more heavily the undesired errors related to the class with the smallest population [26],[27]. The determination of w_{-1} and w_1 is discussed in the next section.

B. Optimization using PSO

A PSO can be considered as a population-based technique. An individual, which is referred as particle, of population, which is referred as swarm, moves through an n-dimensional solution space with adjusted velocity and position considering to the experience of particles in the swarm. The position of particle n p_n at iteration $(t+1)$ is changed by its velocity v_n [22],

$$p_n(t+1) = p_n(t) + v_n(t+1), \tag{8}$$

where

$$\begin{aligned} v_n(t+1) = {} & w v_n(t) + c_1 r_1(t)[p_{bn}(t) - p_n(t)] \\ & + c_2 r_2(t)[p_{gn}(t) - p_n(t)]; \end{aligned} \tag{9}$$

p_{bn} is the personal best position and p_{gn} is the best global position of particle of the swarm. $r_1()$ and $r_2()$ are random functions in the range [0 1] for weighting acceleration constants, c_1 and c_2, and w is inertia weight [28]. Those velocity and position are iterated until the convergence is reached.

In the system, PSO algorithm is used to obtain the best parameters C, w_{-1} and w_1 in (7), γ in (6) so that the SVM results the best performance. To measure the performance, sensitivity and specificity are used. Sensitivity is defined as the ratio of positive hypoglycemia decision number to the number of actual hypoglycemia cases, and specificity is defined as the ratio of non-hypoglycemia decision number to the number of actual non-hypoglycemia cases.

The objective of the PSO algorithm is to maximize the sensitivity and specificity of the detection and therefore the fitness function is to maximize both values. The fitness function can be defined as

$$f = \alpha\psi_{tr} + (1-\alpha)\zeta_{tr} + \alpha\psi_{v} + (1-\alpha)\zeta_{v} + \rho \quad (10)$$

where ψ_{tr} and ζ_{tr} are the sensitivity and specificity in training, respectively, and ψ_{v} and ζ_{v} are the sensitivity and specificity in validation, respectively. The inclusion of validation performance in the fitness function is to reduce the risk of overtraining [29]. $\alpha \in [0\ 1]$ is a constant value to control the ratio of sensitivity and specificity. The ratio of sensitivity/specificity is made with 0.58/0.42 in order to keep a higher value of the sensitivity than the specificity; α is set to 0.58. ρ is a penalty function to force the sensitivity and specificity to be more than 70% and 40%, respectively. To find this, the following formulation is created. Thus, by using ρ=10, the fitness function is more than 10 if sensitivity and specificity are more than 70% and 40%, respectively, and is less than 10 if sensitivity and specificity are less than 70% and 40%, respectively.

$$\rho = \begin{cases} 10 & if\ \psi_{tr} > 0.7,\ \zeta_{tr} > 0.4,\ \psi_{v} > 0.7,\ \zeta_{v} > 0.4 \\ 0 & otherwise \end{cases} \quad (11)$$

III. Results and Discussion

Electrocardiographic signals have been obtained from the five patients with type-1 diabetes. The signals are resulted from an overnight hypoglycemia study at the Princess Margaret Hospital for Children in Perth, Australia. Data are collected with approval from Women's and Children's Health Service, Department of Health, Government of Western Australia, and with informed consent.

The ECG signals are recorded using Compumedics System and the correlated blood glucose levels (BGL) are measured using Yellow Spring Instrument. The ECG parameters, such as *QTe* interval, of 30-second epoch and the correlated BGL are captured in each five minutes. Based on these ECG parameters, the repolarization variability indexes are calculated using (1).

TABLE I
Statistical Description of The Repolarization Variabilities

Repolarization Variability	**Nonhypoglycaemia** (*mean±std*)	**Hypoglycaemia** (*mean±std*)	***p*-value**
QTeVI	-3.46±1.37	-2.32±2.00	0.0003
TpTeVI	-0.26±1.53	0.99±2.19	0.0004
ToTeVI	-0.08±1.54	0.74±1.50	0.0091
RTpVI	-3.11±1.37	-2.05±2.11	0.0011

The resulted repolarization variabilities of both nonhypoglycemia and hypoglycemia are described in Table I. In this paper, hypoglycemia is defined as the hypoglycemic level of less than 2.8 mmol/l. The table data show that the four variabilities are significantly higher in hypoglycemia than in non-hypoglycemia (p<0.01). The physiological mechanism of the higher variabilities in hypoglycemia than in non-hypoglycemia is not studied in this paper. Considering (1), the higher variabilities might be affected by either the heart rate variance or by the variance of repolarization parameters, or by both variances.

The hypoglycemia detection has been developed using a swarm-based SVM algorithm. The inputs of the detection are the repolarization variabilities from the obtained clinical data as listed in Table I. The obtained repolarization variabilities data set, involving nonhypoglycemia and hypoglycemia parts, is randomly separated to training and validation data sets which are used for four-fold cross validation. The training set is used to build detection model and the model is validated using the validation set. The detection performance is measured in terms of sensitivity ψ, specificity ζ and geometric mean gm. A geometric mean $gm=\sqrt{(\psi.\zeta)}$ is suitable to indicate performance of detection for inputs consisting of imbalanced data [30],[31], in which the data number of one class is far higher than the data number of another class. This paper employs imbalance data, in which the data number of non-hypoglycemia is more than triple of the hypoglycemia data number.

TABLE II
Performance of the Hypoglycemia Detection with Different Inputs in the Cross Validation

Input	Training			Validation		
	Sens (%)	*Spec* (%)	*gm* (%)	*Sens* (%)	*Spec* (%)	*gm* (%)
QTeVI	84.52	51.23	64.17	85.71	49.07	61.47
TpTeVI	95.24	35.80	57.68	89.29	34.26	54.73
ToTeVI	75.00	58.33	65.98	67.86	57.41	61.27
RTpVI	79.76	54.94	61.00	78.57	45.37	52.69
QTeVI, TpTeVI, ToTeVI, RTpVI	100.00	62.35	78.85	82.14	60.19	70.25

Sens: sensitivity, *Spec*: specificity, *gm* : geometric mean

The performances of the detection using different inputs are presented in Table II. Five types of inputs consisting repolarization variabilities, as described in Table II, are used. In general, the detection using the all four variabilities as inputs has the best performance with sensitivity, specificity and *gm* are 82.14%, 60.19% and 70.25%, respectively. The validation results show contributions of the repolarization variability as inputs for the hypoglycemia detection; it contributes to the detection sensitivity of more than 67%. The contributions might correlate to that the all variability indexes change during hypoglycemic phases against non-hypoglycemic phases as described in Table I. Among the detection using the individual inputs, the hypoglycemia detection with input of *QTeVI* and *ToTeVI* yields the best performances, about 61% in terms of *gm*. The highest sensitivity in the validation is the detection with input of *TpTeVI*, but its associated specificity is low.

Employing PSO in SVM is a suitable way to compare the

performance of the hypoglycemia detection having different inputs. By this method, the SVM parameters in (6) and (7) are automatically selected so that the detection has the best performance according to the correlated input. This method yields a better performance compared to the case when the SVM parameters are selected arbitrarily.

IV. CONCLUSION

A novel hypoglycemia detection algorithm using ventricular repolarization variabilities has been developed. The repolarization variabilities *QTeVI, TpTeVI, ToTeVI* and *RTpVI* all contribute to the hypoglycemia detection strategy significantly. A swarm-based SVM-RBF algorithm has been developed successfully. Using all four variabilities as inputs, this new hypoglycemia detection algorithm yields the best performance with a sensitivity of 82.14% and specificity of 60.19%.

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