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ORIGINAL PAPER

Automated Diagnosis of Diabetes Using Heart Rate Variability Signals

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Abstract An automated diagnostic system for diabetes mellitus (DM), from heart rate variability (HRV) measures, using feed forward neural network has been developed. Changes in autonomic nervous system activity caused by DM are quantified by means of time domain and frequency domain analysis of HRV. Electrocardiograms of 70 DM patients and 65 healthy volunteers were recorded. Nine time domain measures—standard deviation of all NN intervals, square root of mean of sum of squares of differences between adjacent NN interval (RMSSD), number of adjacent NN intervals differing more than 50 ms. (NN50 count), percentage of NN50 count, R-R triangular index, triangular interpolation of NN intervals (TINN), standard deviation of the mean heart rate, mean R-R interval and mean heart rate—were used as the input features to the neural network. This diagnostic system classifies DM patients and normal volunteers from morphologically identical ECGs. Diagnostic results show that the system is performing well with an accuracy of 93.08%, specificity of 96.92% and sensitivity of 89.23%.

Keywords Autonomic nervous system · Diabetes mellitus · Feed forward neural network · Heart rate variability

Introduction

Heart rate variability (HRV) analysis is a simple noninvasive electrocardiographic (ECG) marker that could give an insight into hidden pathological conditions in living organisms and is valuable as the HRV indices may be early markers of diseases. HRV refers to the beat-to-beat alterations in heart rate. It reflects the activity of the sympathetic and vagal components of the autonomic nervous system (ANS) on the sinus node of the heart. It expresses the total amount of variations of both instantaneous heart rate and R-R intervals [1].

The ANS or visceral nervous system is the part of the peripheral nervous system that acts as a control system maintaining homeostasis in the body. The ANS affects heart rate, digestion, respiration rate, salivation, perspiration, diameter of the pupils, micturition (urination), and sexual arousal. The ANS can be divided into subsystems viz. the parasympathetic nervous system and sympathetic nervous system. Under resting conditions, the ECG of healthy individuals exhibits a trend of periodic variation in R-R intervals. This rhythmic phenomenon, known as respiratory sinus arrhythmia (RSA), fluctuates with the phase of respiration: i.e. cardio-acceleration during inspiration and cardio-deceleration during expiration. RSA is predominantly mediated by respiratory gating of parasympathetic efferent activity to the heart: vagal efferent traffic to the sinus node occurs primarily in phase with expiration and is absent or attenuated during inspiration [2]. HRV decreases with age, and shows a circadian variation, being maximum during sleep [3, 4]. It is also rate dependent. The heart rate showing more variability at lower heart rates. The loss of this beat—to—beat variability is a sign of disease [4].

One of the major reasons for the interest in measuring HRV stems from its ability to predict survival after heart attack. Many prospective studies have shown that reduced HRV predicts sudden death in patients with myocardial infarction (MI), independent of other prognostic indicators such as ejection fraction. Reduced HRV appears to be a marker of fatal ventricular arrhythmia. Some studies have begun to suggest that reduced HRV may predict risk of

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survival even among individuals free of coronary heart disease (CHD) [2].

Diabetes mellitus

Diabetes mellitus (DM) is a metabolic disorder characterized by hyperglycemia (high blood sugar) and other signs, as distinct from a single illness or condition. It may be considered as a group of diseases with one thing in common—a problem with insulin. The world health organization (WHO) recognizes three main forms of diabetes: type I, type II and gestational diabetes, which have similar signs, symptoms and consequences, but different causes and population distributions [5]. DM is a major, fast growing and one of the most prevalent health issues facing the world community, especially, the developing countries [5]. The WHO expects that, more than 366 million people would be affected by the same in 2030 [6]. Prevalence of diabetes mellitus in the general population is approximately 5–6%, with a considerably higher proportion of up to 20–25% in the elderly and with a higher prevalence in some ethnic minorities [5]. In 2025, projections are that there may be a staggering 70 million Indian diabetics [7]. Type 1 diabetes has now become very common and one of primary vital dieses in children and teenagers. Studies indicate that an average of 200 persons (aged below 15 years) per day is affected by this disease and also that type 2 diabetes is also spreading in to youngsters. It is estimated that 4 million people per year are dying due to different side effects of diabetes [7].

Diabetes commonly causes wide spread damage to the ANS. About half of all people with diabetes have some form of nerve damage [8]. The autonomic neuropathy (AN) is caused by damage to the small afferent and efferent nerve fibers that innervate visceral organs including the heart. It is estimated that cardiovascular AN is detected in at least one quarter of Type I and one third of Type II diabetes that shows symptomatic diabetic AN. Diabetic AN increases the risk of ventricular arrhythmias and cardiac mortality when compared with people who have no diabetes or patients with diabetes but no AN [9]. Reduced HRV is an independent marker of poor prognosis after an acute MI [10] and in diabetes reduced HRV indicates the presence of cardiovascular autonomic neuropathy (CAN), which implies poor prognosis. People with diabetes have an increased risk of cardiovascular disease (CVD) [11], 14.9% of people with diabetes have heart disease compared to 2.5% of the general population. People with diabetes can also develop CVD at a younger age. Diabetic cardiac autonomic dysfunction often causes lethal arrhythmia and sudden cardiac death [12]. Almost all coronaries are simultaneously affected by the diabetes. Due to the diabetics, patients are unable to identify the heart attacks and hence unable to provide treatment on time. 80% of the diabetes patients are dying due to coronary artery problems [7]. People with diabetes are 25 times more likely to develop blindness, 17 times more likely to develop kidney disease, 30–40 times more likely to undergo amputation, four times more likely to develop MI and twice more likely to suffer a stroke than non-diabetics [5, 7, 9].

Diabetes associated cardiovascular changes related to ANS damage may be present anytime prior to manifestation of diabetes. It has been established that variation of the HRV parameters can detect changes before clinical signs appear [4, 9, 12–16]. Early detection of subclinical autonomic dysfunction in diabetic individuals is important for risk stratification and subsequent management, possibly including pharmacologic and lifestyle intervention [7, 13].

In this work, the HRV measures of the ECGs (which are morphologically identical) recorded from the DM patients and normal subjects have been evaluated. The time domain parameters of these HRV measures were used as the input to the neural network for the diagnosis of DM patients.

Subjects and methods

We have studied 70 people suffering from non-insulin dependent DM and 65 non smoking normal healthy volunteers without DM or any other cardiac disorders. The DM group was age and sex matched with the control group. The subjects under study were in the age group of 40–72 years and the duration of the diabetes for the patient group was 1–20 years. Blood glucose level of the selected diabetic patients were measured to ensure that they still have diabetes. Electrocardiograms (ECG) and the other details such as blood sugar level, weight, blood pressure etc. of the subjects were recorded. The ECG was recorded using the BIOPAC ™ MP 100 data acquisition system. The ECG recording was performed with sampling rate of 2,000 Hz, on each investigated subjects during day time, in the relaxed lying position for 60 min, after informing them about the purpose of this study and obtaining the consent. The recordings of ECG of all subjects were done by the same person in order to avoid any inter observer error. Heart rate (HR) computations were done using AcqKnowledge® and MATLAB software. Error due to movement artifacts was manually edited. Time domain and frequency domain measures were computed for all these HR data.

Time domain and frequency domain analysis of HRV

The HRV is comprised of multiple frequencies. Frequency domain method analyses the different spectral components

of this waveform. The time domain measures used for the analysis are—standard deviation of all NN intervals (SDNN) in seconds, square root of the mean of the sum of the squares of differences between adjacent NN interval (RMSSD) in milliseconds (ms), number of adjacent NN intervals differing more than 50 ms. (NN50 count), percentage of difference between adjacent NN intervals differing more than 50 ms. (pNN50%), the integral of sample density distribution of RR intervals divided by the maximum of the density distribution (R- R triangular index) and baseline width of the minimum square difference triangular interpolation of the maximum of the sample density distribution of NN intervals in seconds (TINN) [17]. Mean R-R interval in seconds, mean heart rate and standard deviation (STD) of the mean heart rate (per minute) were also computed.

The two main frequency components that represent ANS activity are the low frequency (LF) components (0.04–0.15 Hz) and the high frequency (HF) components (0.15–0.4 Hz). Frequency domain measures confirm that the LF and HF oscillatory components are relative indices of cardiac sympathetic and vagal activity respectively and HF and RMSSD indicate parasympathetic activity [1, 3, 4, 11, 12]. We have evaluated and analyzed the very low frequency (VLF) components (0.003–0.04 Hz) peak, VLF power,% VLF power in the signal, LF peak, LF power,% LF power, LF power in normalized unit, HF peak, HF power,% HF power, HF power in normalized unit and the ratio LF/HF [17]. Normalized units are obtained by the equation

$$\text{LF or HF norm (nu)} = \frac{\text{LF or HF}(ms^2)}{\text{Total power}(ms^2) - \text{VLF}(ms^2)} * 100 \quad (1)$$

Frequency domain analysis was done by non- parametric method (fast Fourier transform (FFT) based).

Classification using artificial neural network

Artificial neural network (ANN) has been shown as a powerful tool to enhance current medical diagnostic techniques. The potentials of the ANN over conventional computation and manual analysis in medical application includes: implementation using data instead of possibly ill defined rules, noise and novel situations are handled automatically via data generalization, predictability of future indicator values based on past data and trend recognition, automated real time analysis and diagnosis enables rapid identification and classification of input data, eliminating error associated with human fatigue and habituation. Different network topologies with powerful learning strategies to solve linear and nonlinear problems have been reported [18, 19]. Application of ANN in automated ECG analysis includes arrhythmia detection and classification, ischemia detection, left and right ventricular hypertrophy, bilateral ventricular hypertrophy, different MI [20–23].

In this work, for the classification between diabetic and normal persons, we have used a multilayer feed forward neural network (MLFFNN) architecture with 9 input units, one hidden layer with 20 neurons and the output layer with a single neuron. Input to the neural networks were the nine time domain HRV parameters—SDNN, RMSSD, NN50 count, pNN50%, R- R triangular index, triangular interpolation of NN intervals (TINN), Standard deviation of the mean heart rate, mean R-R interval and mean heart rate—of the recorded ECGs. The back propagation (BP) algorithm with momentum was used to train the ANN.

Back propagation algorithm was formulated by generalizing the Widrow-Hoff learning rule to multiple-layer networks and nonlinear differentiable transfer functions. Input vectors and the corresponding target vectors are used to train a network until it can approximate a function, associate input vectors with specific output vectors, or classify input vectors in an appropriate way as defined by the user. Standard BP algorithm is a gradient descent algorithm in which the network weights are moved along the negative of the gradient of the performance function. Properly trained BP networks tend to give reasonable answers when presented with inputs that the ANN have never seen. Typically, a new input leads to an output similar to the correct output for input vectors used in training that are similar to the new input being presented. This generalization property makes it possible to train a network on a representative set of input/target pairs and get good results without training the network on all possible input/output pairs.

The architecture of the implemented feed forward neural network (FFNN) is shown in Fig. 1. The output unit (Y unit) has weights ω_{jk} and the hidden units have the weights υ_{ij}. During training phase, output neuron compares its computed activation Y_k with its target value d_k to determine the associated error E for the pattern with that neuron. The ANN weights and biases are adjusted to minimize the least-square error E. The minimization problem is solved by gradient technique, the partial derivatives of E with respect to weights and biases have been calculated using the generalized delta rule or the Widrow-Hoff rule. This is achieved by back—propagation of the error. When using momentum, the ANN is proceeding not in the direction of the gradient, but in the direction of a combination of the current gradient and the previous direction of the weight correction. Convergence is sometimes faster if a momentum term is added to the weight update equation. The weights and biases are initialized to some initial random values, and updated in each iteration

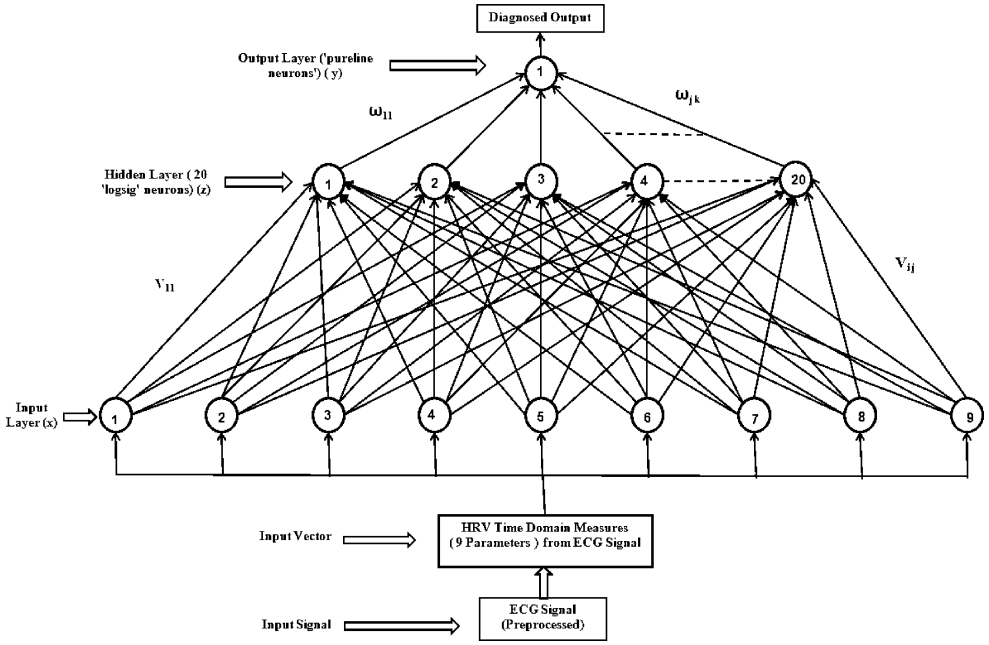

Fig. 1 Architecture of the implemented feed forward neural network

(called an epoch) until the net has settled down to a minimum.

This algorithm appears to be the fastest method for training moderate-sized feed forward neural networks (up to several hundred weights). It also has a very efficient MATLAB® implementation, since the solution of the matrix equation is a built-in function, so its attributes become even more pronounced in a MATLAB setting.

In general, on function approximation problems, for networks that contain up to a few hundred weights, the Levenberg-Marquardt algorithm will have the fastest convergence. This advantage is especially noticeable if very accurate training is required. In many cases, 'trainlm' is able to obtain lower mean square errors than any of the other algorithms tested.

The input/hidden layer uses the 'Log sigmoid' transfer function, which is commonly used in back propagation networks, in part because it is differentiable.

Preprocessing and postprocessing

Neural network training can be made more efficient and faster if certain preprocessing steps are performed on the network inputs and targets. In order to accelerate the back-propagation learning process, the normalization of the inputs should also include two other measures (a) the input variables contained in the set should be uncorrelated- this can be done by using principal components analysis and (b) the decorrelated input variables should be scaled so that their covariance are approximately equal, thereby ensuring that the different weights in the network learn at approximately the same speed [24].

Before training, it is useful to scale the inputs and the targets so that they remain within a specified range. The network normalized output obtained after simulating the network normalized input is converted back into output in original units by using the reverse scaling.

The ANN's performance is usually quantified by means of three parameters: sensitivity, specificity and accuracy. *Sensitivity (i)* indicates the rate of true positive events for class *i, specificity (i)* measures the rate of true negative events for class *i*, and accuracy *(i)* is the rate of the correctly classified events among all the classified events in class *i* [25]. In general, if we have 'N_C' number of diagnostic classes, then

$$Sensitivity(\%) = \frac{tp(i)}{tp(i) + fn(i)} * 100, \qquad i = 1, \ldots\ldots.., N_C \tag{2}$$

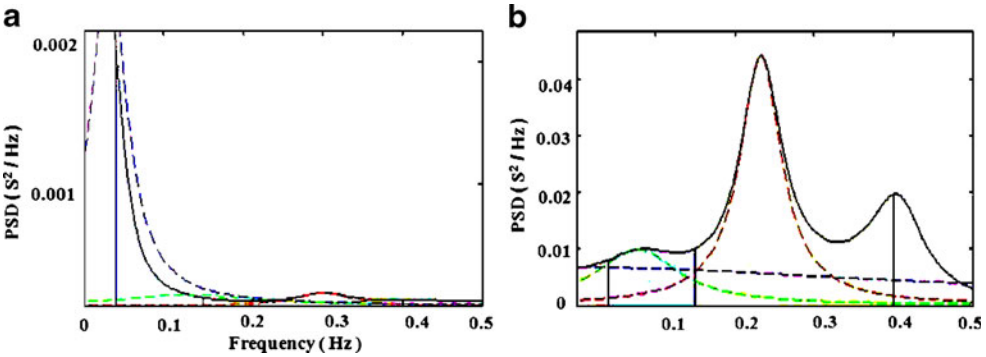

Fig. 2 PSD of the RR interval of (**a**) a 68 year old woman, suffering from diabetes for the last 17 years, without any cardiac disorders (ECG recorded on 29th November 2007) and (**b**) a 52 year old healthy volunteer (ECG recorded on 21st November 2007)

$$Specificity(\%) = \frac{tn(i)}{tn(i) + fp(i)} * 100, \qquad i = 1, \ldots\ldots.., N_C \quad (3)$$

$$Accuracy(\%) = \frac{(tp(i) + tn(i))}{(tp(i) + fn(i) + tn(i) + fp(i))} * 100, \quad i = 1, \ldots\ldots.., N_C \quad (4)$$

where *tp, tn, fp and fn* stands for true positive, true negative, false positive and false negative respectively.

Results

HRV parameters from the R-R interval data extracted from the preprocessed ECG signals of 70 diabetic patients and that of 65 age and sex matched healthy volunteers have been computed. Power spectral density (PSD) of the R-R interval of these two groups are shown in Fig. 2. Time domain analysis of HRV shows that there is significant reduction in the measures SDNN, RMSSD, NN50 count, pNN50, HRV triangular index, TINN, mean RR interval, and STD (1/min) of the diabetic data compared with the normal data.

The results of time domain analysis are summarized in Table 1.

Table 2 summarizes the results of the frequency domain analysis. HRV measures of frequency domain analysis (Table 2) shows that there is significant reduction in the HF power, HF% power, HF power (nu), LF power and VLF% power in the RR interval data from ECGs of the diabetic patients compared with the normal control group. The VLF% power and LF power (nu) are found to be significantly less in normal person compared with the diabetic.

The classification of the ECGs into normal and diabetic patient based on the HRV measures are done by using the ANN presented in ''classification using artificial neural network''. Here nine time domain measures of the HRV analysis of each person, is taken as the input to the neural network. The hidden layer of this network has 20 neurons. The input layer uses the 'logsigmoid' transfer function and the hidden layer uses the 'pureline' transfer function. The training goal (mean square error between the network output and target output) was set at 0.002. The learning rate was set to 0.001. Maximum epochs for training were set to 10,000 epochs. During training session the network was able to converge to our goals with these settings.

25 set of normal data and 25 set of diabetic data have been used for training. After training we presented a new set of 65 diabetic and 65 normal data for this classifier. The network was able to classify these data satisfactorily with an accuracy of 93.08%. This network

Table 1 Summary of results of the time domain analysis of the HR data

Indices	Control group Mean±SD	Diabetes mellitus Mean±SD	*p* value
SDNN (seconds)	0.042±0.0231	0.0226±0.0108	0.000543
RMSSD (ms)	43.62±35.1386	18.708±10.462	0.0015
NN50 count	336.2917±52.6530	53.4583±9.5748	0.0185
pNN50 count	9.0708±1.4410	1.2792±0.23575	0.0177
HRV Δlar index	0.068±0.0275	0.0431±0.0209	0.0021
TINN (ms)	531.2±231.9675	313.6±190.8398	4.75e-05
Mean RR(sec.)	0.8954±0.1323	0.7681±0.1365	0.0019
Mean HR (per min.)	68.4992±9.3605	80.36±12.4022	0.0004
STD (1/min.)	3.5792±1.7517	2.65±1.1559	0.0039

Table 2 Summary of results of the time domain analysis of the HR data

Indices	Control group Mean±SD	Diabetes mellitus Mean±SD	*p* value
VLF peak(Hz)	0.0202±0.0066	0.0242±0.0241	0.4212
VLF power (ms^2)	211.36±178.0468	92±77.0438	0.0064
VLF% power	28.192±11.9627	37.912±12.9328	0.0073
LF peak(Hz)	0.0745±0.0859	0.0577±0.0164	0.3389
LF power (ms^2)	321.88±36.0222	177.44±117.3727	0.016
LF% power	37.86±12.7947	39.604±10.7395	0.5779
LF power(nu)	55.276±21.1252	65.16±15.9402	0.043
HF peak(Hz)	0.2677±0.0818	0.2571±0.0818	0.6313
HF power (ms^2)	496.8±102.32	60.7±55.9449	0.0427
HF% power	33.936±21.4	22.492±13.1759	0.0116
HF power(nu)	44.724±21.1	34.84±15.9402	0.043
LF/HF	1.8181±1.5	2.4134±1.3994	0.1707

has got a sensitivity 89.23% and specificity of 96.92%. So this network performed well when compared with other ANN used for the identical purposes in the field. Table 3 gives the performance summery of the designed ANN.

Discussion

In the recent years the ANN is widely used in the automation of medical diagnostic field. A lot of works have been reported in the field of ECG classification. They include, the ECG classifier using weightless neural network based on 'Fisher's ratio extraction' (for normal beats, left bundle branch block, right bundle branch block, atrial premature contraction, premature ventricular contraction (PVC) etc.) with an accuracy of 95.61% [26], ANN for coronary artery disease diagnosis (96% accuracy) [27], ANN classifier with back propagation algorithm (for chronic myocardial disease) with sensitivity of 65%, and specificity of 94% [20], FFNN classifier with back propagation algorithm for arrhythmias (12 different arrhythmias) with an accuracy of 96.77% [21], Bayesian ANN classifier for arrhythmia identification (accuracy 75%), ECG beat recognition using fuzzy hybrid neural networks (accuracy 96.04%) [22], MLFFNN with back propagation for arrhythmia (PVC, atrial and ventricular fibrillation, and 2^0 heart block) with an accuracy of 99.38% [23] etc.

Table 3 Summary of the classification results and performance of the ANN

Performance criteria	Normal	Diabetes mellitus
No. of data	65	65
Correctly classified	63	58
Sensitivity	–	89.23%
Specificity	96.92%	–
Overall accuracy	93.08%	

All these are classifiers of the ECGs, based on morphological changes. In our work, we had considered ECGs of normal and DB patients which are morphologically identical. In this attempt, we have succeeded in classifying morphologically indistinguishable ECGs, by using HRV measures. Hence this ANN provides an attractive potential tool for ECG diagnostic technique mainly based on variation in the HRV parameters. HRV analysis is now being used in a variety of applications like diagnosis of diabetes, myocardial infarction etc. HRV analysis is also used as an early marker of the different pathological conditions, including the diabetes. Hence ANN may be used in a variety of applications which are not confined to the morphological changes only.

Conclusions

MLFFNN has been successfully used in the classification of ECG that are morphologically indistinguishable (ECG of normal person and diabetic patients), by using the linear HRV measures. As the time domain and frequency domain measures of normal person shows significant difference with that of diabetic patients, this property enables the classification of these groups using the ANN. It has already established that HRV analysis can detect changes before the clinical changes appear in the case of diabetes [14–16]. Hence we can effectively utilize these two properties- early detection of diabetes using HRV analysis and classification of diabetes and normal person using ANN—for automation of the diabetes detection, with acceptable accuracy.

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