Diabetes Detection Using ECG Signals: An Overview

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Abstract

Diabetes Mellitus (or diabetes) is a clinical condition marked by hyperglycaemia and it affects a lot of people worldwide. Hyperglycaemia is the condition where high amount of glucose is present in the blood along with lack of insulin. The incidence of diabetes affected people is increasing every year. Diabetes cannot be cured. It can only be managed. If, not managed properly, it can lead to great complications which can be fatal. Therefore, timely diagnosis of diabetes is of great importance. In this chapter, we see the effect of diabetes on cardiac health and how heart rate variability (HRV) signals give an indication about the existence and acuteness of the diabetes by measuring the diabetes-induced cardiac impairments. Extracting useful information from the nonstationary and nonlinear HRV signal is extremely challenging. We review that deep learning methods do that extricating task very effectively so as to identify the correlation between the presence of diabetes and HRV signal variations in the most accurate and fast manner. We discuss several deep learning architectures which can be effectively used for HRV signal analysis for the purpose of detection of diabetes. It can be seen that deep learning methods is the state of art to understand and analyse the fine changes from the normal in the case of HRV signals. Deep learning networks can be developed to a scalable framework which can process large amount of data in a distributed manner. This can be followed by application of distributed deep learning algorithm for learning the patterns so as to do even correct predictions about future progress of the disease. Presently, there is no publicly available data of normal and diabetic HRV. If large amount of private data of diabetic HRV and normal HRV can be made available, then deep learning networks have the capability to give the authorities different kind of statistics from the stored data and projections of future prognosis of diabetes.

Key words: ECG, Diabetes, Machine Learning, Heart Rate Variability, Deep Learning, Cardiovascular Autonomic Neuropathy

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1 Introduction

Biosignals are biological signals extracted from the human body or in general human beings. Commonly referred biosignals are electrical in nature, but there are nonelectrical biosignals also. Some examples of biosignals are electrocardiography (ECG) which measures electrical activity of the heart, electroencephalography (EEG) which measures brain activity, photoplethysmography (PPG) which depicts the volumetric changes of an organ. ECG signals is employed for the noninvasive diagnosis of diabetes. ECG is used by clinicians to electrically measure rhythm of the heart, attaching electrodes to the skin surface. ECG depicts the complete electrical patterns of the heart including atrial depolarization and ventricular repolarization. Heart rate variability (HRV) data is extracted out of ECG signal. HRV is a simple, but powerful signal which clearly reflects the condition of cardiovascular system.

From the initial days, biosignals are processed and analysed mainly through extracting features and then classifying them. These processes are performed by developing computer-aided design (CAD) systems. The features are manually selected and need to be optimal since identification of suitable features requires domain knowledge. The performance of above-mentioned approaches is not satisfactory as the complexity of the data increases. The analysis of complex, high dimensional, real-world data can be effectively done using deep learning. Deep learning is done using deep learning architectures typically made up of very large number of hidden layers and containing millions of neurons interconnected in a structure similar to a 2D matrix. These complex networks are capable of handling and analysing complex, very large sized and very high dimensional data. Raw data (or data undergone very little signal processing) can be directly fed into these networks. Each layer of the network produce at its output, representations which are automatically designed by the deep learning network, using a general learning method (in place of manually decided feature extraction in the case of machine learning based typical neural networks, which are very small sized and of very simple structure compared to deep learning networks). Though deep learning networks are commonly used for two-dimensional image analysis problems, it can be very effectively used for one-dimensional data also. We review application of deep learning based methods to one-dimensional HRV data. The main bottle neck of applying deep learning to biosignal in general is the present non-availability of very large sized training data belonging to medical domain which is required for training deep learning networks having gigantic number of parameters.

Diabetes mellitus, which is usually called diabetes, is a long-term metabolic disorder wherein the body is incapable of metabolizing glucose (sugar) properly. This creates a very high level of glucose in the blood (this condition is known by the term hyperglycaemia). Insulin is a hormone that is necessary for the body cells to absorb blood glucose (produced from the carbohydrates in the food we intake) and to store glucose for future needs. The condition of diabetes is either because of the incapability of the body to generate sufficient insulin or because of the state where body cells do not react to the generated insulin. Medically, there is no cure for diabetes. Hence it should be properly controlled. Below are the different types of diabetes.

Type 1 diabetes is the name of the diabetes found in children. In type 1 diabetes, the immune system of the body destroys its own beta cells resulting in deficiency of insulin. Type 2 diabetes is the common type of diabetes that develops in adults usually above the age of 40. The cells generally become insensitive to the insulin produced or the cells are unable to use the produced insulin properly. This is known as insulin resistance. Gestational diabetes is the glucose intolerance developed during pregnancy period. Out of these three types, type 2 diabetes is the most commonly prevalent type. In this chapter, we mean type 2 diabetes by the word diabetes.

A 2017 statistics estimates that 8.8% of people worldwide have diabetes. It is rising more alarmingly in underdeveloped countries. According to National diabetes statistics report 2017 (pertaining to United States), about 9.4% of U.S. population has diabetes in 2015. Of these, about 23% were not aware or did not report having diabetes (diabetes was undiagnosed for them).

As per the statistics of International diabetes federation, India has a diabetes population of 6.9 crores. India is the country having the second largest diabetes population in the world. Kerala is one among the states having the largest number of diabetes affected people in India. As per the new statistics of Indian medical association (IMA), in Kerala every year, 138 people are being newly diagnosed by diabetes out of a population of 1000 people. Some of the consequences due to diabetes have been briefed by World health organization (WHO) as follows. In 2015, approximately 1.6 million deaths globally were directly caused by diabetes. Almost 50% of these deaths happen earlier to 70 years of age because of increased blood sugar.

Diabetes causes damage to nerves known as diabetic neuropathy. Diabetes increases the possibility of heart ailments and stroke. About 50% of diabetes inflicted people die due to heart related complications. Diabetes can lead to amputation of limb caused by neuropathy in feet. Another problem caused is diabetic retinopathy wherein the nerve problem caused by diabetes can cause heavy damage to blood vessels in retina which may affect eye vision (10% of diabetic people), may lead to blindness (2% of diabetic people) also. Death comes in the form of kidney failure in average 15% of diabetic people. Thus, over time, uncontrolled diabetes leads to serious damage of many vital organs of the body like heart, blood vessels, kidneys (nephropathy), nerves, feet and eyes. Diabetes deaths are mainly due to complications caused by the disease.

Hyperglycaemia in less severe condition is known as impaired glucose tolerance. This condition is characterised by high risk of large blood vessel disease and may lead to complications like myocardial infarction. The impaired glucose tolerance condition does not considerably lead to microvascular disease similar to the condition of diabetes induced hyperglycaemia.

All the above data and reports underline the necessity and challenges in the development of effective diabetic detection and management methods. Some of the symptoms of hyperglycaemia due to diabetes are enormous urine excretion, high levels of thirst, hunger and fatigue. Reduction in weight and impairment in vision are likely to happen. In terms of diagnosis, major challenge is the fact that these symptoms are not that marked at the onset of diabetes. Symptoms get pronounced only after diabetes worsens to the extent of leading to complications. To minimize such complications, early detection of diabetes is important. Methods should be developed that will help to prevent or delay diabetes. Effective ways should be developed for diagnosis and treatment of this disease. Further challenge is developing methods which are capable to predict much early diabetes in a cost effective way so that corrective steps and treatment can be given in time to avert diabetes, thus also saving the person from the serious complications to which diabetes if undetected or not properly managed can lead to.

Here, we review methods that are related to non-invasive diagnosis methods of diabetes with high accuracy using HRV signals derived from ECG signals. Heart rate value based diabetes detection has been observed to be computationally efficient than the decision theoretic approach and hence has been heavily explored. Deep learning methods are now being increasingly used in healthcare analytics. Initially, machine learning techniques were extensively used for HRV based diabetes detection. Deep learning architectures have the potential to improve the accuracy of diabetes detection by capturing minute variations in ECG. Further big stride possible in future is the prediction of diabetes if sufficiently large amount of training and testing data are made available.

In this chapter, section 2 and 3 provide discussion of the relevant medical aspects of diabetes and its detection methods. Section 4 and 5 detail the machine learning and deep learning methods used by researchers for diabetes detection. Section 6 gives the detailed literature survey of works using ECG-derived-HRV as input for diabetes detection. A sample architecture and implementation details are described in section 7. The limitations and challenges of deep learning methods are discussed in section 8. The chapter concludes with section 9.

2 Diabetes

2.1 Diabetes and its associated mechanism

Glucose homeostasis is the natural regulation mechanism of the body by which the blood glucose (blood sugar) levels are maintained within a narrow range. Diabetes refers to a group of conditions which indicates that blood glucose balance in the body has gone out of control. For proper functioning of the body, the blood glucose values have to strictly fall between a very narrow range (70 ml/ dl and 110 mg/dl)(ml is millilitre and dl is decilitre). The pancreatic endocrine hormones namely insulin and glucagon make this happen. Insulin and glucagon are the vital hormones secreted by pancreatic islet cells in response to the level of blood sugar, but in an opposite manner.

The beta cells of the pancreas secrete insulin. Glucose is the main source of energy for the body cells. But glucose is a large molecule which cannot be passed through the cell membrane through simple diffusion mechanism. Insulin enables glucose transport into the cells. There is a very low base level of insulin always secreted. When we take food, carbohydrates are converted to glucose and most of it is sent to the blood. When blood glucose is high, then a proportional amount of insulin is produced. When insulin is present, the cells of the body can absorb glucose out of the blood thus leading to the reduction of blood glucose level. The cells use the absorbed glucose for getting energy for carrying out their assigned functions. When the blood glucose decreases to the normal level, then the amount of insulin secreted also goes down to the base minimum. Thus high blood glucose serves as a signal to pancreas to release insulin to the blood. Suppose the level of blood glucose remains high even after cell absorption, then insulin facilitates the storage of the excess glucose in the cells of the liver in the form of a substance known as glycogen by the process called glycogenesis.

The alpha cells of the pancreas secrete glucagon whose action is opposite to that of insulin. Glucagon production is inversely proportional to the amount of blood glucose. If blood glucose is high, no glucagon is produced. If blood glucose is low (for example when there is long gap after taking food), large amount of glucagon is secreted. Glucagon induces liver to release its stored glucose by converting the glycogen to glucose by the process called glycogenolysis. Thus, the level of blood glucose is increased. Glucagon also induces liver and some muscle cells to produce glucose from other nutrients such as protein. The above mentioned processes are summarized in the Fig. 1 below.

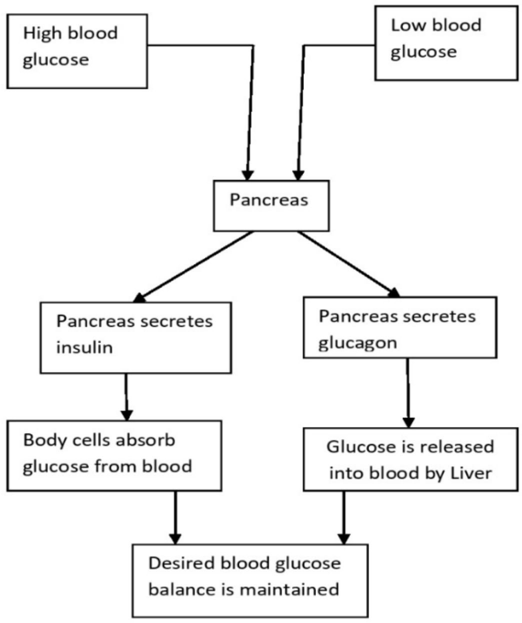

Fig. 1. Mechanism of maintaining desired blood glucose levels

2.2 Types of diabetes

Type 1, 2 and gestational diabetes are the commonly seen categories of diabetes. The type 1 is mainly found in children. This is characterized by the incapability of the body to generate insulin, mainly because of the autoimmune damage of beta cells in the pancreas which produces insulin. The people having this diabetes have to live their whole life with the support of insulin injections; otherwise complications will occur due to the increased blood glucose. Type 1 diabetes people commonly show symptoms of fast weight loss, polydipsia (abnormally high thirst), polyuria (large amount of urine production) and the associated nocturia (tendency to urinate more times during night). There will be presence of ketone bodies in urine (condition known as ketonuria).

Type 2 diabetes is the state of decreased sensitivity to the action of insulin. They need external insulin support for maintaining the proper balance of blood glucose. If not treated properly, the diabetes is likely to progress. This is the most prominent type of diabetes prevalent.

Table 1. Important distinguishing features of type 1 and 2 diabetes

Different features	Type 1	Type 2
Age of the start of disease	< 40 years	> 50 years
Duration of symptoms	Weeks	Months to years
Body weight	Normal or low	Above normal
Ketonuria	Present	Absent
If insulin treatment is not given	Can lead to rapid death	Does not pose immediate threat to life
Complications at the time of diagnosis	No	Around 25%
Family history of diabetes	Need not be there	More likely to be there

Gestational diabetes develops in pregnancy (gestation) period. The blood sugar levels, which are normal before pregnancy, increase beyond allowable ranges. If not properly managed, it will affect pregnancy and baby's health.

There is another term related to diabetes known as prediabetes. It is the condition where sufficient insulin is produced in the body, but the body doesn't make use of it properly. The blood glucose levels are high in the case of prediabetes, but not as high as found in type 2 diabetes. Prediabetes is an indicator of the future high risk of developing type 2 diabetes.

Diabetes, if not treated properly, result in too much increased blood glucose (hyperglycaemia) leading to complications. If the diabetes affected people take too much insulin or if they exercise without sufficient food, it can lead to low blood sugar condition known as hypoglycaemia which is highly life threatening.

2.3 Complications due to diabetes

Uncontrolled diabetes over a long duration can lead to many complications. Type 2 diabetes doesn't show noticeable symptoms at the initial stage. Because of this, about 25% of the people show evidences of diabetic complications at the time of diagnosis only.

70% of the deaths in diabetes are due to cardiovascular diseases. A statistics from USA indicate that diabetic people have 1.7 times higher cardiovascular death rates than their non-diabetic counter parts among people aged 20 and above. The chance of diabetic people affected by myocardial infarction and stroke are 1.8 and 1.5 times higher when compared to non-diabetic people. The effects of cardiovascular risk factors like smoking and hypertension gets magnified by the presence of diabetes.

Macrovascular (large blood vessel) disease caused by diabetes lead to fatal complications like angina, stroke, myocardial infarction, cardiac failure, intermittent claudication (cramping pain in leg) etc. Diabetic people suffer from atherosclerosis (deposit of fatty material in the inner walls of the arteries) much earlier with much severity than non-diabetic people. Diabetes also affects the small blood vessels in the body. This condition is also known as microvascular disease (also known as diabetic microangiopathy) and it leads to thickening of the basement membrane of the capillaries and further leads to increase in the vascular permeability throughout the body.

Retinopathy induced by diabetes is the most common form of vision related impairment in adults. Capillary occlusion (blockage) due to hyperglycaemia increases local vascular endothelial growth factor (VEGF) in retina. The occlusion of a lot of capillaries leads to the growth of new vessels in retina. There will be swellings called microaneurysms in capillary vessels in retina which leak fluid and blood resulting in retinal haemorrhages. The most serious form of diabetic retinopathy is called proliferative retinopathy which if left untreated causes extensive visual damage in the form of retinal detachment and frequent haemorrhages.

Diabetic nephropathy refers to the damage caused to the kidneys which may finally lead to kidney failure. Kidney is made up of microscopic units called nephrons which filter out impurities from the blood. Diabetes induced hyperglycaemia affects the proper filtering functions performed by the nephrons. Diabetic nephropathy is a prominent reason for long-term kidney disease and end-stage renal disease (ESRD) wherein the kidneys do not work properly. ESRD is the last stage in diabetic nephropathy where the person cannot survive without dialysis.

It is found that diabetic neuropathy is an important cause of morbidity and mortality in diabetes. In peripheral neuropathy, peripheral nerves are affected resulting in problems like deficiencies in motor and sensory functions. Weakening of the proximal muscles (muscles close to the body's midline), abnormality in gait, pain in limbs and feet can happen. In autonomic neuropathy, parasympathetic or sympathetic nerves may be affected in many visceral systems. There are innumerable clinical features of autonomic neuropathy affecting different systems of the body like cardiovascular systems (e.g. resting tachycardia), gastrointestinal systems (e.g. constipation, abdominal fullness, nocturnal diarrhoea), pupillary systems (e.g. reduced reflexes to light, reduction in pupil size) etc. All the above described complications are shown in below Fig. 2

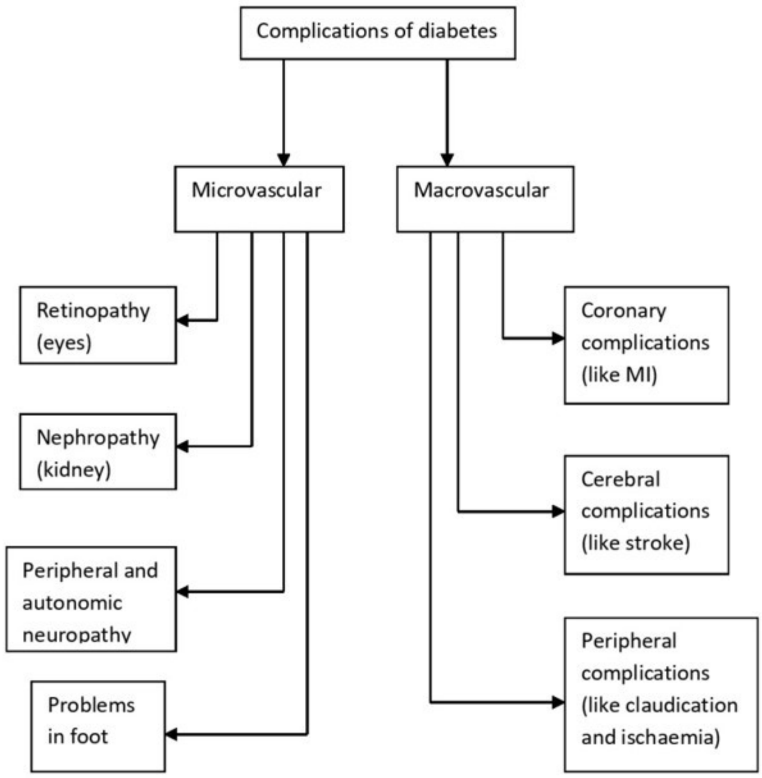

Fig. 2. Complications of diabetes

2.4 Causes (risk factors) of diabetes

Overeating, under activity and obesity may lead to diabetes in the case of middle-aged people according to the epidemiological studies conducted. People with a body mass index (BMI) larger than 30 kg/m2 are 10 times more prone to getting type 2 diabetes. Middle-aged and elderly people are also at greater risk of diabetes.

Ethnic origin is another major risk factor of diabetes. It is found that in USA, only 5.5% of the Alaskan people are affected by diabetes, while it is 7.1% for non-hispanic white people and 13% for non-hispanic black people. The highest value of 33% is for native Americans in USA. These disparities observed based on ethnicity may be due to a variety of unknown and known factors like life style, BMI related etc.

2.5 Treatment and management of diabetes

Proper treatment, effective blood glucose monitoring and control are very essential in preventing diabetes causing complications. Popular treatment is through the oral intake of effective drugs in order to maintain proper blood glucose level for diabetic people. Another mode of treatment is by insulin injection subcutaneously applied commonly to upper arms, thighs and buttocks with a disposable plastic syringe and a sharp needle. They are normally given in multiple doses several times a day. In acute cases, especially to those belonging to type 1 diabetes, continuous subcutaneous insulin therapy (or insulin pump) is administered. A further improvement of insulin pump which incorporates a closed loop system is known as artificial pancreas. Artificial pancreas is an integrated system working in closed loop consisting of insulin pumps along with continuous glucose monitoring systems (CGMS). The CGMS system can be considered to include interstitial glucose measurement done every 5 to 15 minutes, a personal glucose monitor which uses the glucose information to calculate the amount of insulin to be delivered into the body by the insulin pump and finally the insulin pump that delivers insulin.

It is important to adopt a healthy lifestyle by doing regular physical activity and maintaining proper BMI. Healthy diet is very important. Alcohol consumption, smoking and stress have to be avoided. Many of the important medical aspects discussed in this paper are taken from book Davidson's Principles and practice of Medicine [1].

3. Common methods of diabetes detection

3.1 Invasive methods of diabetes detection (blood testing)

As said initially, blood glucose level has to be maintained between 70 mg/dl and 110 mg/dl in the fasting condition. If it is below 70, then the condition is hypoglycaemia. If food is taken within two or three hours, then the glucose level can exceed 110. Irrespective of the amount of food one has taken, blood sugar should not exceed 180 in the normal case. If it is more than 180, the condition is hyperglycaemia indicative of diabetes. All the commonly used methods for detecting diabetes are invasive in nature. It generally involves extracting blood sample from the person and testing it for the possible anomaly. Popular invasive tests for diabetes detection and its acuteness are explained below. Table 2 also highlights the importance of these tests in diabetes detection.

3.1.1 Oral glucose tolerance test (OGTT)

OGTT is mainly done to check for gestational diabetes in pregnant woman. A prescribed amount of sugar contained drink is given to the person under test. Blood samples are tested at the prescribed time intervals. Blood glucose measurement greater than 200 indicates the presence of diabetes. If diabetes is undetected in pregnant woman, it may lead to complications.

3.1.2 HaemoglobinA1c (HbA1c)

HbA1c blood test gives the average blood sugar value for the past three months. HbA1c means glycated haemoglobin. Haemoglobin is a protein contained in red blood cells whose task is to carry oxygen throughout the body. Haemoglobin is glycated when haemoglobin combines with blood glucose. HbA1c greater than 6.5% is indicates diabetes.

Table 2. Indication of diabetes and prediabetes

Indication of diabetes	Indication of prediabetes
Fasting blood sugar ≥ 126 mg/dl	Fasting blood sugar ≥ 110 mg/dl and ≤ 126 mg/dl
Blood sugar two hours later a 75g oral glucose drink ≥ 200 mg/dl	Blood sugar two hours later a 75g oral glucose drink in range 140-200 mg/dl
HbA1c ≥ 6.5%	HbA1c in the range 5.7% - 6.4%

3.1.3 Interstitial glucose monitoring

This is a recently developed test to detect diabetes through interstitial continuous glucose monitoring (CGM). This test involves insertion of a tiny sensor under the skin in order to measure the glucose level in the interstitial fluid. One sensor can remain in that place for two weeks after which it has to be replaced by a new sensor. The sensor measures glucose level every one or five minutes in real time. In a span of two weeks, the sensor collects a substantial amount of data which can be analysed to get a variety of information like daily glucose profile, night-time glucose profile etc. It is possible to incorporate alarms into the sensor so that it can give the individual who wears it, warning in case hypoglycaemia occurs.

3.2 Non-invasive methods of diabetes detection (using ECG analysis)

3.2.1 Diabetes and associated cardiac changes

Diabetes can cause severe autonomic impairments. Diabetes induced high blood glucose/sugar (hyperglycaemia) causes cardiovascular malfunction and precapillary damage. This damage will affect the endothelial cells' normal working and blocks the normal route of passage of nitric oxide (NO) [2]. NO is essential for vasodilation. Diabetes-induced-hyperglycaemia causes reduced activation of phosphorylation cascade, leading to less endothelial NO synthase which is required to synthesize NO. Diabetes, thus leads to reduction in the availability of NO. The endothelial cell damages due to diabetes cause the blood vessels to be vasoconstricted and it affects the normal blood circulation.

Hyperglycaemia results in the production of free oxygen radicals which activate NO (derived from endothelium) and protein kinase C which boosts vasoconstrictive prostanoid production [3]. Hyperglycemia leads to endothelial damages, increases the activity and aggregability of the platelets [3] [4]. Eventually, monocytes, leukocytes and platelets are strongly adhered to endothelium. Blood coagulability is increased and fibrinolitic activity is decreased.

Thus, fatty material is increasingly deposited on the inner side of the blood vessel wall due to the high blood glucose condition. The deposit leads to production of blocks and hardening of blood vessels (atherosclerosis), obstructing flow of blood through the blood vessels. Two major types of cardiovascular disease are coronary artery disease and cerebral vascular disease. Coronary artery disease (ischemic heart disease) is caused by thickening of blood vessels that go to the heart by deposits of fatty material. Heart's blood flow is thus decreased or blocked leading to a heart attack. Increased blood sugar levels not only damage blood vessels, but also change the level of blood lipid. Diabetic people are at least twice more probable to develop heart disorders or stroke than non-diabetic people. Heart attacks in people with diabetes are more serious (more likely to result in death).

60 to 70% of diabetic patients have some form of neuropathy caused by diabetes. Diabetic neuropathy can be further grouped as autonomic, focal, peripheral and proximal neuropathy. Our focus is on the diabetic neuropathy affecting the nerves connected with the functioning of the heart (neuropathy known by cardiovascular autonomic neuropathy (CAN)). Heart rate and blood pressure are affected by CAN. High glucose level associated with diabetes causes serious problems in different organs of the body. All the autonomic microvascular damages also cause decrease in local reflexes. CAN leads to diminished HRV indicative of diabetic neuropathy [5]. Diabetes induced CAN may cause ECG alterations like ST-T changes, sinus tachycardia, heart rate variability changes, long QTc etc. It was also confirmed that QT, QTc and ST dispersions are predictors of death in diabetic patients [6] [7].

Among these ECG alterations, we are concentrating on the HRV signal which can be used for diabetes diagnosis since HRV is indicative of cardiac disorders developed due to diabetes.

3.2.2 ECG changes due to diabetes

ECG represents the role of autonomic nervous system (ANS) in regulating heart's natural rhythm. The generation method of ECG signal is as follows. The origin of the heartbeat is in a form of an electric impulse from sino-atrial (SA) node. This contracts both atria and then activates atrioventricular (AV) node and spreads through both ventricles. The complete activity is represented in the ECG waveform (figure 3).

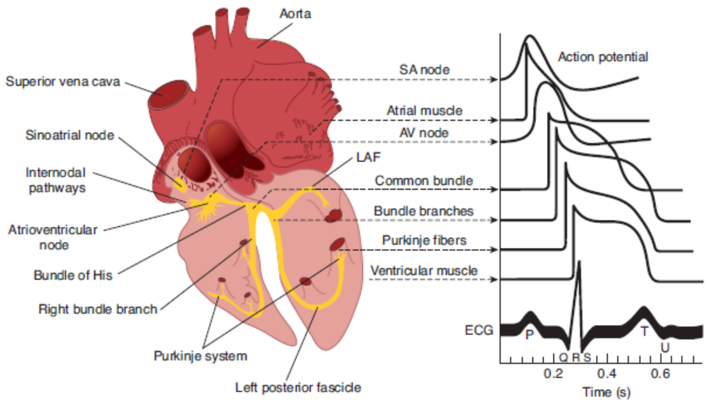

Fig. 3. Conducting system of the heart [8]

P, QRS, T and U are the prominent electrocardiographic deflections in the ECG signal. The activation or depolarization of the atria is represented by the P wave. Ventricles' depolarization is represented by the QRS. The repolarization of the ventricles is the T wave. U wave represents the papillary muscle repolarization. Normal duration of P wave is 0.11 second while that of QRS complex is 0.10 second. The normal range of QT interval is 0.35 - 0.43 seconds while normal PR interval is 0.12 - 0.20 seconds.

The widely used configuration for ECG measurements consists of 5 electrodes. One electrode each is positioned on the left arm (LA), right arm (RA), left leg (LL), right leg (RL) and chest to the right of the reference electrode. Another widely used ECG capture system consists of 10 electrodes (12 leads).

Stern et al. found out from ECG that a diabetes affected person who showed no indications of CAN develop left ventricular hypertrophy [9]. This shows the high risk of a diabetic patient to develop cardiovascular disease in future. The work by Stern et al. did not stop there. Diet was strictly monitored and proper measures were taken to ensure cardiac health for the patient. Under these conditions, a six year follow-up was performed. Their observation was that the diabetes of this person remained well controlled and his ECG did not change further and he did not further show any clinical or ECG signs of neuropathy.

The shape of the ECG indicates the cardiac health of the person [10].The difficulty in using ECG for the purpose of analysis is due to the fact that the delicate variations in the ECG waveform are extremely difficult to be differentiated by human perception. The performance of usual biosignal analysis methods is thus not upto the mark on ECG signals.

3.2.3 Heart rate variability

SA node functions as the heart's pacemaker. The cardiac impulse generated here is influenced by the parasympathetic and sympathetic nervous systems. Cardio-acceleration is caused by enhanced activity of sympathetic nervous system (SNS) or decreased parasympathetic nervous system (PNS) activity. Cardio-deceleration is caused by decreased SNS or increased PNS activity. Thus the status of the ANS is clearly understood from HRV signals. The SNS and PNS are the two branches of the ANS which together control the heart rate. Thus HRV can give a clear picture about sympathetic-parasympathetic balance. The instantaneous heart rate, together decided by the SNS and PNS, is strongly influenced by different kinds of neural, myocardial and hormonal factors [11].

The analysis of the non-invasive HRV data has innumerable applications in clinical areas of cardiology, physiology and pharmacology. HRV related cardiological impairment analysis is of real significance. They are simple and non-invasive, can detect impairments which have not gone to the stage of showing clear symptoms. If detected, the patient can further go in for detailed clinical tests. Research showed that the non-invasive HRV measurements are also reproducible if done under standard conditions [12] [13].

Heart rate signal contains the RR interval information ordered in time. The variation of RR intervals is known as HRV. The variations in the ANS due to hyperglycaemia can be represented well by HRV signals. Shape is an irrelevant feature for the discrete HRV signal. The HRV data available (i.e. instantaneous heart rate against time axis) can be analysed by different methods. It can serve as an excellent and accurate non-invasive technique to understand the state of the ANS which regulates the cardiac activity and heart rate.

4 Machine learning for diabetes detection

Before deep learning techniques emerged, biosignals were analysed mainly using machine learning (ML) techniques. ML applies artificial intelligence (AI) to systems to make them capable of automatic learning without explicit rule-based programming and without human assistance. In anomaly detection case, ML algorithm finds a mathematical function by itself that produce the correct outcome (anomaly present or absent) from the input training data (data from diagnostic tests like ECG, HRV), understanding the hidden patterns in input data. With this learned mathematical function, it should be able to predict the output state for a new set of input data with high accuracy.

Extensive domain knowledge of the human system and its intricate mechanism coupled with deep understanding of the biosignal variations happening during the anomaly is imperative to decide what type of features has to be extracted from the biosignal and analysed. So the initial step required is the selection of desirable features which can be effectively used for the purpose of anomaly detection. Then these features are extracted and fed to classifiers to detect the presence of anomalies. In the case of diabetes detection using HRV, the initial research used different methods like time, frequency, nonlinear methods etc.. All these methods gave different ranges for the parameters for the normal and abnormal signals. These distinctive ranges enabled classifiers to classify with accuracy above 85%. The nonlinear methods were specifically suited to biosignals like ECG which are inherently nonlinear and nonstationary in nature. The important methods of HRV analysis for diabetes detection using ML techniques are discussed below briefly. The features belonging to the below described domains are then passed through suitable classifiers.

4.1 Time domain methods

Time domain measures involve statistical operations that involve calculating the mean and variance of the RR interval of HRV data. Important time domain parameters are average of heart rate, RMSSD and SDNN. Parameters like RMSSD are indicators of high frequency changes affecting heart rate and thus reflect the state of parasympathetic activity. The shortcoming of time domain measurements is that they are very easily prone to outliers and artifacts. Hence, elimination of these artifacts has to be necessarily done for the data analysis.

4.2 Frequency domain methods

Frequency domain measures analyze all available frequency components present in the HRV. Power spectrum density (PSD) can give valuable information about the neurogenic heart rhythms [14]. The high frequency region (0.15-0.5Hz) is an indicator of the parasympathetic activity, the low frequency region (0.04-0.15Hz) indicates the complete sympathetic and parasympathetic activities. Fast Fourier transform (FFT) is generally used for the estimation of PSD. Autoregressive (AR) model is another popular frequency domain representation very much suitable for analysis of biosignals like ECG and EEG. The reliability of frequency domain based methods decrease with the decrease in signal-to-noise power.

4.3 Wavelet transform

The traditional frequency domain techniques are incapable to provide exact time localization in a typical nonstationary biosignal. To overcome these, better techniques were developed. The wavelet analysis, which shows very good performance, involves comparison of the signal with a selected wavelet of limited duration and finding parameters. HRV analysis can thus be effectively performed making use of wavelet transform and also be used to obtain the time related information of various frequency bands [15].

4.4 Nonlinear methods

Nonlinear methods are much suited for analysing the nonlinear and nonstationary biosignals like ECG. Some of the important nonlinear parameters used for HRV analysis are approximate entropy (ApEn), higher order spectrum (HOS), detrended fluctuation analysis (DFA), correlation dimension (CD), recurrence quantification analysis (RQA) features and empirical mode decomposition (EMD) features.

4.4.1 Detrended fluctuation analysis (DFA)

DFA (Peng et al.) is very useful in assessing the fractal scaling characteristics of HRV data [16]. The fluctuation inherent in the data is represented by parameter α (indicates irregularity of input data). Typically, α is closer to 1 for normal (young and healthy) people. α varies according to different cardiac disorders.

4.4.2 Correlation dimension (CD)

CD is a nonlinear feature which can be effectively used for detecting anomalies. CD is a type of fractal dimension. Popular technique for finding out CD (proposed by Grassberger et al.) constructs a function C(r) by finding out the distance among all data points and then grouping them [17].

CD is found out by the expression given by

$$CD = \lim_{r \to 0} \frac{log[C(r)]}{log(r)} \qquad (1)$$

The normal people produce a higher CD value when compared to the diabetic signal because normal RR signal has higher RR variability.

4.4.3 Approximate entropy (ApEn)

ApEn is a measure of disorder in HR signal [18]. The value of ApEn is larger for more complex or irregular data (the normal case) and vice versa for cardiac impairment (diabetic) cases.

4.4.4 Recurrence quantification analysis (RQA)

Recurrence plot (by Eckmann et al.) is a graphical aid to identify concealed reoccurrences in time domain signal which may not be pronounced [19]. It measures the nonstationarity of the time-series. Several important parameters can be calculated from recurrence plot. Example of these parameters are laminarity (LAM), mean diagonal line length, recurrence rate (RR), determinism (DET), entropy and trapping time (TT).

4.4.5 Higher order spectrum (HOS)

HOS is very useful in the dynamical analysis of nonlinear, nonstationary and non-gaussian biosignals. HOS (also called polyspectra) represents the cumulants and moments of order three and above. HOS can be effectively used for the analysis of HRV signals. Several useful HOS features can be extracted from HRV data and fed to different classifiers for the purpose of diabetes detection.

4.4.6 Empirical mode decomposition (EMD)

EMD will split the input signal into intrinsic mode functions (IMFs). The IMF generated features are well suited to effectively capture the nonlinearity and nonstationarity characteristics of biosignals like HRV.

5 Methodology of deep learning techniques

A variety of time, frequency, wavelet, nonlinear based features along with classifiers have been used for detecting diabetes in previous works. Our concentration in this chapter is on deep learning. Deep learning is an improvisation of machine learning and it is particularly suited to high dimensional data and for complex artificial intelligence problems. The shortcomings of machine learning led to development of deep learning [20].

All the explicit feature-related processes found in the conventional machine learning networks are implicitly performed in deep learning networks. Deep networks self-learn from the data and its efficiency is much better compared to the traditional feature extraction networks.

Deep learning networks use cascaded layers of nonlinear processing units. These units do the task of feature extraction and transformation. The output of one unit is fed as input to the succeeding unit. The learning can be performed in a supervised or unsupervised manner. They normally use some kind of gradient descent method for training using backpropagation method. Popular deep learning networks are briefly explained below.

5.1 Autoencoder (AE)

AE is a type of neural network using unsupervised learning techniques and back propagation methods. Its target values are set to be equal to the inputs [21]. AE is built up of two symmetrical deep networks (typically four or five layers deep), one is for encoding and the other is for decoding. AE is thus implemented very similar to conventional neural networks except for the novelty that its goal is to recreate the input by learning the input data [22] [23].

5.2 Convolutional neural network (CNN)

CNN is modified multilayer perceptron (MLP) employing convolution operation as one of its layers. CNN is basically built of three layers; convolutional layer followed by pooling and fully connected layers. CNN resembles neural networks in many of its characteristics. In conventional neural network, it is $y = f(x.w)$ where x and y denote input vector and output vector respectively and w the set of weights. But in the convolutional layer of CNN, it is $y = f(s(x.w))$ where s indicates the convolution operation between inputs and weights. CNN can be applied on a time series input data (1D) or on an image (2D).

5.3 Recurrent structures (RNN, LSTM and GRU)

5.3.1 Recurrent neural network (RNN)

RNN is an improvement on feedforward network. RNN contain feedback loops (Fig. 4.) which serve as short-term memory using which past information (in time scale) can be stored and retrieved. Temporal tasks can be adeptly executed by this modernization. There is no constraint on the permitted length of temporal sequences in RNN, unlike MLP. Parameters can also be shared across time-steps in RNN. In brief, the storage of RNN is replaced by another model incorporating feedback loops and these controlled states are named as gated memory. RNN is widely used in the areas of speech recognition, language modelling and machine translation.

The cyclic connections present in RNN architecture makes it difficult to understand the working of RNNs in entirety. For better understanding and analysis purpose, RNN's intricate network structures can be intelligently converted to FFNs form by unfurling in time scale (Fig. 4).

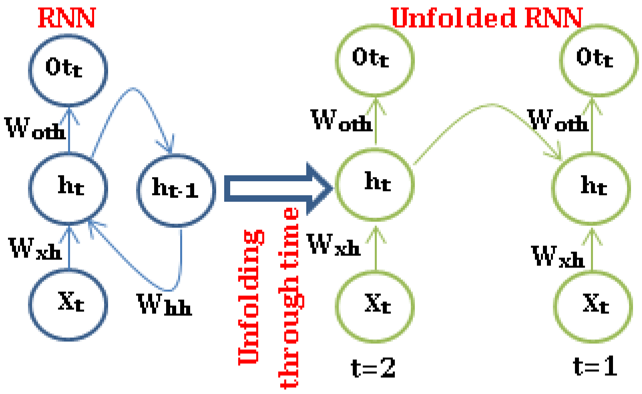

Fig. 4. Schema of RNN and unfolded RNN in time (t=1, t=2) in onward path

5.3.2 Long short-term memory (LSTM)

LSTM (Hocreiter et al.) is an enhanced model of RNN, developed in order to model long-range dependencies of temporal sequences more accurately than conventional RNNs [24]. LSTM contains memory blocks in place of simple memory units of RNN (Fig. 5). LSTM take care of long-term dependencies in an effective manner compared to conventional RNN. This property of LSTM made it of wide use in complex tasks like language modelling. Generally, it is of wide use in areas where long time series data analysis is required.

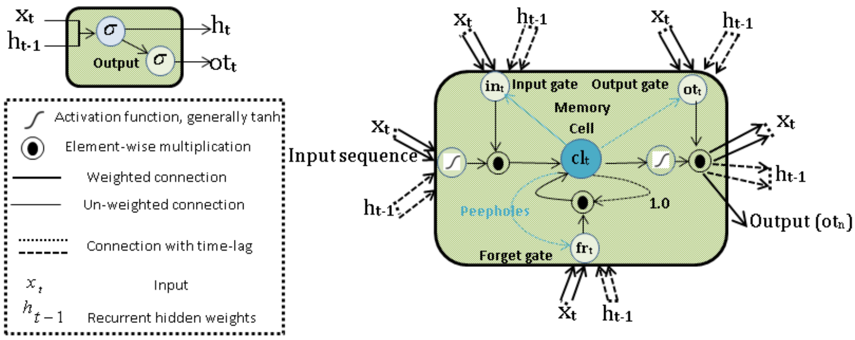

Fig. 5. Memory blocks in RNN (left) and LSTM (right)

Memory block in LSTM can be considered as a complex processing centre built of memory cells. The input and output gates are multiplicative gates which can permit or block the flow of cell activation through the memory unit to nodes coming further in the path. A set of modifiable multiplicative gates manage the entire processes happening in the memory block. Peephole connections and forget gate are the new additions to the LSTM architecture as research progressed. The forget gate can be used in place of CEC (constant error carousel). These three gates also assist the memory cell to store the information ranging across many time steps.

5.3.3 Gated recurrent unit (GRU)

GRU is an improved variety of LSTM having less number of parameters. GRU enable each recurrent unit to capture dependencies corresponding to different time scales in an adaptive manner. GRU has gating units that modulate the flow of information inside its memory, but unlike LSTM, it doesn't have separate memory cells. The memory consumption and computational cost of GRU is much smaller than that of LSTM.

5.4 Hybrid of CNN-RNN, CNN-LSTM, CNN-GRU

Hybrid deep neural network, in general, is a fusion of generative and discriminative neural networks so that the advantages of both can be combined effectively. Hybrid deep learning networks can be built out of cascading heterogeneous networks like CNN-LSTM. CNN extracts the spatial features and LSTM extracts the sequential information. This means CNN-LSTM collectively helps to extract spatio-temporal information of signals like ECG (The details of experimental analysis and topology of work using CNN and CNN-LSTM are explained in section 7).

In the case of hybrid architectures like CNN-LSTM, CNN is made up of convolutional1D and maxpooling1D layers alone. Maxpooling layer's output is passed as input to subsequent network.

$$y_i = CNN(x_i) \qquad (2)$$

The input and output of the CNN is x_i and y_i respectively. Each data type of x_i has an associated class label. y_i is the output vector of the maxpooling layer in CNN. y_i is fed to the next deep learning network placed after CNN. The deep learning network can be of RNN, LSTM and GRU.

6. Literature survey

6.1 Earlier methods of analysis of HRV signals

HRV signals are earlier analysed using the above described time, frequency and nonlinear based parameters. Evidences suggest that heart does not oscillate periodically under normal conditions [25]. Thus, nonlinear techniques, capable of extracting and analysing nonlinear features from HRV signals, are also widely used. Nonlinear features like lyapunov exponent (Rosenstien et al.), 1/f slope (Kobayashi et al.), approximate entropy (ApEn) (Pincus), detrended fluctuation analysis (DFA) (Peng et al.) can be extracted from the HRV signals for further analysis [26] [27] [18] [16]. The range of the feature values gives indication of the possible anomaly. HRV signals classification is also done by nonlinear techniques [28] [29]. Nonlinear techniques are employed for the cardiac signal analysis for developing cardiac arrhythmia detection algorithms [30] [31].

6.2 Previous works of diabetes detection using heart rate (including machine learning based)

Wheeler et al. first reported a reduced beat-to-beat variation is caused by diabetic neuropathy during deep breathing [32]. The works of Pfeifer, Singh, Villareal RP had confirmed that parasympathetic autonomic activity was reduced in diabetes affected people much earlier to clinical visibility of neuropathic symptoms [5] [33] [34]. Researchers have found out that diabetes patients who produced negative results after undergoing traditional cardiac function tests showed a decreased HRV. Correlation between fasting blood sugar and cardiovascular complications has been clearly established by many works [35] [36]. About one-fourth of the patients with serious coronary disorder turned out to be diabetic patients too [37] [38]. This is because diabetes results in early development of coronary disease and atherosclerosis. All these results proved that HRV analysis can be used to identify diabetes.

Diabetes-induced-CAN can be very damaging. Hence, early detection of CAN due to diabetes is very important. Ahsan et al. showed the HRV analysis using features likes sample entropy (SampEn) and poincare plots are very useful in detecting CAN present in diabetic people [39].

Kirvela et al. performed frequency and time domain analysis of HRV (extracted from 24 hour duration ECG recordings) [40]. All analysis parameters (both time and frequency) were significantly reduced in diabetic HRV samples compared to those from normal people. Mackay measured heart rate variation at different levels of breathing modes for normal and diabetic patients. It was observed that heart rate variation was markedly lower in diabetic people [41].

Herbert et al. researched on the consequences of QT dispersion on normal and diabetic people also ensuring that people belonging to both classes had no previous history of cardiac diseases [42]. Heart rate variability was measured through a parameter named tone-entropy (T-E) where tone (T) is the representation of sympatho-vagal balance and entropy (E) is the representation of the autonomic regularity. T-E was observed to be reduced in diabetic people. On similar group of people on similar conditions, Awdah et al. observed that time domain parameters like St. George index, RMSSD, SDRR etc. were reduced in diabetic cases in comparison to normal cases [43]. Chemla D et al. used the method of autoregressive frequency modelling for studying of the effect of HRV signals in diabetes affected people [44].

Emily et al. found out that time domain parameters of RMSSD, SDNN and R-R interval were lower in diabetic people. They also observed that as diabetes progresses, proper autonomic function of the body will be badly affected [45]. Seyd et al. did time and frequency analysis of HRV [46]. The time domain parameters like mean RR interval, TINN, RMSSD, SDNN, NN50 count, HRV triangular index were reduced in diabetic patients than normal people. It was observed that there is considerable difference in power across different frequency ranges between diabetes people and normal people when frequency domain analysis was done.

Trunkvalterova et al. proved that multiscale entropy (MSE) is capable of detecting very small aberrations in the cardiovascular systems of patients having type 1 diabetes. In their work, they used the estimator parameter of SampEn and linear measures like RMSSD [47]. Faust et al. analysed time, frequency and nonlinear features derived from HRV signals and showed that nonlinear methods gave better results in the diagnosis of diabetes compared to time domain and frequency domain methods [48]. Jian et al. applied principal component analysis (PCA) to HOS bispectrum magnitude plots obtained out of HRV signals. These were fed to SVM classifier to obtain diabetes detection accuracy value of 79.93% [49].

Acharya et al. arrived at an innovative diabetic integrated index (DII) making use of nonlinear features derived from HRV signal [50]. They obtained diabetes detection accuracy of 86% using AdaBoost classifier. Swapna *et al.* used HOS based features for diabetes detection with an accuracy of 90.5% [51]. Acharya *et al.* obtained accuracy of 90% extracting four nonlinear features using adaboost classifier [52]. Acharya *et al.* used entropies, energy skewness and kurtosis to achieve diabetes detection accuracy of 92.02% employing decision tree (DT) classifier [53]. Pachori *et al.* used EMD on HRV signals along with morlet wavelet kernel function to achieve the very high accuracy of 95.63% [54]. Table 3 summarises all the above works.

Table 3. A summary of machine learning methods used for detecting HRV parameters that were significantly different in diabetic patients (DM=Diabetes Mellitus)

Authors	Methods/features	Observed activity for extracted features for DM

Pfeifer *et al.* [5]	Time domain	
Kirvela *et al.* [40]	Frequency domain, time domain	HRV reduced
Singh *et al.*[33]	Frequency domain, time domain	Reduced LF power
Awdah *et al.* [43]	Time domain	Reduced
Flynn *et al.* [55]	DFA	Reduced short-term correlation in DM
Chemla *et al.*[44]	FFT , Autoregressive spectral analysis	decreased
Schroeder *et al.* [56]	Time domain	decreased
Seyd *et al.* [46]	Time, frequency domain	decreased
Trunkvalterova *et al.* [47]	Nonlinear methods (multiscale entropy (MSE))	decreased MSE
Faust *et al.* [48]	Time, frequency, nonlinear	decreased
Acharya *et al.*[50]	Nonlinear (RQA , CD)	Accuracy is 86%
Swapna *et al.* [51]	HOS	Accuracy is 90.5%
Jian *et al.* [49]	HOS	Accuracy is 79.93%
Acharya *et al.* [52]	Nonlinear features	Accuracy is 90.0%
Acharya *et al.* [53]	DWT	Accuracy is 92.02%
Pachori *et al.* [54]	EMD related features	Accuracy is 95.63%

6.3 Deep learning based diabetes detection works using HRV

These are some of the works connecting deep learning analysis methods and ECG. CNN based deep learning methods were used to analyse ECG to detect coronary artery disease (Acharya *et al.*), myocardial infarction (Acharya et al.), classify heartbeats (Acharya *et al.*) [57] [58] [59]. Sujadevi *et al.* analysed ECG to detect atrial fibrillation [60].

Regarding diabetes detection using ECG signals, Swapna *et al.* employed hybrid deep learning CNN-LSTM network with HRV as input to achieve a very high accuracy value of 95.1% which is comparable to maximum accuracy achieved so far [61]. Swapna *et al.* improved the above diabetes detection accuracy to 95.7% by adding SVM classifier after the CNN-LSTM network [62]. Accuracy details are given in table 4.

Table 4. Deep learning methods used for diabetes detection (with HRV as input)

Authors	Methods/features	Accuracy
Swapna *et al.* [61]	Deep learning (CNN-LSTM)	Accuracy is 95.1%
Swapna *et al.* [62]	Deep learning (CNN-LSTM) followed by SVM	Accuracy is 95.7%

7 Architecture and implementation of deep learning architecture – sample study

The hybrid architecture for diabetes detection is discussed in detail in [61], [62]. The workflow of hybrid architecture is shown in Figure 6. Deep learning architecture is implemented using powerful software framework of TensorFlow [63] in the case of [61], [62]. TensorFlow is Google's open-source software libraray. TensorFlow allows modelling of numerical systems as unified data flow graphs which in turn can be modelled as math related operations using tensors, nodes and edges. Heterogeneous platforms like CPUs, GPU and mobile devices can be used for performing computations.

Regarding the work of Swapna *et al*. [61], the following network structure was implemented. The input layer was made of 1000 neurons (number of samples in the input data set was 1000). The values of the input data were normalized to fall between 0 and 1. The hidden layers consist of a CNN layer (with pool size as 2, stride as 1, number of filters as 64, kernel-size as 3), after that came the maxpooling, flatten and drop-out of 0.5 and ended with a fully-connected layer with sigmoid activation function. There was full connectivity between input, hidden and output layers. Three trials were made to run for 300 epochs (learning rate as 0.001, batch size as 16). All the final values of the above mentioned hyperparameters were fixed after experimenting with different values and then finding out the optimum values based on the performance of the deep learning network. These hyperparameters were corresponding to the first network architecture CNN1 (number of CNN networks in the topology is 1) we tried. The number of CNN layers were increased one by one to five and then we went to the hybrid architecture of attaching LSTM to each of the above five configurations. The accuracy of diabetes detection was found to be 95.1% (maximum value) for CNN5-LSTM.

With respect to the second work of Swapna *et al*. [62], same configuration of the above work was used with the modification that the features extracted from the CNN/CNN-LSTM architecture were passed to the SVM classifier. This improved the accuracy of diabetes detection. Figure 6 shows the network topology comparison of the works [61] and [62].

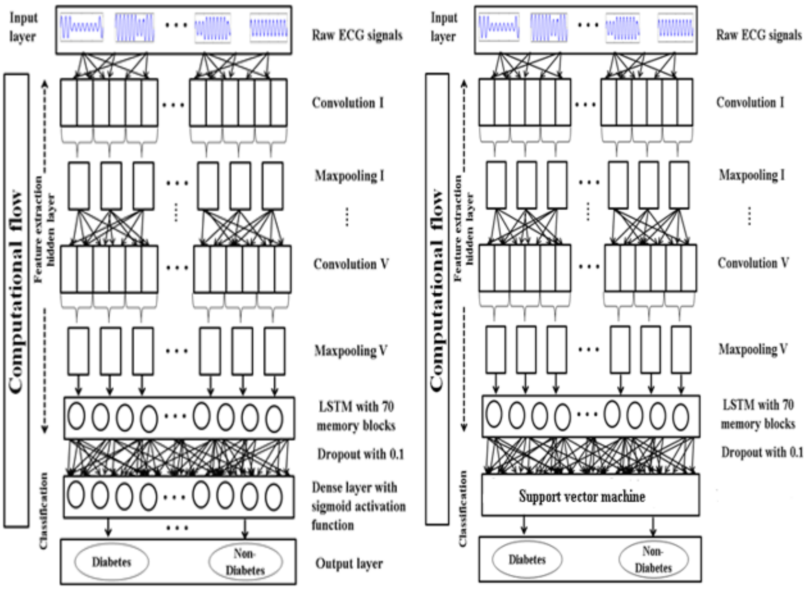

Fig. 6. The architecture of proposed system of [61] and [62] (with and without SVM)

8 Deep learning in big data analysis: limitations and challenges

The amount data handled is increasing to unimaginable proportions in size as well as dimensions today, take the case of applications like twitter and facebook. Related to biomedical area, if data is continuously taken from patients in real time, then the collected data can be viewed as big data making big data analysis or analytics capable of playing a remarkable role. For big data analytics, the traditional machine learning based analysis techniques are inadequate.

In big data, volume of data handled is very high. In vertical dimension, it is number of records or samples present in the dataset and in horizontal dimension, it is number of features or parameters handled in the dataset. This data volume explosion has brought with it huge challenges in analysing the data. The time and memory taken for computations will have an exponential increase with increasing dataset size. The solution to handle this challenge is to develop architectures capable of parallel processing of data. Another issue is that as the data volume is very high, it may not be possible to store the entire data in memory or disk. Many training/testing algorithms are designed assuming that the data is available in its entirety in memory. Because of this, such algorithms cannot be run successfully. This is known as the curse of modularity. Distributed computing and parallelization can be resorted to tackle this challenge. Further, there are challenging issues of high dimensionality of the data, highly diverse nature of data and high variation in the probability of occurrence of classes in data which if not handled, will deteriorate the performance of the machine learning network. In machine learning, proper selection of features is crucial using domain knowledge. As the dataset grows in dimension as well as in sample size, it is extremely difficult to create relevant features. Feature selection is also very difficult in high dimensional data. These issues in handling and analysing big data led to the situation of deep learning networks occupy the stage instead of traditional machine learning networks.

Concentrating on applying deep learning techniques to ECG-derived-HRV data for the purpose of diabetes detection, the best performed models [61] [62] applied it on real-time data and these works can be considered as the foundation stone towards future work in this direction. Further improvements in accuracy can be tried by giving larger sized input data into the developed architecture compared to the data given in the above works.

Present advanced ECG measurement equipment take very less duration (less than 5 minutes) to extract ECG signal for analysis. On the other hand, there are Holter monitors which do a continuous (for at least 24 to 48 hours) monitoring of ECG signal of a person to check for possible abnormalities which cannot be known by the short-term ECG monitoring. Machine learning techniques are sufficient to handle short-term ECG data. Deep learning networks and algorithms are suitable for relatively short-term data also considering the fact that analysis results can be obtained very quickly in real time. The second case of analysis of large amount of data (continuous ECG signal with duration more than 24 hours), say from Holter monitors, also requires big data analytics and deep learning algorithms. If long duration ECG data are available to researchers, deep learning architectures like LSTM and hybrid systems like CNN-LSTM are available which are capable of analysing the non-invasive data for the future possibility of being affected by diabetes. Hence if real time big data is made available to deep learning networks, the scenario will shift fast from the problem of detection of a disease to that of prediction of a disease in near future.

9. Conclusion

The body of the diabetes affected person is either incapable of producing sufficient insulin or resistant to the produced insulin leading to unbalanced high blood sugar. Autonomic impairments which are nonsymptomatic, but can only be clinically detectable, are evident only after many years have passed after the onset of diabetes. Thus, HRV can be used as an early sign of the impending diabetic neuropathy and can be used for diabetes detection with high accuracy. HRV analysis is thus a simple, non-invasive and reproducible detection method of diabetes. Deep learning methods can be used to detect diabetes with very high accuracy. Distributed deep learning systems can give results very fast that can turn real time analysis of biosignals a reality. So it can be said for sure that the future of biomedical engineering belongs to the featureless, deep learning based systems which can do big data analytics with no necessity of domain knowledge.

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