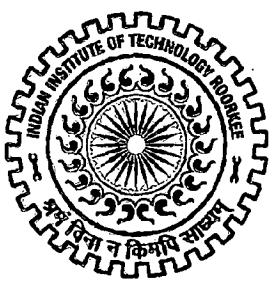
ARTIFICIAL NEURAL NETWORK BASED ABNORMALITIES CLASSIFICATION USING HEART RATE VARIABILITY SIGNAL

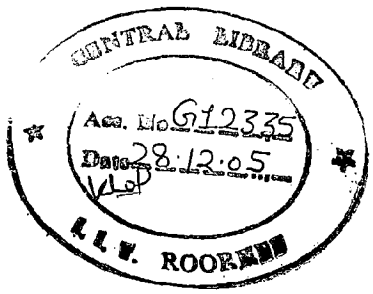
A DISSERTATION

Submitted in partial fulfillment of the
requirements for the award of the degree
of
MASTER OF TECHNOLOGY
in
ELECTRICAL ENGINEERING
(With Specialization in Measurement and Instrumentation)

By

BIRHANU MENGISTU





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CANDIDATE'S DECLARATION

I hereby certify that the work which is being presented in this thesis entitled "**Artificial Neural Network Based Abnormalities Classification using Heart Rate Variability Signal**" in fulfillment of the requirement for the award of Masters Degree in electrical engineering (measurement and instrumentation) and submitted in Department of Electrical Engineering of Indian Institute of Technology Roorkee, is an authentic record of my own work carried out during a period from June'04 to June'05 under the supervision of Dr. Vinod Kumar, Professor , Department of Electrical Engineering, of Indian institute of Technology Roorkee.

The matter presented in this thesis has not been submitted by me for the award of any other degree of this or any other institute/University

(Birhanu Mengistu)

This is to certify that the above statement made by the candidate is correct to the best of my knowledge.

Date: 24.6.05

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Place: Roorkee

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This work was carried out at the Department of Electrical Engineering, Indian Institute of Technology Roorkee, from June 2004 to June 2005.

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(BIRHANU MENGISTU)

List of Symbols and Abbreviations

AIC	Akaike information criterion
AIIMS	All Indian institute of medical science
ANN	Artificial neural network
ANS	Autonomic nervous system
AR	Autoregressive
ARMA	Autoregressive moving average
ART	Adaptive resonant theory
AV	Atrioventicular
CHF	Congestive heart failure
DB	Database
DM	Diabetic mellitus
ECG	Elcetrocardiogram
EP	Well controlled epilepsy
ESC	European society of cardiology
Fcentlf	The central frequency of HRV power in low frequency region
Fcenthf	The central frequency of HRV power in highfrequency region
FFT	Fast Fourier transforms
FPE	Final prediction error
HF	High frequency
HR	Heart rate
HRV	Heart rate variability
KB	Knowledge base
LF	Low frequency
MA	Moving average
NASPE	North American society of pacing and Electro- physiology
N_c	Number of negative cases correctly classified
N_I	Number of negative cases incorrectly classified
NN	Neural network
NN50count	Number of pairs of adjacent NN intervals differing by more than 50ms in the entire recording

NN interval	Normal-to-normal interval
N_T	Total number of negative cases.
n.u	Normalized unit
pNN50count	Percentage of adjacent NN differing by more than 50ms over an entire recording
P_c	Number of positive cases correctly classified
PEWT	Prediction error whiteness test
Phf	Power in high frequency (0.15-0.5Hz) range
Phfnorm	Normalized HRV power in high frequency region
P_I	Number of positive cases incorrectly classified
Plf	Power in low frequency (0.04-0.15Hz) range
Plfnorm	Normalized HRV power in low frequency region
PSD	Power spectral density
P_T	Total number of positive cases
Ptot	Total HRV power
Pvlf	Power in very low frequency (0.01-0.04Hz) range
RMSSD	Root mean square value of successive differences between adjacent intervals
RR	Time interval between two successive R-peaks
SA	Sinoatrial
SDANN	Standard deviation of the averages of NN intervals in all five-minute segments of the entire 24-hour recording
SDNN	Standard deviation of normal- to- normal interval
$SDNN_{index}$	Mean of the standard deviations of all NN intervals forall 5-minute segments of the entire (24-hr) recording
SDSD	Standard deviation of differences between adjacent NN intervals
UC	Ulcerative colitis
ULF	Ultra low frequency
VLF	Very low frequency
θ	Neuron bias (or threshold)

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Abstract

Since the late 1980s, the study of heart rate variability as a measure of autonomic modulation of the cardiovascular system has grown with pace. For this reason, the analysis of their variability has gained growing importance both for the clinical evaluation and physiological studies. This noninvasive measure provides important information about the cardiovascular function in healthy and diseased subjects. Different time domain and frequency domain measures are used for the quantification of autonomic involvement in the cardiovascular system.

In this thesis, Once the RR intervals were extracted from ECG signal, missing beats and ectopic beats were taken care of using Cheung's algorithm and visual inspection. The beat-to-beat variability, normally called heart rate variability (HRV) analysis was made using Autoregressive (AR) modeling. In AR modeling, the input time series should be equi-spaced. Since the time interval between two R-peaks is not uniform, interpolation and resampling algorithm was implemented to convert it to equi-spaced RR time series. In AR modeling, the current sample was estimated as the weighted linear sum of previous values plus white noise. The order of the model (the number of previous values to be added) was selected by using standard order selection criteria called Akaik's information criteria (AIC) and final prediction error (FPE), where we observed no noticeable difference between the two in our study. The validity of the selected model was tested by using Anderson's test.

Feed-forward network with backpropagation algorithm were developed for disease classification. During this study, one hundred forty eight cases comprising four diseases were used for training and testing of different networks developed for diagnosis of four diseases, namely, congestive heart failure (CHF), diabetic mellitus (DM), controlled epilepsy (EP) and Ulcerative colitis (UC). The inputs to each network developed were three time- and five frequency- domain measures of HRV obtained from the AR model we developed. These eight features were selected after rejection of redundant features using correlation test. The two main focuses covered in developing the networks were to check the presence/ absence of a particular disease and to check whether the subject is

normal or abnormal due to the presence of one/or more of the four diseases considered. The networks developed give good results as their performance was measured on sensitivity, specificity, accuracy and positive predictive value.

Contents

CHAPTER # 1

INTRODUCTION

1.1 Why HRV and ANN?

Since the late 1980s, the study of heart rate variability as a measure of autonomic modulation of the cardiovascular system has grown with pace. Heart rate is simply the R-R interval of two consecutive cardiac cycles. The variation in the duration of R-R interval is called heart rate variability (HRV). In normal rhythmic action, the heart rate is controlled by the frequency at which the sinoatrial node generates (fires) impulses. However, this rhythm is under continuous disturbance from the brain through the autonomic fibers, to fulfill the demand of the body. Different activities are involved in heart rate variability. Some of these are: position of the body, exercise, smoking, alcohol, drugs. It is also found out to be affected by age (one paper to be published), sex, race... etc. Emotional states also contribute to its variation (like anger, hostility, appreciation... etc.).

Putting all factors aside, our main interest here is the awareness that different diseases (both cardiac and non-cardiac) leave their signature on HRV. So far, different diseases have been found out with vivid evidence on HRV. Some of them are: diabetes, epilepsy, hypertension, congestive heart failure, arrhythmia, myocardial infraction, and ventricular fibrillation. And the list is growing by day following introduction of new computing techniques and analysis strategies.

However, the main limitation for HRV not to be fully implemented in clinical applications is its complexity. It is influenced by many factors affecting the mental and physical condition of the subject during ECG recording. Apart from this, the lack of gold standard in quantitative HRV measures has also its own part to play. But, it is evident that subjects of a particular disease have some pattern on HRV measures. This pattern is too complicated for mathematical formulation and even not fully understood.

This is the point where artificial neural networks come to help to approximate the unknown complicated relationship between a particular disease and the hidden pattern in it [discussed in later sections]. The remaining sections of this chapter would deal with the basic concepts, terms and their brief definitions for a better understanding of the chapters to follow.

1.2 Cardiovascular Signals

The quantification of the variability in cardiovascular signals provides information about the autonomic neural regulation of the heart and circulatory system. The heart rate may be increased or decreased from its mean value by slow acting sympathetic activity or fast-acting parasympathetic activities respectively. At any instant both activities exist, though with different proportion called sympatho-vagal balance depending on the physical and mental condition of the subject. Sympathetic activity dominates while exercising and parasympathetic dominates during rest. Periodic fluctuation around the mean heart rate mainly originates from regulation of respiration and thermoregulation systems.

1.2.1 Heart Beat

The overall contraction of the myocardium starts due to the depolarization of Sinoatrial (SA) node, which is a group of excitable cells found on the top of the right atrium near the entrance of superior vena cava. This is followed by depolarization of the cardiac muscle in its surroundings. The stimulation from the SA node is regular and spontaneous and is the source of primary pacemaker with in the heart. The potential generated by the SA node propagates from the node in all directions along the surface of both atria towards the junction of atria and ventricles called atrioventricular(AV) node. If the AV node fails to receive it takes over as the cardiac pacemaker but with different resonance frequency. The SA node inhibits this pace making whenever its impulses reach the AV node. At AV node, the propagation of impulse is delayed by special nerve fibers so as to provide proper timing between the pumping action of the atria and the ventricles. From AV node, the impulse traverses through the bundle of His, which in turn spreads out to right bundle branch and left bundle branches. Both bundle branches further fan out into widely distributed rich network specialized conducting fibers, called Purkinji fibers in their corresponding ventricular endocardium.

Different parts of the heart are involved mainly in two primary and well synchronized physiological events, namely, the heart's mechanical activity (pumping of the blood) and the heart's electrical activity (the transmission of electrochemical impulses for the coordination of the heart's effort). These two activities give rise to heart beat.

1.2.2 ECG

The ECG signal is a recording of the time varying electrical activity of the heart. Thus, it is primarily a tool for evaluating the electrical events within the heart. The action potential of the cardiac muscle cells can be viewed as batteries that cause charge to move throughout the body fluids. These moving charges-ions represent the sum of the action potentials occurring simultaneously in many individual cells and can be detected and converted to electron currents by the recording electrodes at the surface of the skin. There are different ECG recording arrangements depending on the number of electrodes employed and their position on the body. The typical clinical ECG is recorded using a 12-Lead arrangement where six of them are placed across the chest and the rest are on the extremes of the body. This is mainly used to obtain as much information as possible concerning different areas of the heart. The other one is a three-lead arrangement, which is commonly used for HRV analysis. In this arrangement, the two leads can either be on left arm and left leg (lead I) or left arm and right arm (lead III) or right arm and left leg (LEAD II). The third lead is connected to the right leg as a ground point. Out of these three configurations, Lead II is commonly used because maximum deflection is obtained as per Eithoven's triangle.

Each beat of the heart can be viewed as a series of deflections away from the baseline on the ECG. These deflections reflect the time evolution of electrical activity in the heart, which initiates muscle contraction. A single normal cycle of the ECG corresponding to one heartbeat is traditionally labeled with the letters P, Q, R, S, T on each of its turning points (figure1.1). The ECG is divided in to the following segments and intervals:

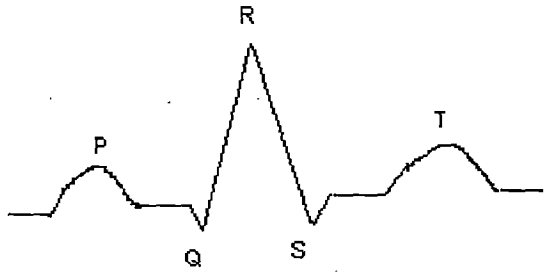


Figure 1.1 Electrocardiogram

P-wave: This is the first deflection, which corresponds to current flows during atrial depolarization i.e., a small low-voltage deflection away from the baseline caused by the depolarization of the atria prior to atrial contraction as the depolarization wavefront propagates from the SA node through the atria.

PQ-interval: This is the time between the start of atrial depolarization and the beginning of ventricular depolarization

QRS complex: This is the second deflection, which occur approximately 0.15 secs later and the largest amplitude(R=1.60mV) portion of the ECG, caused by currents generated when the ventricles depolarize prior to their contraction. It is a complex deflection because the paths taken by the wave of depolarization through the thick ventricular walls differ from instant to instant, and currents generated in the body fluids change direction accordingly. Regardless of its form, for example, the Q and/or S portions may be absent; the deflection is still called QRS complex. Although atrial repolarization occurs before ventricular depolarization, the latter waveform (i.e. the QRS complex) is of much greater amplitude and atrial repolarization is therefore not seen on the ECG.

QT interval: This is the time between the onset of ventricular depolarization and the end of ventricular repolarization. Clinical studies have demonstrated that the QT interval increases linearly as the RR interval increases. Prolonged QT interval may be associated with delayed ventricular repolarization, which may cause ventricular tachyarrythmias leading to sudden cardiac death

ST interval: This is the time between the end of S-wave and the beginning of T-wave. Significantly elevated or depressed amplitude away from the baseline are often associated with cardiac illness.

T-wave: This is the final deflection, which is the result of ventricular repolarization, whereby the cardiac muscle is prepared for the next cycle of the ECG.

1.3 Cardiovascular Regulation

The role of the ANS is to regulate and coordinate activities to ensure homeostasis so that we can cope with ever-changing demands in our daily lives. Though the relationship between heart rate, cardiac output and blood pressure is not yet clearly known, it is still possible to study how the cardiovascular system responds to physiological and pathological changes.

1.3.1 Autonomous Control

The aim of cardiovascular system is to provide sufficient blood for tissues and especially the vital organs under all conditions. To carry out this demanding task, a variety of different interacting control systems are needed. The heart causes the blood to flow. Although the inherent rhythmicity of the heart is due to a natural pacemaker (SA node), the rhythm is continuously modulated by the input from sympathetic and parasympathetic nerve impulses from the brain to the sinus node. While the sympathetic nerves terminate at the SA node, conduction system, atria, ventricles and coronary vessels, the parasympathetic fibers of the vagus nerve terminate at the SA and AV nodes, atrial and ventricular musculature and coronary vessels. The balance between parasympathetic and sympathetic impulses governs the overall pace of the heart.

1.3.2 Reflexes Controlling Heart Rate

The stimulus response sequences like the thermoregulatory systems; homeostatic control systems etc... are known as reflexes. Although in some reflexes we know the stimulus and/or the response, many reflexes regulating the internal environment occur with out any conscious awareness. Many reflexes in the cardiovascular and central nervous systems simultaneously stimulate the vagal and sympathetic centers. The overall autonomic function is controlled by a central command from the brain. The autonomic nervous system operates as a feedback system, and many reflexes regulate heart rate, which may increase and/or decrease the sympathetic or parasympathetic activity.

1.4 Abnormalities in the ECG Rhythms

HRV analysis is based on the study of the SA node activity as the source of repetitive impulses that generate normal heartbeats. The normal activity of the SA node is assumed to be regulated, amongst others, by the autonomic nervous systems. In addition to the SA

node, other latent pacemakers exist through the heart. Normally, regular conduction of the electrical impulse from the SA node and the refractory period of the cells reject any other electrical source except from the SA node. However, some of the additional pacemakers may, in certain cases, interpose additional electrical impulses that generate ectopic beats, which are usually manifested as a premature beat followed by a longer than normal RR interval up to the next normal beat due to a compensatory delay. Therefore, a sharp transient appears in the HRV signal. Ectopic beats can appear in ECGs recorded from normal subjects as well as from the subjects with cardiac diseases.

1.5 Pattern Classification using Neural Network (NN)

Neural networks are used to solve problems in which the complete formulation is unknown. That is, no causal model or mathematical representation exists, usually because the problem itself is not completely understood. The neural network uses data to derive patterns that are relevant in differentiating the groups. Neural network models fall in to the category of soft computing, in that solutions are found to approximate problems rather than approximating solutions of exact formulations.

The main objective of neural network for pattern classification is to classify datasets in to their respective classes. This is done by finding the optimum class separator. There are different learning algorithms to estimate the class separator. They are mainly divided in to two main streams: those that are used for linearly separable sets and those that are used for classification of nonlinearly separable sets. Selection of an appropriate algorithm depends on the nature of the problem and the type of the data involved. Though many learning algorithms may produce results, there is no one answer in defining classification functions. Some factors to consider while selecting a learning algorithm are: Convergence properties, Stability, Accuracy in classifying new cases and ability to interpret results. The classification problem involves the following basic procedures:

i) Feature Extraction

The first objective of pattern classification system is to determine which parameters enabled the expertise in the problem domain to distinguish between classes. These parameters are often called features. Identification of possible features requires domain knowledge relevant to the problem.

ii) Learning

The second objective of a pattern classification system is to find a separator that will divide different classes by placing as many samples in to the correct category as possible. This process of searching for the optimum separator is called learning. In other words, learning is finding out the proper weights between each neuron in the network. The choice of separator depends on the complexity of the function (relationship between classes). The simplest separator is a straight line, which is used only when the functions are linearly separable while complex non-linear functions are separated by hyper surfaces in the ideal hypothesis space.

iii) Generalization

Once the separator is defined using a set of training datasets, the final objective of pattern classification is to use the separator to classify new cases. This is called generalization. A well-trained network would give good generalization accuracy. In this way, the pattern classification system is used as a decision aid for real world applications. Normally, the performance of the network is tested at this stage with different measures like accuracy, sensitivity, specificity and positive predictive value.

1.6 Methodology

The methodologies implemented in this thesis are i) AR (Autoregressive) modeling of HRV for estimating the power spectral density of the R-R time series and extracting its different spectral and temporal measures (features) and ii) feed-forward neural network with backpropagation learning algorithm for classification of diseases based on the features extracted from i).

1.7 Conclusion

In this chapter: sources of HRV, configurations of ECG recording for HRV analysis, factors affecting HRV, and limitation of HRV for clinical application, have been discussed. Also, fundamentals of NN and their importance to robust the clinical importance of HRV were highlighted. Finally, the methodologies to be followed through out this paper have been pointed.

CHAPTER # 2

HEART RATE VARIABILITY

2.1 Introduction

The awareness that the physiologic cardiac rhythm is not entirely regular has been widely appreciated for many years. However, until two decades ago, heart rhythm variations were virtually ignored in practical cardiology and it was generally believed that any irregularity of cardiac function is a pathological phenomenon. This was mainly the result of clinical experience with atrial fibrillation and ventricular premature beats both of which indicate impaired intracardiac conduction and/or regulatory mechanisms and are negative prognostic factors in many cardiac diseases. Therefore, the observations that an absolutely regular sinus rhythm is also a negative prognostic factor came as a surprise to clinical cardiologists. However, in the last two decades, the interest and the research in heart rate variability as a measure of autonomic tone has grown exponentially and along with it the need for standards of heart rate variability measures, their clinical interpretation arises. This problem was addressed in 1996 by the joint operation of European Society of Cardiology and the North American Society for Pacing and Electrophysiology. These days, the effects of different activities like smoking, alcoholism, exercise and pathological conditions like diabetes, epilepsy, hypertension, on heart rate variability draws a huge clinical and research interest[6]

2.2 Origin of Heart Rate

Unlike most other muscle innervations, excitation of the heart doesn't proceed directly from the central nervous system but is initiated in the sinoatrial(SA) node, or pacemaker, a special group of excitable cells. The SA node, situated at the top of the right atria, creates an impulse of electrical excitation that spreads across the left and right atria ; the right atrium receives the earlier excitation because of its proximity to the SA node. This excitation causes the atria to contract, and a short time later, stimulates the atrioventricular(AV) node. The activated AV node, after a brief delay, initiates an

impulse into the ventricles, through the bundle of His, and in to the bundle branches that connect to the Purkinje fibers in the myocardium. The contraction resulting in the myocardium supplies the force to pump the blood into the circulatory systems. This process repeats for life long. The process from the firing of impulses to the contraction of the ventricles is called one complete cardiac cycle. The time its takes for one cardiac cycle is called Heart Rate. However, in practice, the heart rate is calculated as the time interval between consecutive ventricular depolarizations (or R-R intervals in ECG).

2.3 Ectopic Beats

The conclusion of RR interval analysis methods (both time domain and frequency domain) would be misleading, if ectopic beats, which are reflected on RR series as a very small interval followed by exceptionally big interval, are not taken care of.

2.3.1 Sources of ectopic beats

The sinoatrial (SA) node is the source of repetitive electrical impulses, which generate the electrocardiogram (ECG) waveforms. In addition to the primary pacemaker in the sinus node, latent pace makers exist throughout the heart, particularly in the atrioventricular (AV) node and the His-Purkinje system. These latent pacemakers may interpose additional electrical impulses, which appear as ectopic beats. Therefore, disturbances due to either abnormal impulse formation or impaired conductiongives rise to extra electrical wavelets or non-sinus beats, disrupting normal sinus-conducted RR interval variability. Since modulatory signals from the brain to the heart are embedded as variations to beat-to-beat intervals of sinus rhythm, a locally generated aberrant beat will appear to temporarily disrupt neurocardiac modulation. The ectopic beat, often premature, produces a short beat-to-beat interval followed by a compensatory delay and hence, a longer than normal interval. Therefore a sharp transient appears in the heart rate variability (HRV) signal. Ectopic beats can appear in ECGs recorded from both normal subjects and heart disease patients and, therefore, represent a major source of error when analyzing HRV data in both the time and frequency domain.

The issue of ectopic beats is dealt usually after QRS detection has been performed on the analog ECG signal and before the RR interval time series undergoes HRV computation. Computation of either short –or long-term HRV indices is adversely affected by the presence of even a small number of ectopic beats.

2.3.2 Effect of Ectopic Beats on HRV Analysis

Whether dealing with time -domain or frequency-domain analysis, ectopic or missing beats introduce significant errors into the HRV statistics. For a patient with a 0.2% incidence of ectopy (about 7 ectopic beats/hour) with a 50% overlap of HRV data, only 30% of the data is useful. During time-domain analysis of HRV, data is passed through various filters, which incorporate only normal sinus beats. Additional logical conditions are imposed on the data to eliminate beats, which appear before and after an ectopic beat.

Figure 2.1 shows the effect of ectopic beats on the spectrum analysis of HRV:

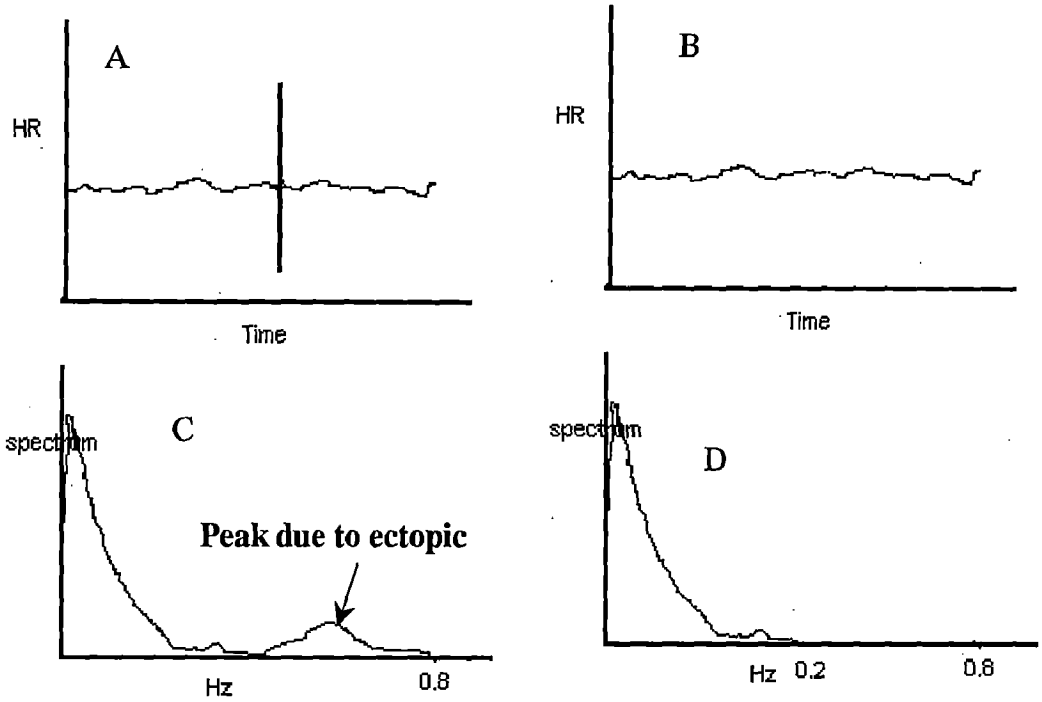


Figure 2.1 A single premature beat causes an abrupt increase followed by a decrease in heart rate. A:frequency content of the impulse-like 'artifact' is broad; C: is eliminated ; D: by removing the spike in time series B:

For power spectral analysis, HRV signal may be corrected by using either of the two methods:

1. If the HRV time series contains occasional ectopic or anomalous beats, one can interpolate around the extra beat(s) and then perform the subsequent power spectral analysis

2. If there are frequent ectopics, it is better to eliminate the segments of the HRV signal that contain the ectopics.

The first procedure assumes that the beat-to-beat control exerted by the autonomic nervous system didn't play a significant role in the generation of ectopics and hence ignores such effects. The second procedure simply reduces the number of useful data segments for estimation of HRV indices.

2.3.3 Ectopic Beat Correction Algorithm

Though there are different algorithms, which correct HRV signals for ectopics beats generated by errors in detection, we used spline interpolation technique, as it gives better estimate for HRV signal because it introduces less high-frequency noise in to the computation process[6].

Linear spline interpolation is used to compute the value of the heart rate at any instant where an ectopic beat appears. If $x(n)$ is the HRV signal for which an ectopic beat exists at instant ,n, then estimate:

$x(n)=x(n0)+(x(n1)-x(n0))*(n-n0)/(n1-n0)$

Where $x(n0)$ is the value of the signal at instant immediately prior to n and $x(n1)$ is the value of HR at an instant subsequent to n. The algorithm implemented is shown below

1. Read in the RR interval data from a file [x]
2. Initialize i=2,where i is the counter of the RR interval series
3. Compare x (i) with x (i-1)
4. While x (i) <1.32*x (i-1) and x(i)>0.245*x(i-1) go to step 5 else go to step 6
5. Increment i and go to step 3
6. Apply linear interpolation and estimate x (i) using x (i-1) and x (i+1)
7. Substitute original x (i) by the estimated x (i)
8. Increment i and go to step 3
9. Repeat step 3 to step 8 until the last data point is reached

Figure2.2 Ectopic beat correction algorithm

After implementing this algorithm, we made a visual inspection and manually adjusted the still remaining ectopic beats by substituting the ectopic beat using three consecutive beats before the ectopic beat as:

$x(n)=(x(n-1)+x(n-2)+x(n-3))/3$

The detection of ectopic beat is done by using Cheung's recommendation that the maximum expected increase over a single RR interval and the maximum expected decrease over a single RR interval are less than 32.5% and 24% respectively of the previous interval [6].

2.4 Vagal Effects

The vagal nerves innervate the sinoatrial node, the AV conducting pathways, and the atrial muscle. However, whether the vagi provide an efferent control of ventricular muscle or not, is not yet resolved. In some animals, like toad and duck, a full efferent vagal innervation of ventricles is observed.

Stimulation of either vagus nerve slows the heart, although the right nerve is said to have a greater effect than the left. In addition to its effect on the sinoatrial node, vagal activity also slows the AV conduction. This effect seems to be greater in response to the left rather than right vagal stimulation and high frequencies of left vagal activity are likely to result in complete AV conduction block.

The most obvious effect of vagal stimulation is to slow, or even to stop the heart. The latency of the response of the sinus node is very short, and the effect of a single vagal impulse depends on the phase of the cardiac cycle at which it is applied. After a single stimulus, the maximum response has been reported to occur within only 400milliseconds. Thus, vagal stimulation results in a peak response either in the first or second beat after its onset. After cessation of vagal stimulation, HR rapidly returns to its previous level. The speed of recovery is a little slower than that of the onset, but HR is usually restored in less than 5seconds.

Although the high levels of vagal activity slow the heart, there may be circumstances in which small increases in frequency may actually accelerate it. This is because at vagal frequencies close to that of the heart, the cardiac pacemaker cell tends to become entrained by the vagal impulses and small increase in vagal frequency may cause the heart rate to increase.

The slowing of HR to vagal stimulation increases with the frequency of stimulation. Most of the change in HR is obtained at frequencies of up to 5Hz, and the relationship between the change in HR and stimulus frequency can be fitted to hyperbola. The gross non-linearity of this relationship suggests that HR may not be the appropriate

variable to measure when quantifying the autonomic effects. If pulse-interval, which is a function of the reciprocal of HR, is plotted against stimulus frequency, the relationship then does become linear.

2.5 Sympathetic Effects

Sympathetic postganglionic fibers innervate the entire heart, including the SA node, the AV conducting pathways, atrial and ventricular myocardium. Increased activity in the sympathetic nerves results in increases in both HR and the force of contraction. In addition, the rate of conduction through the heart of cardiac impulse is increased and the duration contraction shortened.

An increase in sympathetic activity forms the principal method of increasing HR above the intrinsic level generated by the sinuatrial node to the maximum levels achieved. Following the onset of sympathetic stimulation, there is a latent period of up to 5 seconds followed by a progressive increase in HR, which reaches a steady level in 20 to 30 seconds. Note the contrast with the vagal responses, which are almost instantaneous. The relationship between frequency of sympathetic efferent activity and HR, like that for response to vagal activity, is nonlinear. It can be approximately linearized by use of pulse-interval instead of HR, or by plotting stimulus frequency on a semi-logarithmic scale. Studies have shown that there is a greater effect on HR from stimulation of the right sympathetic nerves than the left, particularly at low frequencies of stimulation.

2.6 Sympatho-Vagal interaction

In most circumstances, there is tonic activity in both divisions of the autonomic nervous system, and the net effect on HR represents the balance between the two antagonistic effects. Clearly, at rest the vagal influence is dominant, but with increasing levels of exercise, the vagal activity declines and that of the sympathetic increases. However, although the resulting HR is influenced by the activity in both autonomic divisions, it cannot be computed by simple addition or subtraction of the separate effects. Studies by Levy and Zieske shows that the effects of simultaneous sympathetic and vagal activity are probably equal to the algebraic sum of their independent effects, but only as long as these effects are expressed as pulse interval, which is the variable actually to be controlled by the autonomic nerves, rather than the heart rate.

2.7 Reflexes Influencing Heart Rate

Heart rate, at any instant in time, represents the resultant of many influences on the vagal and sympathetic centers (see Table 2.1 below). Some reflexes may increase HR through a decrease in vagal tone, an increase in sympathetic activity, or both. Others exert the opposite effects. In the intact person or animal, several reflexes are likely to operate simultaneously and, for at least some of these, the interaction may be complex.

Table 2.1. Reflexes influencing Heart Rate

Reflexes Influencing Heart Rate	
Reflexes causing Bradycardia	**Reflexes causing Tachycardia**
Baroreceptors	Atrial receptors
Carotid chemoreceptors	Aortic chemoreceptors
Coronary chemoreflex	Muscle receptors
Lung hyperinflation	Lung inflation

In addition to the above-listed reflexes, almost all parts of the body, when subjected to intense or noxious stimuli, may result in cardiovascular reflexes. However, several regions have been shown to be able to induce reflex cardiovascular effects in response to physiological stimuli. The lungs, including airways, pulmonary circulation and pulmonary artery, are richly innervated. Lung inflation, with moderate pressures, stimulates airways stretch receptors, which are attached to myelinated nerves. This results in a reflex increase in HR. The abdominal viscera are richly supplied with afferent nerves and the activity in these increases in response to venous congestion. The resulting reflex is to increase sympathetic activity to the circulation, leading to hypertension and tachycardia.

Apart from the reflexes, different physiological mechanisms, like breathing influences the heart rate regularly, which is commonly termed as rhythmic sinus arrhythmia (RSA). It is reflected as an increase in vagal tone.

2.8 Standards of HRV measurement

Heart rate variability represents one of the most promising markers of Autonomic activity. The easy derivation of this measure has popularized its use. However, the significance and meaning of the many different measures of HRV are more complex than

generally appreciated and there is a potential for incorrect conclusions. Recognition of this problem led the European Society of Cardiology and the North American Society of Pacing and Electrophysiology to constitute a Task Force charged with the responsibility of developing appropriate standards (measures) of HRV.

2.8.1 Time Domain Measures

Variations in heart rate may be evaluated by a number of methods. Perhaps the simplest to perform are the time domain measures. With these methods either the heart rate at any point in time or the intervals between successive normal complexes are determined. In a continuous electrocardiographic (ECG) record, each QRS complex is detected, and the so-called normal-to-normal (NN) intervals (that is all intervals between adjacent QRS complexes resulting from sinus node depolarizations), or the instantaneous heart rate is determined. Simple time–domain variables that can be calculated include the mean NN interval, the mean heart rate, the difference between the longest and shortest NN interval, the difference between night and day heart rate... etc. Some of the most important time domain measures are briefly discussed:

SDNN (standard deviation of the NN interval): SDNN is the square root of variance. Since variance is mathematically equal to total power of spectral analysis, SDNN reflects all the cyclic components responsible for the variability in the period of recording. Mathematically,

$$SDNN = \sqrt{\frac{\sum_{i=1}^{N}(NN_i - Mean)^2}{N}}$$, where $$Mean = \frac{\sum_{i=1}^{N} NN_i}{N}$$ and N is the number of NN intervals in the record.

RMSSD: The square root of the mean of the sum of the squares of differences between adjacent NN intervals.

$$RMSSD = \sqrt{\frac{\sum_{i=1}^{N-1}(NN_{i+1} - NN_i)^2}{N-1}}$$

pNN50count: the number of interval differences of successive NN intervals greater than 50 ms,

$pNN50count = NN50count/N$ Where NN50count is the number of pairs of adjacent NN intervals differing by more than 50ms in the entire recording

SDSD: Standard deviation of differences between adjacent NN intervals.

$$SDSD = \sqrt{\frac{\sum_{i=1}^{N-1}(ND_i - MeanND)^2}{N-1}} \quad \text{Where } ND_i = NN_{i+1} - NN_i \text{ and } MeanND = \frac{\sum_{i=1}^{N-1} ND_i}{N-1}$$

Some of the measures are used for both long- term (12-24Hr) and short-term (2-5minutes) ECGs, while others are specifically defined for a long-term recording. For example SDANN (Standard deviation of the average of NN intervals in all 5minute segments of the entire recording), SDNN index (the mean of the standard deviations of all NN intervals for all 5minute segments of the entire recording) are some of the indices to address the issue of non-stationarity of the long term recording. It should be noted that in all the above time domain measures, they could be classified into two main groups: measures derived from direct measurement of NN intervals or instantaneous heart rate, and those from the difference between NN intervals. Because some of the time domain measures like SDNN are dependent on the length of the recording, it is inappropriate to compare time domain measures obtained from recordings of different duration.

2.8.2 Frequency Domain Measures

Various spectral methods for the analysis of the tachogram have been applied since the late 1960s. Power spectral density (PSD) analysis provides the basic information of how power (i.e. variance) distributes as a function of frequency. Independent of the method employed, proper mathematical algorithms can obtain only an estimate of the true PSD of the signals. Just like time domain measures the number of useful spectral measures is dependent on the duration of the recording. Three main spectral components are distinguished in a spectrum calculated from short –term recordings (2-5minutes): very low frequency (VLF), low frequency (LF), and high frequency (HF) components. The distribution of the power and the central frequency of

LF and HF are not fixed but may vary in relation to changes in autonomic modulations of the heart period. The physiological explanation of the VLF component is much less defined and the existence of a specific physiological process attribuTable to these heart period changes might even be questioned. The non-harmonic component which does not have coherent properties and which is affected by algorithms of baseline or trend removal is commonly accepted as a major constituent of VLF. Thus VLF assessed from short-term recordings (e.g. ¦5 min) is a dubious measure and is avoided when interpreting the PSD of short-term ECGs. Measurement of VLF, LF and HF power components is usually made in absolute values of power (ms2), but LF and HF may also be measured in normalized units (n.u.) which represent the relative value of each power component in proportion to the total power minus the VLF component. The representation of LF and HF in n.u. emphasizes the controlled and balanced behavior of the two branches of the autonomic nervous system. Moreover, normalization tends to minimize the effect on the values of LF and HF components of the changes in total power. Nevertheless, n.u. should always be quoted with absolute values of LF and HF power in order to describe in total the distribution of power in spectral components. In the long-term analysis, in addition to VLF, LF and HF, ULF (ultra low frequency) component is included. The problem of 'stationarity' is frequently discussed with long-term recordings. If mechanisms responsible for heart period modulations of a certain frequency remain unchanged during the whole period of recording, the corresponding frequency component of HRV may be used as a measure of these modulations. If the modulations are not stable, interpretation of the results of frequency analysis is not well defined. In particular, physiological mechanisms of heart period modulations responsible for LF and HF power components cannot be considered stationary during the 24-h period. Thus, spectral analysis performed in the entire 24-h period as well as spectral results obtained from shorter segments (e.g. 5 min) averaged over the entire 24-h period (the LF and HF results of these two computations are not different) provide averages of the modulations attributable to the LF and HF components. Such averages obscure detailed information about autonomic modulation of RR intervals available in shorter recordings. It should be remembered that the components of HRV provide measurements of the degree of autonomic modulations

rather than of the level of autonomic tone and averages of modulations do not represent an averaged level of tone.

Selected frequency domain measures are shown in Table 2.2 below [1].

Table2.2 Selected frequency domain measures of HRV

Variable	Units	Description	Frequency Range
		Analysis of short -term recording (5min)	
5min total power	ms^2	Variance of NN interval over temporal segment	<=0.5Hz
VLF	ms^2	Power in very low frequency range	<=0.04Hz
LF	ms^2	Power in low frequency range	0.04-0.15Hz
LF norm	n.u	LFpower in n.u.=LF/(Total power-VLF)*100	
HF	ms^2	Power in high frequency range	0.15-0.5Hz
HF norm	n.u	HF power inn.u.=HF/(Total power-VLF)*100	
LF/HF		Sympatho-vagal ratio	
		Analysis of long-term recording (24Hr)	
Total Power	ms^2	Variance of all NN intervals	<=0.5Hz
ULF	ms^2	Power in ultra low frequency range	<=0.003Hz
VLF	ms^2	Power in very low frequency range	0.003-0.04Hz
LF	ms^2	Power in low frequency range	0.04-0.15Hz
HF	ms^2	Power in high frequency range	0.15-0.5Hz

2.9 Approximate correspondence between time-and frequency-domain measurements

When analyzing stationary short-term recordings, more experience and theoretical knowledge exists on the physiological interpretation of the frequency-domain measures compared to the time-domain measures derived from the same recordings. However, many time- and frequency-domain variables measured over the entire 24-h period are strongly correlated with each other [1] (see Table 2.3). These strong correlations exist because of both mathematical and physiological relationships. In addition, the physiological interpretation of the spectral components calculated over 24 h is difficult, for the reasons mentioned (section entitled Long-term recordings). Thus, unless special investigations are performed which use the 24-h HRV signal to extract information other

than the usual frequency components the results of frequency–domain analysis are equivalent to those of time–domain analysis, which is easier to perform.

Table 2.3 Correlation between time-and frequency-domain measures of 24 Hr ECGs

Time domain variables	Approximate frequency domain correlates
SDNN	Total Power
RMSSD	HF
SDSD	HF
NN50count	HF
PNN50count	HF
SDANN	ULF
SDNN index	Mean of 5 minute total power

2.10 Pathological Signs on HRV Indices

Different cardiac and non-cardiac diseases causes the dysfunction of autonomic nervous system, either vagal or sympathetic. These dysfunctions are reflected on the spectral and temporal measures of HRV [10]. There are lots of conflicting ideas on the clinical interpretation of HRV, mainly due to large inter subject variation and many factors like smoking, age, sex, race, alcohols, emotion which further complicate the system are involved on the intact heart rate and heart rate variability. However, still subjects of a particular disease reflect some uniform pattern. For example, diabetic patients generally show a reduced HRV than normal subjects. In hypertension patients, LF power is higher than normal subjects. And epilepsy patients are associated with higher HF power than normal subjects. Though, the relationship between HRV measures and a particular disease is not quantitatively defined, by incorporating artificial intelligence (neural network, or neuro-fuzzy systems), it can be estimated and HRV can be a useful tool for diagnosis of different diseases. Some of the diseases (conditions), along with their effect on HRV are listed in Table 2.4 below [10].

Table 2.4 Sample lists of diseases (conditions) and their effect on HRV

Disease	PLF	PHF	PVLF/PHF	Ptotal
CHF	Low	-	-	-
Hypertension	High	-	-	-
Epilepsy	-	High	-	-
Asthma	Low	High	-	-
Sleep apnea	High	Low	-	-
Diabetes		-	-	Low
COPD(chronic obstructive pulmonary disease)	Low	-	Low	
Acute Myocardial infraction	-	-	-	Low

Note: Low and High terms are used in comparison with Normal subjects.

2.11 Results and Conclusions

We implemented Cheung's algorithm, and for some data, it detected all the ectopic beats, and for others, it didn't detect all ectopics, so we made visual inspection and implemented manual corrections. In the following discussions, we take only those cases for which the algorithm detects all ectopic beats. Figure 2.3 shows the plot of the RR interval from automatic QRS detection algorithm:

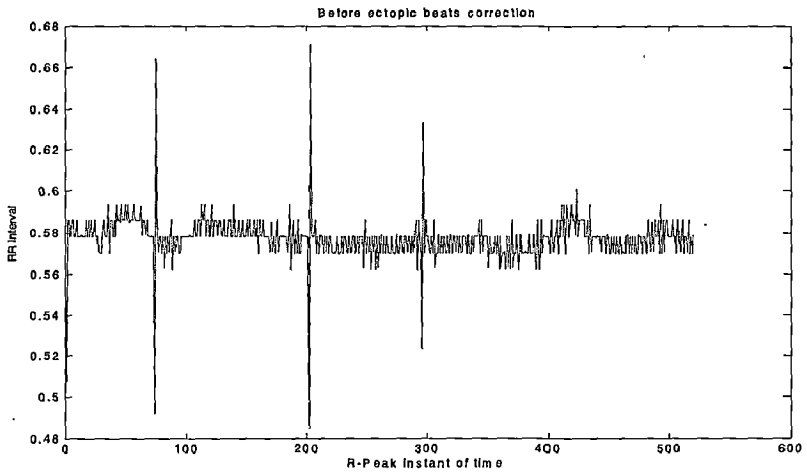


Figure2.3 RR Tachogram before ectopic beat correction algorithm is implemented

As can be seen clearly, there are three ectopic beats, and after the ectopic beat correction algorithm is implemented, the same tachogram looks as shown in Figure 2.4 below:

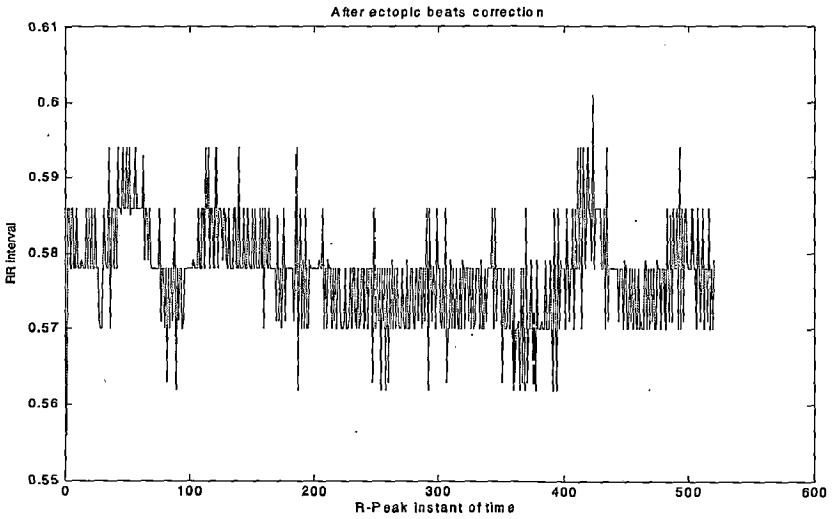


Figure2.4 RR Tachogram after ectopic beat correction algorithm is implemented

After removal of ectopic beats we implemented different time domain measures of HRV, discussed in the previous sections, for the whole one hundred and forty-eight cases under study. The four diseases, CHF, DM, UC, EP and normal cases all are found out to have different ranges of those features. This is an early indication of HRV as a diagnosis tool. Table 2.5 summarizes the results obtained.

Table 2.5 Ranges of temporal features for respective diseases (Mean ± SD)

Parameter	Normal	CHF	DM	EP	UC
SDNN	54.3700 ± 23.130	32.99 ± 23.7900	15.3700 ± 20.03	42.8800 ± 17.200	28.2700 ± 14.19
RMSSD	15.2200 ± 6.6670	15.72 ± 15.3500	3.9100 ± 1.9600	19.7200 ± 10.6900	9.9100 ± 7.1300
pNN50count	0.0110 ± 0.0119	0.0012 ± 0.0016	0.0001 ± 0.0004	0.0227 ± 0.0221	0.0055 ± 0.0114
SDSD	15.2190 ± 6.6670	15.721 ± 15.360	3.9100 ± 1.9600	19.7208 ± 10.6900	9.9100 ± 7.1280

The results show that SDNN for Normal subjects (54.3700 ± 23.130) is the highest where as DM patients have the lowest SDNN (15.3700 ± 20.03). RMSSD for the EP patients (19.7200 ± 10.6900 was found out to be the highest and once again, DM patients were reflected as having the lowest RMSSD (3.9100 ± 1.9600). DM and EP subjects were also reflected on having the highest and the lowest SDSD and pNN50count measures respectively.

Table 2.5 indicates that different diseases leave their signature on different HRV time domain measures.

In this chapter, origin of HRV, its temporal and spectral measures, correlation between them and finally, some of the diseases, which were found out to be prominent on HRV measures, were discussed.

Two algorithms were implemented: one for detection and correction of ectopic beats and the other for computing the time domain features. The results showed that Cheung's algorithm along with visual inspection removes all ectopic beats detection and the simple temporal measures computed for the four diseases and normal cases studied gave good basis for further classification.

CHAPTER #3

AUTOREGRESSIVE (AR) MODELING

3.1 Spectral Analysis Techniques

There are two approaches in frequency domain to deal with HRV analysis: parametric and non-parametric. Non-parametric approach utilizes FFT and periodiograms directly to the signal. However, this approach has a limitation of low frequency resolution in the case of short records and the requirement for windowing to reduce the spectral leakage. Parametric approach however, models the data (time series) and from the frequency response of the model, the spectral density is calculated. This approach gives a better spectral resolution, no spectral leakage and hence no need for windowing.

The widely known parametric methods are based on modeling the data sequence $x(n)$ as the output of linear system characterized by a rational system function of the form

$$H(z) = \frac{B(z)}{A(z)} = \frac{\sum_{k=0}^{q} b_k z^{-k}}{1 + \sum_{k=1}^{p} a_k z^{-k}} \qquad \text{----------(3.1)}$$

The corresponding difference equation is:

$$x(n) = -\sum_{k=1}^{p} a_k x(n-k) + \sum_{k=0}^{q} b_k w(n-k) \qquad \text{----------(3.2)}$$

where $w(n)$ is the input sequence to the system and the observed data, $x(n)$, represents the output sequence.

In power spectrum estimation, the input sequence is not observable. However, if the observed data are characterized as a stationary random process, then the input sequence is also assumed to be a stationary random process. In such a case the power density spectrum of the data is

$$p_{xx}(f) = |H(f)|^2 \Gamma_{ww}(f) \quad \text{----------(3.3)}$$

where $\Gamma_{ww}(f)$ is the power density spectrum of the input sequence and $|H(f)|$ is the frequency response of the model.

Since the objective is to estimate the power density spectrum $p_{xx}(f)$, it is convenient to assume that the input sequence $w(n)$ is a zero-mean white noise sequence with autocorrelation

$$\gamma_{ww}(m) = \sigma_w^2 \delta(m)$$

where σ_w^2 is the variance. Then the power spectrum of the observed data is simply

$$p_{xx}(f) = \sigma_w^2 |H(f)|^2 = \sigma_w^2 \frac{|B(f)|^2}{|A(f)|^2} \quad \text{----------(3.4)}$$

Note that the random process $x(n)$ generated by the pole-zero model in equation 3.1 and 3.2 is called an **autoregressive –moving average (ARMA)** process of order (p,q). If q=0 and b=1, the resulting system model has a system function $H(z) = 1/A(z)$ and it's output $x(n)$ is called an **autoregressive (AR)** process of order p. The third possible model is obtained by using $A(z)=1$, so that $H(z) = B(z)$. Its output $x(n)$ is called a **moving average (MA)** process of order q.

Since the estimation of the AR parameters results in linear equations (would be seen later), AR models are employed for the analysis of HRV in place of ARMA or MA. It is also known from Wold decomposition theorem that any stationary ARMA or MA process of finite variance can be represented as a unique AR model of appropriate order. Hence from now onwards the analysis of AR modeling will be discussed in detail.

3.2 Autoregressive Spectrum Estimation

In this method the digitized signal is modeled as an autoregressive (AR) time series plus a white noise error term. The spectrum is then obtained from the AR model parameters and the variance of the error term. The model parametersare found by solving a set of linear equations obtained by minimizing the mean squared error term (the white noise power) over all the data. An important consideration is the choice of the number of terms in the AR model. That is its order. If the order is too low the power density

estimate will be excessively smoothed, so some peaks may be obscured. If the order is too high, spurious peaks may be introduced. Hence it is important to determine the appropriate model order for each set of data. The design of AR model generally involves the following procedures:

1. Autoregressive model definition
2. Power spectrum density of AR series
3. Computation of model parameters-Yule-Walker equations
4. Model order selection

3.2.1 Autoregressive Model Definition

In an AR model of a time series the current value of the series, x(n) , is expressed as a linear function of previous values plus an error term, e(n),thus:

$$x(n) = -a(1)x(n-1) - a(2)x(n-2) - ... - a(k)x(n-k) - ... - a(p)x(n-p) + e(n) \text{---(3.5)}$$

This equation incorporates p previous terms and represents a model of order p. It is more compactly written as

$$x(n) = -\sum_{k=1}^{p} a(k)x(n-k) + e(n) = -\sum_{k=1}^{p} a(k)z^{-k}x(n) + e(n) \text{ ----------(3.6)}$$

where z^{-k} is the back-shift operator which denotes a delay of k sampling intervals. Rewriting equation 3.6:

$$x(n)/e(n) = 1/(1 + \sum_{k=1}^{p} a(k)z^{-k}) \text{ ----------(3.7)}$$

Here, H(z) is interpretable as the z-transform of all- pole IIR digital filter with coefficients ,a(k). This filter is called an autoregressive (AR) filter.

From equation 3.7 x(n) may be regarded as the outputs of this filter caused by the random inputs e(n). e(n) represents the error between the value predicted by the model x'(n) , and the true datum value ,x(n). e(n) is usually assumed to have the properties of white noise, i.e. , it is assumed to have a uniform power density spectrum. Thus x(n) may be regarded as having been generated by the AR filter from a white noise source. The frequency response of the filter H(f) ,is obtained by substituting $z = e^{jwT}$ in eqn.7 , where w is the angular frequency and T is the sampling period. Hence,

$$H(f) = \frac{1}{1+\sum_{k=1}^{p} a(k)e^{-jkwT}} \quad \text{----------(3.8)}$$

3.2.2 Power Spectrum Density of AR Series

The power spectrum density, $p_x(f)$, of the AR series x(n), which is our ultimate objective of the analysis ,is related to the spectrum density of the white noise error signal , $p_e(f)$, which is its variance $\delta_e^2(n)$, by

$$p_x(f) = /H(f)/^2 p_e(f) = \delta_e^2(n)/(1+\sum_{k=1}^{p} a(k)e^{-jkwT})^2 \quad \text{----------(3.9)}$$

Note that the variance of the noise is the mean square value, which will be denoted by E in the next sections. Once the model parameters are derived, E can be derived from those parameters and hence the power spectrum density can be found.

3.2.3 Computation of Optimum Model Parameters

The optimum model parameters will be those which minimize the errors, e(n) , for each sampled point, x(n). i.e.

$$e(n) = x(n) + \sum_{k=1}^{p} a(k)x(n-k) \quad \text{----------(3.10)}$$

We need to measure the total error over all samples, N(1<=n<=N). The mean square error is used to avoid cancellation of positive and negative errors, which may lead to wrong conclusion.

The mean square error is given by:

$$E = \frac{1}{N}\sum_{n=1}^{N} e^2 = \frac{1}{N}\sum_{n=1}^{N}(x(n) + \sum_{k=1}^{p} a(k)x(n-k))^2 \quad \text{----------(3.11)}$$

The requirement is to minimize error defined in equation 3.11. This is achieved by setting the partial derivative of E to the each parameter to zero.

$$\partial E / \partial a(k) = \frac{2}{N}(x(n) + \sum_{k=1}^{p} a(k)x(n-k))\partial / \partial a(k)\sum_{k=1}^{p} a(k)x(n-k) = 0 \quad \text{----------(3.12)}$$

for 1<=k<=p

$$\frac{\partial}{\partial a(k)}\sum_{k=1}^{p} a(k)x(n-k) = x(n-k)$$

Therefore, equation 3.12 is reduced to

$$\partial E / \partial a(k) = \frac{2}{N}\sum_{n=1}^{N}(x(n) + \sum_{k=1}^{p} a(k)x(n-k))x(n-k) = 0 \text{ ----------(3.13)}$$

giving for the k^{th} parameter:

$$\frac{1}{N}\sum_{n=1}^{N}(\sum_{k=1}^{p} a(k)x(n-k)x(n-k)) = \frac{-1}{N}\sum_{n=1}^{N} x(k)x(n-k) \text{ ----------(3.14)}$$

The left-hand side of equation 3.14 can be expanded for each value of k and it will give, for example, for k=1,

$$R_{xx}(0)a(1) + R_{xx}(1)a(2) + ... + R_{xx}(k)a(k) + ...R_{xx}(p-1)a(p) = -R_{xx}(1) \text{ --------(3.15)}$$

where $R_{xx}(i)$ is the sum of i-lag autocorrelation of the series x(n).

For each value of k, 1<=k<=p, a similar equation can be written. These equations may be written in matrix form as

$$\begin{bmatrix} R_{xx}(0) & R_{xx}(1) & \dots & R_{xx}(p-1) \\ R_{xx}(1) & R_{xx}(0) & \dots & R_{xx}(p-2) \\ R_{xx}(p-1) & R_{xx}(p-2) & \dots & R_{xx}(0) \end{bmatrix} \begin{bmatrix} a(1) \\ a(2) \\ a(p) \end{bmatrix} = - \begin{bmatrix} R_{xx}(1) \\ R_{xx}(2) \\ R_{xx}(p) \end{bmatrix}$$

----------(3.16)

This is a P*P matrix with P equations and p unknown optimal parameters(a(k)s). Hence it is solvable. Hence, by combining equation. 3.11 and equation 3.12 the power spectral density as defined in equation 3.13 can be found.

Once the autocorrelations are evaluated in the process of determining optimum parameters, it will be computationally efficient to take advantage of them than solving equation.3.15 as it is for mean square error calculation as follows:

Expanding equation 3.15,

$$E = \frac{1}{N}\sum_{n=1}^{N}\left\{x(n)+\sum_{k=1}^{p}a(k)x(n-k)\right\}\left\{(x(n)+\sum_{k=1}^{p}a(k)x(n-k))\right\}$$

$$=\frac{1}{N}\sum_{n=1}^{N}\left[\left\{x(n)+\sum_{k=1}^{p}a(k)x(n-k)\right\}x(n)+\left\{(x(n)+\sum_{k=1}^{p}a(k)x(n-k))\right\}\sum_{k=1}^{p}a(k)x(n-k)\right]$$

----------(3.17)

But for all k values it is seen in equation 3.17 that

$$\frac{1}{N}\sum_{n=1}^{N}(x(n)+\sum_{k=1}^{p}a(k)x(n-k))x(n-k)=0$$

Hence equation 3.17 is reduced to:

$$E = \frac{1}{N}\sum_{n=1}^{N}\left\{x(n)+\sum_{k=1}^{p}a(k)x(n-k)\right\}x(n)$$

$$=\frac{1}{N}\sum_{n=1}^{N}\left\{\sum_{k=1}^{p}a(k)x(n-k)\right\}x(n)+\frac{1}{N}\sum_{n=1}^{N}x^2(n)$$

$$= R_{xx}(0)+\sum_{k=1}^{p}\frac{1}{N}\sum_{n=1}^{N}a(k)x(n-k)$$

And finally,

$$E = R_{xx}(0)+\sum_{k=1}^{p}a(k)R_{xx}(k)$$ ----------(3.18)

Equations 3.14 and the model parameters from equation 3.16 may now be solved (efficiently) to obtain the autoregressive power density spectrum.

Note that the mean square error, E in eqn.11, is computed using the available sampled values, x(n), for n=1 to n=N. Previous or succeeding values of x(n) are effectively set to zero. This is equivalent to windowing the data, and in the case of non-parametric method of spectrum estimation this leads to spectral smearing by side lobes and reduced

resolution. But this is not the case with for the AR method.(Kay 1988). Hence AR methods give improved spectral resolution. But, still there is a room for improvement in terms of frequency resolution. This can be achieved by basing the method only upon the available data (unlike the one shown in equation 11 where 0<n<=N, taking only p<=n<=N). There are different methods all based on this concept. Some of them are the covariance method, modified covariance method, burg method... etc.

3.2.4 Model Order Selection

So far in the preceding sections it has been assumed that the order of the AR model which best fits the data is p. If the selection of p is arbitrary, either of the two cases would happen: i) if the model order is selected too high, it results in spurious peaks and spectral instability. ii) if the order is too low, the spectral peaks would be excessively smoothed and the frequency resolution decreases. To avoid these effects standard order selection criteria is used. The most common types of order selection criteria are developed by Akaike. These are final prediction error, FPE (p) given by

$$FPE(p) = \frac{N+p}{N-p}E(p) \quad \text{----------(3.19)}$$

And the Akaike information criterion, AIC (p) which is

$$AIC(p) = N \ln E(p) + 2p \quad \text{----------(3.20)}$$

And AIC (p) is particularly recommended for short data records, while FPE (p) is for longer data records. In this study, emphasis is given for a five-minute recording of ECG and hence the derived QRS is of shorter length. Hence AIC is used to compute the order. FPE was also implemented and it was observed that there was no difference in their order estimation.

3.2.5 AR Algorithm

The algorithm implemented in this thesis is depicted in figure 3.1 below. The detail of the algorithm as implemented in the program is further shown in the block diagram in figure 3.2.

1. Read in the data file, the sampling frequency and maximum order
2. Set the order to 1 and go to step 3
3. Calculate the AR coefficients
4. Estimate the model using AR coefficients, compute the error, and store it.
5. While order is less than the maximum order, increment the order and go tc step 3 else go to step 6
6. Apply AIC order selection criteria on error array, and select the best order
7. Calculate the power spectrum for the order selected
8. Check out the validity of the model using Anderson's test.
9. Calculate the power spectrum in LF and HF region by integration method

Figure 3.1 AR Modeling algorithm

Here, the algorithm is tested using sinusoidal signal of sampling frequency 50Hz and, it is seen that the algorithm effectively estimates the spectrum of the signal. The results of the above algorithm are presented in the later sections. The block diagram of the algorithm implemented is shown in Figure 3.2

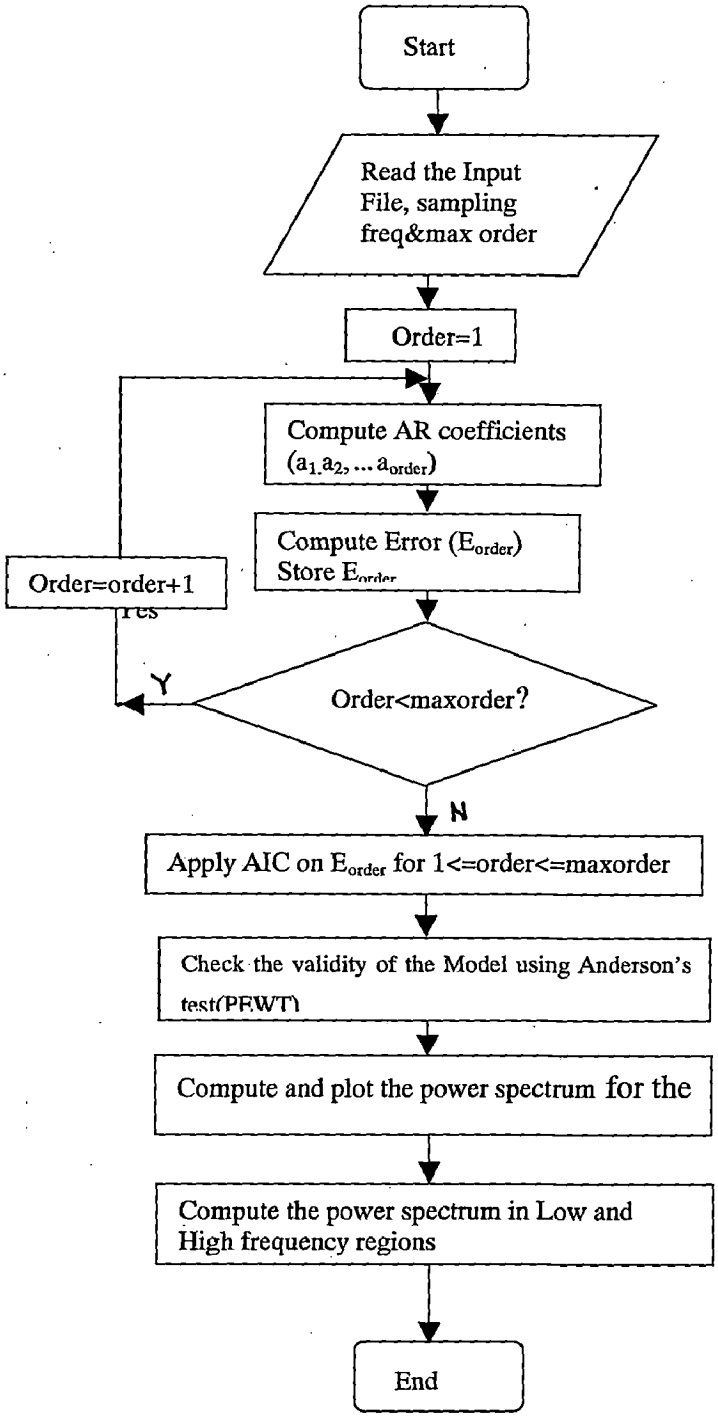


Figure 3.2 Flow chart for AR modeling

3.3 Preprocessors for AR Modeling of HRV

For the afore-mentioned algorithm to be applied to our application, the original recorded ECG should pass through different preprocessing stages, from recording settings to equi-spaced RR intervals generation.

3.3.1 ECG Recording

Short–term ECG of 5minute duration was recorded using BIOPAC machine with ECG100C module at a sampling frequency of 200Hz. Both base-line wander and noise due to power line interference were filtered out using built-in filter circuits. The R-wave is detected using the R-wave detector in the module. The R-wave detector circuitry mainly consist of a 17Hz band pass filter with Q=5, full wave rectifier, and a 10Hz,three pole low pass filter with Q=0.707. Once the ECG is recorded and the corresponding R-peaks are detected, the RR intervals are calculated as:

$RR_i = t_i - t_{i-1}$ ----------(3.21)

3.3.2 Correction of Ectopic Beats

The first preprocessor applied to the RR interval detected from the automatic QRS detection algorithm is the ectopic beat detection and correction algorithm. The algorithm was implemented and results were discussed in the previous chapters. Once the clean RR interval is obtained, the next stage is interpolation and resampling to further prepare our data for AR modeling.

3.3.3 Interpolation and Resampling of Irregularly Sampled R-R Intervals

After ectopic beat correction we have a clean RR time series. However, the RR interval, calculated as $R_i = t_{i+1} - t_i$, where t_i is the time instant of normal R-peak detection, is not yet ready for AR modeling as it needs equi-spaced time series. Consider Figure 3.3 below:

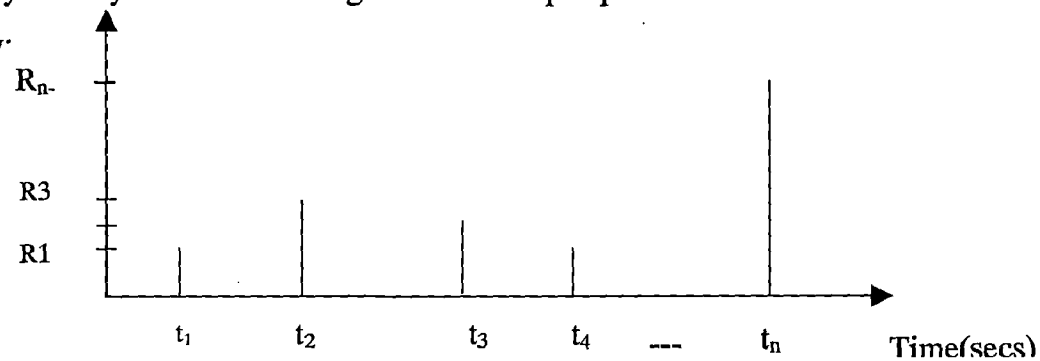


Figure33 Irregularly sampled RR interval before interpolation

As can be seen from the Figure above, the R-peak is sampled randomly at instant of time t_1, $t_2 \ldots t_i$. This randomness causes the variation in the beat-to-beat interval (equation 3.21.). This is actually what is called heart rate variability. But, as mentioned in the

previous sections, to apply AR spectral analysis technique, the time series should be equi-spaced. This conversion from the irregularly sampled RR series to equi-spaced series is achieved through interpolation and resampling algorithm discussed below:

The interpolation technique employed here is linear interpolation based on the assumption that there could be no drastic change between two R-peaks due to autonomic nervous regulation, and if there is, we just simply ignore it because our ultimate purpose is to study the modulation of heart rate only by ANS .The interpolation is shown in Figure 3.4 below.

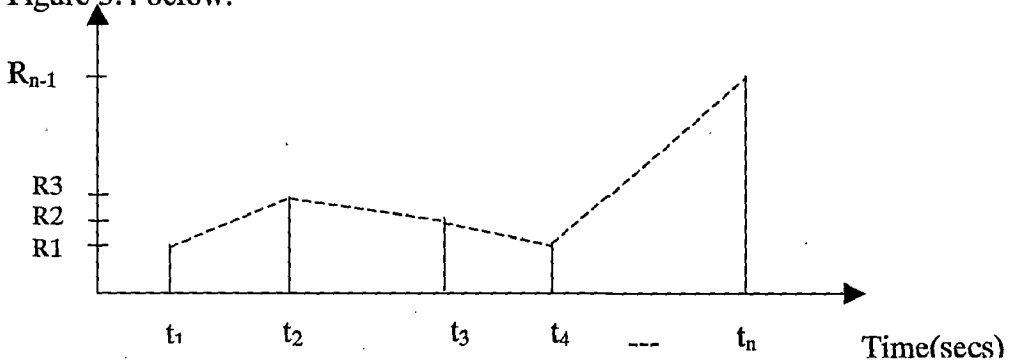


Figure3.4 Interpolation of the irregularly-sampled RR intervals

3.3.3.1 Interpolation Algorithm

A different linear template is used for each RR interval marked by t_i and t_{i+1}. That is different slope and different intercepts. And each template can be sampled at Δt interval where the selection of Δt effectively sets the resampling frequency. If we set $\Delta t = t_{i+1} - t_i$, then there is no resampling.

The general linear function is:

$R = mt + b$

where R is the RR interval and t is the time instant of R-peak detection. The general algorithm is shown in Figure 3.5.

Figure 3.5 Interpolation and resampling algorithm

1. Read in the RR interval data from file to variable R
2. Generate the time instants of each R-peak from R
3. Set the counter i to the first data point.
4. Calculate the slope *m* between two consecutive intervals using

$$m_i = (R_{i+1} - R_i)/(t_{i+1} - t_i)$$

5. Calculate the intercept b between consecutive intervals using

$$b_i = R_{i+1} - \frac{(R_{i+1} - R_i)}{(t_{i+1} - t_i)} t_{i+1}$$

6. For each interval between two R-peak time instants (t_{i+1} and t_i) approximate RR interval at time t. Where t ranges from t_i to t_{i+1} incrementing in Δt interval. $\Delta t = 1/f_s$, where f_s is the resampling frequency

   $R_t = m_i t + b_i$
7. Increment i until it reaches to the point one less than the last data point and go to step 3
8. Save the resampled data and end

Now, after implementing this algorithm, we will have a regularly sampled RR time series with a sampling frequency of $f_s = 1/\Delta t$ as shown in Figure 3.6 below.

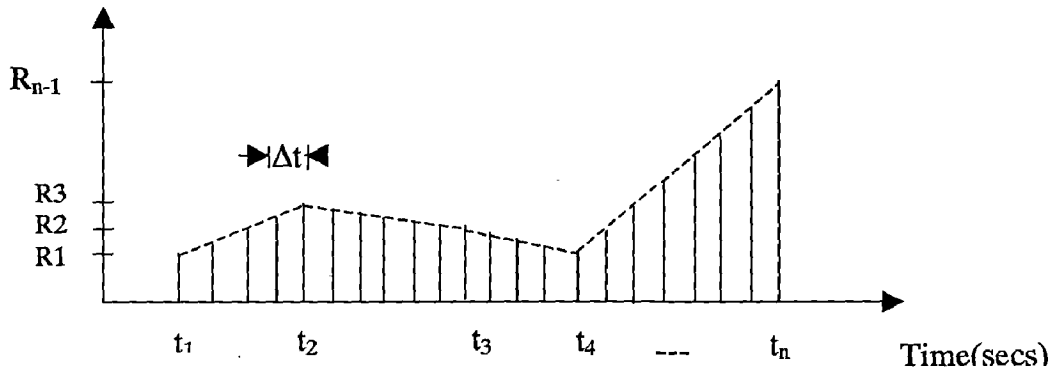


Figure.3.6 Regularly sampled RR interval

Though there are lots of suggestions on the choice of resampling frequency (2Hz, 4Hz, 6Hz, 8Hz...), we set ours to 4Hz. Interpolation means low pass filtering and, the

maximum useful frequency in HRV spectral analysis is 0.5Hz. Using Nyquist's theory, 4Hz would guarantee no signal loss.

3.4 Standard Guidelines

Due to the presence of different approaches in dealing with spectral analysis and the variations in their clinical interpretation, a common standard is provided by the European Society of cardiology (ESC) and the North American Society of Pacing and Electophysiology(NASPE) task force jointly. As per the taskforce recommendations, any parametric algorithm used for HRV analysis should include the following:

1. Spectral features listed in Table 2.2
2. Type of the model used
3. The central frequency of each spectral component (LF and HF)
4. The value of the model order
5. Statistical figures confirming the reliability of the model (Anderson's test)
6. The range of the order should be approximately in the range 8-20 and complying with the reliability test.

3.5 AR Modeling of HRV: Results

The model was first tested using one 50Hz sinusoidal, and one containing sum of 40Hz and 60Hz sinusoidals with a sampling frequency of 120Hz and duration of 1second. As can be seen in the Figure 3.7 below, the algorithm works out as expected giving peak at 50Hz for the first test signal and two peaks at 40 and 60Hz for the second test signal as shown in figure 3.8.

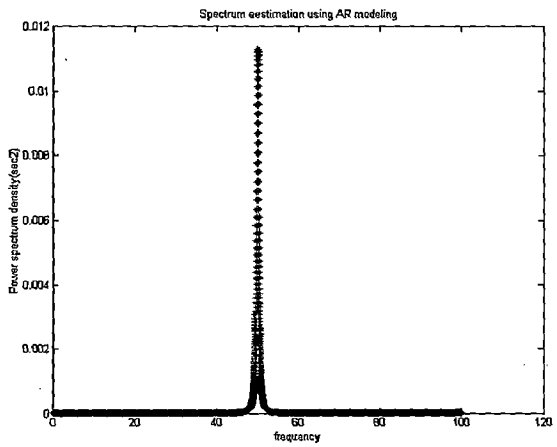


Figure3.7 AR spectrum estimation of 50Hz sinusoidal test signal

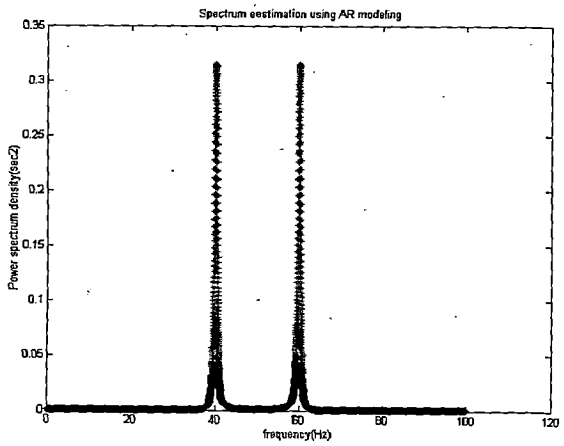


Figure3.8 AR spectrum estimation of the sum of 40Hz and 60Hz sinusoidal signal

And the validity of the model is tested using Anderson's test (Prediction error whiteness Test or autocorrelation test). If the randomness of the input signal assumed is still intact, then autocorrelations of the data computed for any and all time- lag should be near zero. If it is not random, then one or more of the autocorrelations will be significantly non-zero. Mathematically:

Autocorrelation coefficient is calculated as:

$$R_h = C_h / C_0 \quad \text{----------} \quad (3.22)$$

where C_h is the autocovariance function

$$C_h = (1/N)\sum_{t=1}^{N-h}(Y_t - Y_{Mean})(Y_{t+h} - Y_{Mean}) \quad \text{----------} \quad (3.23)$$

And C_0 is the variance function

$$\frac{C_0 = \sum_{t=1}^{N}(Y_t - Y_{Mean})^2}{N} \quad \text{----------} \quad (3.24)$$

where: h is the time lag, Y is the RR time series, N is the length of the RR time series , Y_{t+h} is the h time-lagged RR series and Y_{Mean} is the mean of the RR series.

As can be seen from the Figure3.10 below, there is no strong correlation between the signals with its delayed equivalent, as expected. Once the test is made on the known signals, the model was applied to the equi-spaced RR interval for subjects, whose ECGs are recorded in our laboratory using BIOPAC 's ECG100C module with a sampling

frequency of 200Hz. Some of the results are shown below. The model was also tested for patients with diabetes, Congestive heart failure, Ulcerative colitis and controlled epilepsy obtained from AIIMS (All Indian Institute of Medical Science) and physionet.org. Based on the estimation of features, it was found out that the model was in agreement with the theoretical expectations. For example, in diabetes patients, HRV total power is lower than the normal subjects, and this is confirmed by the model estimation.

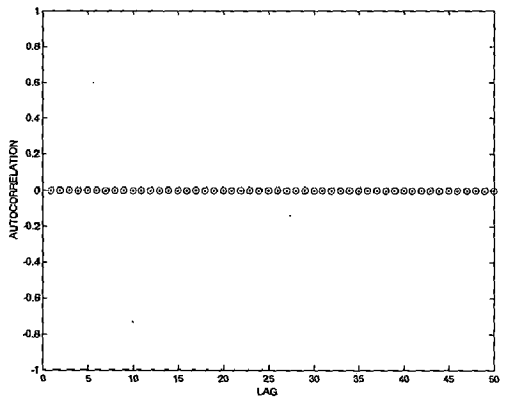
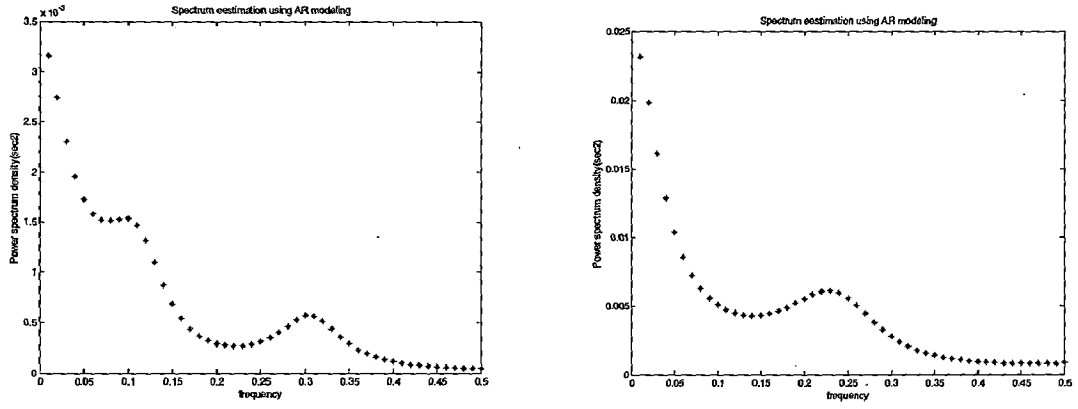


Figure 3.9 Anderson's test for sinusoidal test signal

Here are some of the sample estimates for normal young subjects (21-30Yrs of age).



a) *b)*

Figure3.10 AR spectral estimations of NORMAL subjects

And Anderson's test confirms that the randomness is still intact as shown in figure 3.11

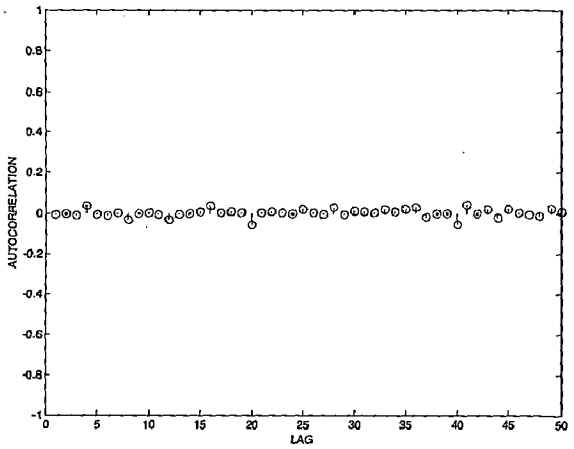
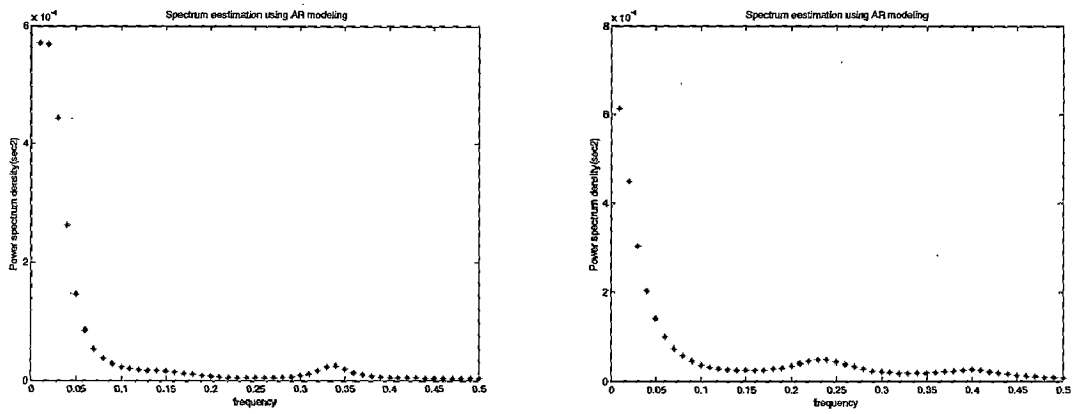


Fig 3.11 Anderson Test for NORMAL HRV signal for figure3.10 a

Different diseases have different signatures on the autonomic nervous system. Some increase either vagal or sympathetic activity or both while others impair both sympathetic and vagal activities. For instance, diabetes generally causes autonomic dysfunction as is reflected on the exceptionally low total HRV power. The algorithm was tested on the data obtained from AIIMS of diabetes patients with , the instance of which is shown below in Figure 3.12. The HRV power is very low for DM patients.



a) *b)*

Figure 3.12 AR estimate of DIABETES patients from AIIMS

The spectral and temporal measures obtained from the model for the two cases (i.e. Normal and Diabetic patients) reflect an instance of pathological signatures on HRV. The simulation obtained from 25 Normal and 30 diabetic patients, obtained from AIIMS (All Indian Institute of Medical Science) is listed in form of Table 3.1 and Table 3.2.

Table3.1: Computed HRV measures for NORMAL subjects

Parameters	Units	Mean	Std
Phf	Sec^2	0.0002	0.0003
Plf	Sec^2	0.0005	0.0003
Pvlf	Sec^2	0.0006	0.0006
Ptot	Sec^2	0.0013	0.0009
Plf/phf	-	3.09	1.558
Fcentlf	Hz	0.0542	0.0153
Fcenthf	Hz	0.1587	0.0300
Plfnorm	n.u	71.74	11.3461
Phfnorm	n.u	28.26	11.3447
SDNN	msec	52.0725	21.1371
SDSD	msec	16.5042	7.4271
PNN50count	-	0.0133	0.0134

Table 3.2 Computed HRV measures for DIABTES patients

Parameters	Units	Mean	STD
Phf	Sec^2	0.0000	0.0000
Plf	Sec^2	0.0000	0.0000
Pvlf	Sec^2	0.0000	0.0001
Ptot	Sec^2	0.0001	0.0001
Plf/phf	-	2.1750	1.2468
Fcentlf	Hz	0.00523	0.0128
Fcenthf	Hz	0.2603	0.1107
Plfnorm	n.u	63.32	15.3968
Phfnorm	n.u	36.69	15.3968
SDNN	msec	15.3733	20.0255
SDSD	msec	3.9057	1.9555
PNN50count	-	0.0001	0.0004

It can be clearly seen that the overall HRV power is highly reduced (0.0001) for Diabetic patients as compared to Normal subjects (0.0013). And all the time domain parasympathetic measures of HRV (SDNN, SDSD, PNN50count), and Phf in frequency domain, are highly reduced for diabetic patients.

The same analysis is made for UC patients, and some of the results are plotted on Figure 3.13.

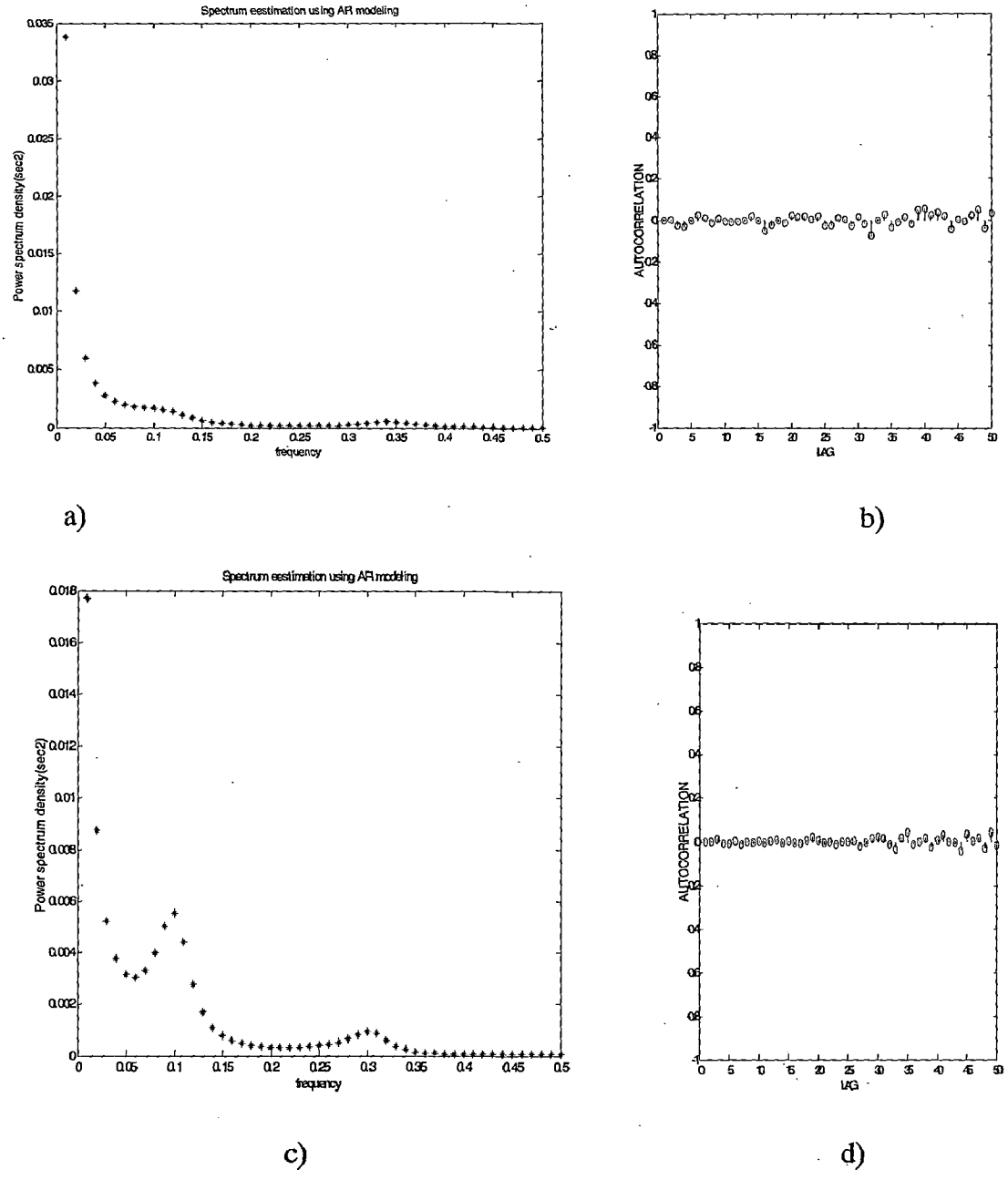


Figure 3.13 AR spectrum estimation of Ulcerative colitis subjects from AIIMS (a, and c) and their corresponding validity check using Anderson's test

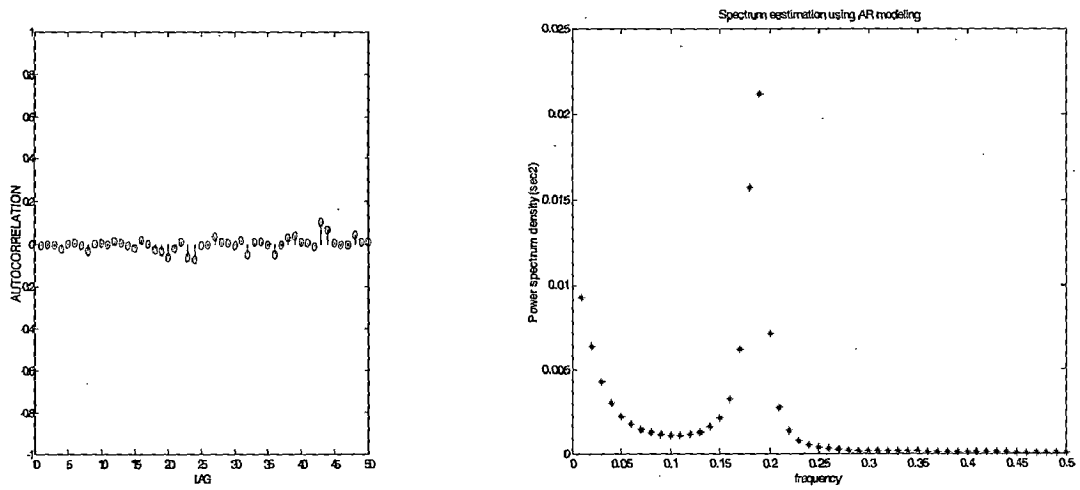
The same process were implemented for twenty three UC patients and their HRV measures were summarized in table 3.3

Table 3.3 Computed HRV measures for UC patients

Parameters	Units	Mean	Std
Phf	Sec^2	0.0001	0.0001
Plf	Sec^2	0.0001	0.0001
Ptot	Sec^2	0.0004	0.0004
Plf/phf	-	2.6800	2.1100
Fcenthf	Hz	0.2200	0.0720
Plfnorm	n.u	66.300	13.750
Phfnorm	n.u	33.7000	13.75
SDNN	msec	28.2700	14.19
RMSSD	msec	9.9100	7.1300
PNN50count	-	0.0055	0.0114

It can be seen from table 3.3 that HRV generally decreases compared to the normal subjects. However; the central frequency for high frequency (parasympathetic component) is seen to shift to higher frequency (0.2200± 0.0720) compared to normal cases (0.1560 ± 0.02500).

The same model was used to test twenty EP patients. The power spectrum density for the two cases is shown in Figure 3.14 along with the Anderson's validity test.



a) b)

Figure 3.14 AR spectrum estimation of EP subjects from AIIMS (a) and its corresponding validity check using Anderson's test(b)

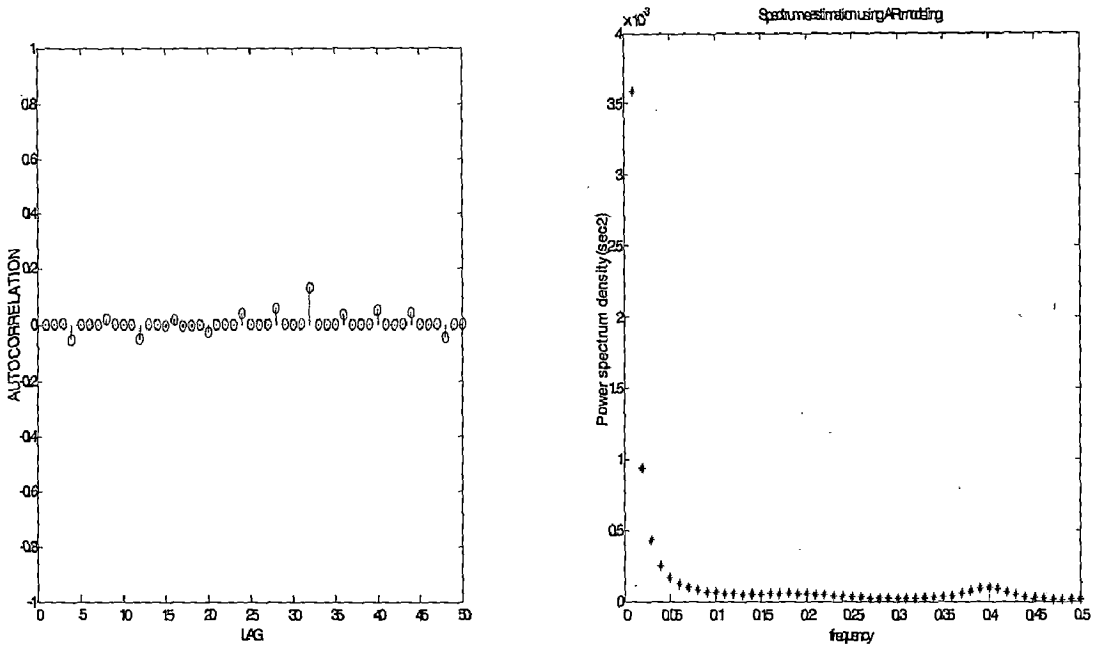
Though the pictorial representation is not telling whether the subject is normal or patient with EP diseases, different measures derived from the model can give a clue as shown in Table 3.4. Figure 3.14 a indicates that there is no strong correlation of any lag, which assures that the assumption of random white noise as an input is still intact.

Table 3.4 Computed HRV measures for EP patients

Parameters	**Units**	**Mean**	**Std**
Phf	Sec^2	0.0004	0.0003
Plf	Sec^2	0.0003	0.0003
Ptot	Sec^2	0.0009	0.0007
Plf/phf	-	1.2100	0.9800
Fcenthf	Hz	0.2400	0.0700
Plfnorm	n.u	47.8700	17.9600
Phfnorm	n.u	52.1200	17.9500
SDNN	msec	42.8800	17.200
RMSSD	msec	19.7200	10.6900
PNN50count	-	0.0227	0.0221

While phf slightly increases for EP patients, all the other spectral parameters decreases. However, in time domain, EP patients have shown an elevated pNN50count and RMSSD. But once again, the total HRV power decreases. HRV being the reflection of complicated feedback system in our body, its decrement can be taken as an early sign of some kind of pathology.

The last disease under our study was CHF. We used twenty-nine cases obtained from physionet.org, and one instance of its spectral estimation is shown in Figure 3.14. Table 3.5 shows the average computed HRV measures of the twenty nine CHF patients.



a) b)

Figure 3.15 *Validity check using Anderson's test(a) and AR spectrum estimation of CHF subject(b) from physionet.org*

Still, the validity is intact, as the maximum correlation being less than 0.2

Table 3.5 Computed HRV measures for CHF patients

Parameters	**Units**	**Mean**	**Std**
Phf	Sec^2	0.0000	0.0000
Plf	Sec^2	0.0000	0.0001
Ptot	Sec^2	0.0002	0.0003
Plf/phf	-	0.715	0.88500
Fcenthf	Hz	0.727	0.86800
Plfnorm	n.u	49.059	19.003
Phfnorm	n.u	50.94	19.0031
SDNN	msec	32.99	23.7900
RMSSD	msec	15.72	15.3500
PNN50count	-	0.0012	0.0016

The HRV generally decreases for CHF patients as can clearly be seen in table 3.5. Generally, for diseased subjects HRV decreases. However, this decrement is highly

emphasized with CHF and DM patients. This may imply that these two diseases cause a dysfunction of both sympathetic and vagal autonomic activities.

3.6 Conclusions

In this chapter, the mathematical background of autoregressive (AR) modeling, preparation of HRV signal for AR modeling were discussed and implemented. Finally, the application of AR modeling for HRV analysis and its credibility using standard algorithmic guidelines have been discussed. Testing of the model using HRV signals (both pathological and normal subjects) was made. It is found out that the model works effectively as a measure of autonomic tone in cardiovascular system with a clean spectral estimation plot. The four pathological cases were studied and we found out that these diseases have different effects on different features of HRV. For example while diabetes causes all HRV features to reduce, one interesting point noted here was that all diseases causes the central frequency of high frequency power to shift to the right [increases].

CHAPTER # 4

NEURAL NETWORK FOR DISEASE CLASSIFICATION

4.1 Introduction

An artificial neural network is an information- processing system that has certain performance characteristics in common with biological neural networks. Artificial neural networks have been developed as generalizations of mathematical models of human cognition or neural biology, based on the assumption that i) Information processing occurs at many simple elements called neurons ii) Signals are passed between neurons over connection links iii) Each connection link has an associated weight, which in a typical neural net, multiplies the signals transmitted iv) Each neuron applies an activation function (usually nonlinear) to its net input, which is sum of weighted input signals , to determine its output signal.

A neural network is characterized by 1) its pattern of connections between the neurons (called its architecture), 2) its method of determining the weights on the connections (called its training, or learning, algorithm), and 3) its activation function.

4.2 Classification Models

The most common application of neural networks in biomedical engineering is in classification problems. Classification models may be based on neural networks that use supervised learning in which data of known classification are used as a training set to develop a decision surface that can be used later to classify new data items. There are numerous supervised learning approaches that differ both in theory and application. Some of them are perceptron, supervised backpropagation, ADALINE, potential functions, and min-max networks. Another type of classification model that uses unsupervised learning techniques relies on data for which the classification of each case is unknown. These methods search for patterns in the data by which each case can be classified and are often referred to as clustering. The data are clustered in to groups that contain similar cases, in

which similarity is determined by one of a variety of measures. Unsupervised learning approaches include Kohnen networks, competitive learning, adaptive resonance theory (ART), and Hebian learning.

Classification networks offer strong techniques for developing decision-making models. From now onwards the focus of this thesis will be particularly on the details on the design of classification networks.

4.3 Design Issues in Classification Models

Unlike other algorithmic solutions, the development of neural networks for a particular problem involves a number of intuitive approaches and experiments. It demands both the knowledge of the problem in hand and the working of the neural networks. Therefore, the following procedure should be followed for using neural network for classification efficiently.

4.3.1 Objective of the Model

If the model is a diagnostic model, the purpose is to find a model that will correctly classify new cases, or to determine which parameters can aid in differentiating among classes, or both? The type of the network affects our ability to obtain the required information

4.3.2 Information Sources

Before settling for a data-driven approach (like neural networks), it is useful to closely examine an application to locate the bulk of the information useful for decision-making, other methodologies (like knowledge-base) available, and determine the amount of the effort that will be required for the full development of the information source. Figure 4.10 below shows the areas that should be addressed before choosing a methodology. If the database exists or can be created with an acceptable amount of additional effort, then the neural network approach is appropriate. If most decision-making information is in the form of expert opinion, then the knowledge-base approach is more appropriate. If a combination of data-derived and expert-derived information is available, a hybrid method should be considered.

The bold arrow shown in Figure 4.10 represents the path followed in this study.

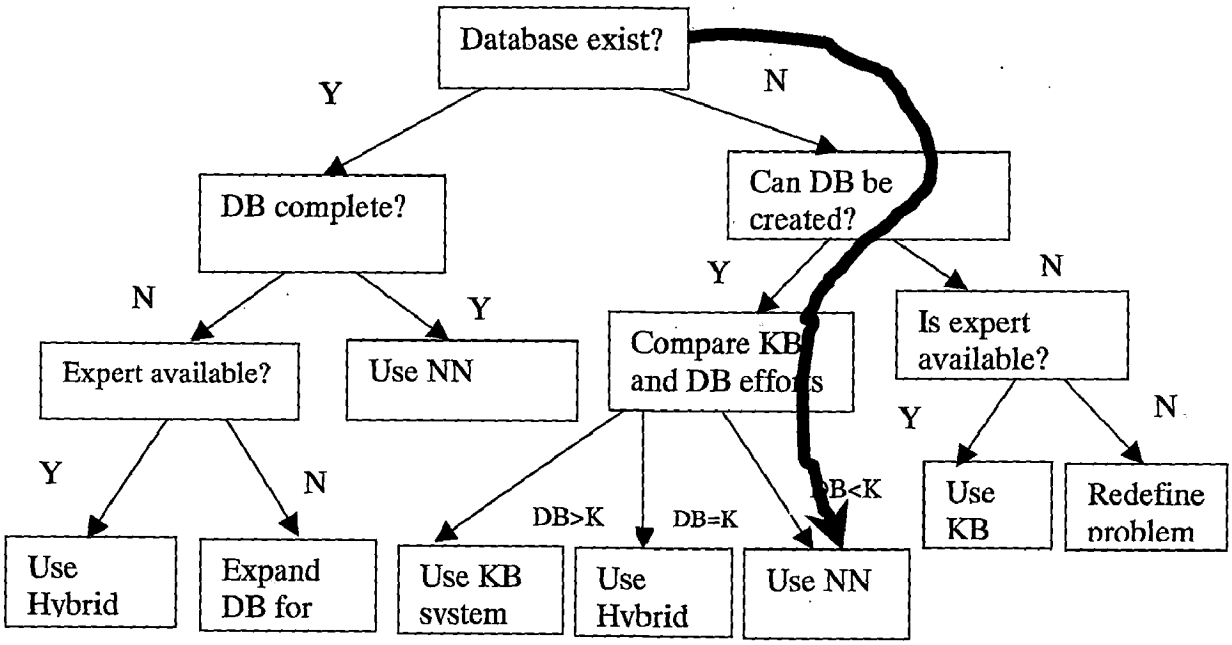


Figure 4.1 methodology selection diagram

4.3.3 Input Data Types

Some neural networks accept only binary input, where as others accept continuous variables as input, or a combination of the two. Decision-making in a number of biomedical applications may utilize the following types of input:

- Binary (y/n, absent/present, 0/1)
- Continuous (blood pressure, heart rate, etc)
- Categorical (stable, improved, diminished... etc.)
- Fuzzy (ranges of test values, partial presence of symptom... etc).

Ideally, the best choice in our case is, fuzzy approach. Because, there are ranges of spectral and temporal features which cannot be defined as a crisp value in any sense. However, selection of a fuzzy membership function, and assigning membership value for ranges of parameters demands expertise in the problem domain, which we don't have[see the methodology path we followed on figure.1]. In addition to that, the variability of our input features due to different factors like age, sex, race, smoking, etc. makes it difficult to have a standard quantitative description. Moreover, for the reason we are going to

mention later, and the continuous nature of our data we chose to have a continuous data type.

4.3.4 Interpretation of Outputs

What type of output do we expect from a classification neural network? The primary output is the assignment of the input vector to the correct classification. However, it may be possible to learn more than this from the process. The weights associated with the input nodes indicate the strength of the contribution of the variable toward the classification decision. There are a number of possibilities, which are often different for supervised and unsupervised learning. We focus here on supervised learning. The three phases of the supervised learning process are training, evaluation, and classification.

i) Training

The objectives of training are:

1. To find a model that correctly classifies all or most of the cases in the training set.
2. To determine which parameters are important in the model
3 To determine the relative importance of each parameter

The first objective is present in virtually all supervised learning approaches. In some cases this may be the only objective. If so, the user is interested only in the result, not in the process that led to the result. If this is the case, the only consideration in selecting an algorithm is its effectiveness in obtaining a reliable separation of the data.

If part of the objective of the training process is to identify the relative contributions of input nodes to the output decision, then more attention is given to the choice algorithm. For fully connected networks, one obtains a matrix of weights that is extremely difficult to interpret. Partially connected networks (like hypernet) provide more direct interpretation of results.

ii) Evaluation

Once training has been completed, the accuracy of the model must be tested on different data set, the test set. Although this is part of the classification phase, the objective is not to classify data, for the proper classification is already known, but to compare the classification obtained by the model to the known classification. The

objective of this phase is to determine the effectiveness of the model, which may be measured in terms of sensitivity, specificity, accuracy, and predictive power

iii) Classification

Use of the model for true classification is seen in the classification of the new data for which the prior classification is unknown. At this point, the user is relying on the accuracy and ability to generalize the network to perform effectively on new cases. Its success in accomplishing accurate classification depends not only on the algorithm but also on the data on which it was trained and tested. In multicategory problems, the objective may be to establish a differential diagnosis list. A case may be classified as belonging to more than one category, which can be accomplished by the following:

1. If the network has multiple output nodes, more than one may fire for a particular case.
2. If the problem is formulated as c problems where each problem is to determine membership (e.g. absence or presence of disease), membership may be found to hold in more than one sub case.

All multiple results would then be considered as possible outcomes. Fuzzy methods may carry on from this point providing additional information for differential diagnosis.

4.4 Network Architecture

Architecture of a network is defined by the number of input nodes, number of hidden nodes, number of hidden layers, number of output nodes and the connection between layers. Appropriate choice of architecture decides on the learning capability and the speed of learning (convergence).

The choice of network architecture varies depending on the application, and the best architecture is usually achieved by experiment or trial and error. However, as a starting point, the following guidelines are useful to avoid unnecessary time wastage in training:

The choice of the number of input nodes and output nodes is completely problem-dictated and known beforehand. At the beginning, all variables, which seem to affect the output of the classification, may be included. After training, depending on the learned weight coefficients, some of the input variables may be rejected. One straightforward approach to reject unnecessary (redundant) variable is by computing the correlation

coefficient between the components of the input vector. If there is a strong correlation, reject one of the correlated components. Still, the third approach is using expertise opinion; some of the components may be regarded as irrelevant by the expertise. The number of output nodes may be equal to number of classes, or can be binary coded such that more than one output node fire to represent a class [for instance, three nodes may be used to represent eight classes from 000 to 111]

Number of hidden nodes and hidden layers is particularly dependent on the complexity of the relation between classes. One way to decide on the number of hidden nodes is to take the average of input and output nodes. The other approach is, if the number of input nodes is N, 2*N+1 number of hidden nodes should be used for a single layer network

Ideally, a single hidden layer with sufficient number of nodes is a universal approximator. But, in some applications, using more than one hidden layer speeds up the convergence.

The connectivity of the layers could be feedforward, where each node in a layer computes its output and feed forward to the nodes in the next layer nodes only, or recurrent, where each node in a layer is connected both to the previous and to the next layer. Also, Each node may be connected to every node in the next layer(full connectivity) or to some of the nodes in the next layer(partial connectivity).

The activation functions to be used in a network is dependent on the learning algorithm to be implemented and would be discussed in the next section.

Depending on the manner in which they adjust the weights during training, there are different learning algorithms. So far, the in depth studied, practically excellent working, and simple learning algorithm is backpropagation. This algorithm is implemented on the feedforward, fully connected architecture. Backpropagation algorithm from the implementation point of view is discussed in detail in the next section.

4.5 Backpropagation Learning

The revival of neural networks in 1980's is due to the development of backpropagation algorithm, which solved the linearly non-separable XOR problem, which was impossible using perceptron learning. Calculation of the error in the hidden layer was a problem because the inputs and the outputs to hidden nodes were unknown to

the user. In backpropagation, the errors are first calculated from the output layer(where the target values are known), and propagated backward to the hidden and the input layers. Then, weights are updated using the error term calculated for each connectivity.

4.5.1 Backpropagation algorithm

/// Stage 0 initialization

Step 0 Initialize weights (set to small random values)

Step1. While stopping condition is false, do step 2-9

Step2. For each training pair, do step 3-8

////stage1 feedforward

Step 3 Each input unit receives input signal x_i and broadcasts this signal to all units in the hidden layer above (the hidden units)

Step4 Each hidden unit (z_j , j=1 ... p) sums its weighted input signals,

$z_{inj} = v_{oj} + \sum_{i=1}^{i=n} x_i v_{ij}$ Where V_{ij} is the weight connecting input unit i to Hidden unit j

Applies its activation function to compute its output signal,

$z_j = f(z_{inj})$

and sends this signal to all units in the layer above (output units)

Step 5. Each output unit (y_k , k=1,m) sums its weighted input signals,

$y_{ink} = w_{ok} + \sum_{j=1}^{p} z_j w_{jk}$

And applies its activation function to compute its output signal,

$y_k = f(y_{ink})$

///Stage 2 [backpropagation of error]

Step 6 Each output unit receives a target pattern corresponding to the input training pattern, computes its error term:

$$\delta_k = (t_k - y_k) f'(y_{ink})$$

Calculates the weight correction term:

$$\Delta w_{jk} = \alpha \delta_k z_j$$

Calculates its bias correction term

$$\Delta w_{ok} = \alpha \delta_k$$

And sends δ_k to units in the layer below

Step7 Each hidden unit sums up its delta inputs

$$\delta_{inj} = \sum_{k=1}^{m} \delta_k w_{jk}$$

Calculates its error term

$$\delta_j = \delta_{inj} f'(z_{inj})$$

Calculates its weight correction term

$$\Delta v_{ij} = \alpha \delta_j x_i$$

Calculates its bias correction term

$$\Delta v_{oj} = \alpha \delta_j$$

///Stage3 [update weights and biases]

Step 8 Each output unit updates its bias and weights

$$w_{jk}(new) = w_{jk}(old) + \Delta w_{jk}$$

(k=1,2,...m and j=0,1,...p)

Each hidden unit updates its bias and weights

$$\Delta w_{ij}(n) = \eta \delta_j x_{ij} + \mu \Delta w_{ij}(n-1)$$

(j=1,..p and i=0,...,n)

Step 9 Test stopping condition

4.5.2 Activation function

An activation function for a backpropagation network should have several important characteristics: It should be continuous, differentiable, and monotonically non-decreasing. Furthermore, for computational efficiency, it is desirable that its derivative be easy to compute. For the most commonly used functions, the value of the derivative can be expressed in terms of the value of the function.

Two of the most typical activation functions are binary sigmoid and bipolar sigmoid functions [see Figure 4.8 and Figure 4.9]

4.5.3 Choice of Initial Weights and Biases

The choice of initial weights will influence whether the net reaches a global (or only a local) minimum of the error and, if so, how quickly it converges. The update of the weight between two units depends on both the derivative of the upper unit's activation function and the activation of the lower unit. For this reason, it is important to avoid choices of initial weights that would make it likely that either activations or derivatives of activations are zero. Normally, random values between –0.5 and 0.5 are used. Inappropriate choice of initialization may cause saturation or extremely slow learning.

4.5.4 How long to Train the Network

The purpose for applying a backpropagation network being to achieve a balance between correct responses to training patterns and good responses to new input patterns (i.e. a balance between memorization and generalization), it is not necessarily advantageous to continue training until the total squared error actually reaches a minimum. For this purpose, the entire dataset is divided into three patterns: training patterns, validation patterns and test patterns. According to Hecht-Nielsen, training set and validation pattern are used during training. The weight adjustments are based on the training patterns; however, at intervals during training, the error is computed using the validation patterns. As long as the error for the validation patterns decreases, training continues. When the error begins to increase, the net is starting to memorize the training patterns to specifically (and starting to lose its ability to generalize). At this point, training is terminated.

However, when the available dataset is not big enough, the entire dataset is divided into two patterns only: the training pattern and the testing pattern usually in 80-20

ratios respectively. In this case, how long the network should be trained is obtained by experiment.

4.5.5 How many Training Patterns should be used

There area number of approaches to decide on the number of training patterns needed to have a reliable learning. The idea that there should be at least between five to ten training patterns for each unit in the network is one empirical approach [11]. i.e.

Number of training pattern=(5 to 10) x(No. of input units +No. of hidden units+ No. of output units)

For example, if the network consists of an input vector of eight components, two hidden units and three output units, then the estimated training pattern needed is between 65 and 130.

4.6 Modifications to Backpropagation Algorithm

Several modifications can be made to the backpropagation algorithm discussed above in such away that its performance is improved. Modifications mainly involve changes to the weight update procedure and alternatives to the sigmoid activation functions, as discussed below:

4.6.1 Alternate Weight Updating Procedures

i) Momentum

The most common variation of the backpropagation algorithm is to alter the weight-update rule $\Delta w_{ij} = \eta \delta_j x_i$ by making the weight update on the nth iteration depend partially on the update that occurred during the (n-1)th iteration:

$$\Delta w_{ij}(n) = \eta \delta_j x_i + \mu \Delta w_{ij}(n-1)$$

where μ is called the momentum .It is in the range between 0 and 1. The effect of μ is to add momentum that tends to keep the 'ball rolling' in the same direction from one iteration to the next. In turn, this can have the effect of keeping the ball rolling through small local minima or along flat regions where the ball would stop if there were no momentum. It also has the effect of gradually increasing the step size of the search in regions where the gradient is unchanging, thereby improving convergence.

Limitation to the effectiveness of the momentum include the fact that the learning rate places the upper limit on the amount by which a weight can be changed and momentum can cause the weight to be changed in a direction that would increase the error.

ii) Batch updating of weights

The weight updating procedure discussed in the algorithm is called online updating, where the weights are updated after each training pattern is presented to the network. In some cases; however, it is advantageous to accumulate the weight correction term for an entire epoch if there are not too many patterns and make a single weight adjustment, which is the average of the weight correction terms. This procedure has a smoothing effect on the correction terms.

4.7 Performance Measure of Neural Network

Once the network is trained, the accuracy of the model should be tested using test set patterns. Four measures are often used in medical applications:

Let P_c=number of positive cases correctly classified

P_I=number of positive cases incorrectly classified

P_T=Total number of positive cases

N_c=number of negative cases correctly classified

N_I=number of negative cases incorrectly classified

N_T=total number of negative cases. Then,

Sensitivity=P_c/P_T

Specificity=N_c/N_T

Positive predictive value=$P_T/(P_c+N_I)$

Accuracy=$(P_c+N_c)/(P_T+N_T)$

In the following sections positive cases refer to diseases and negative cases refer to normal

4.8 Results of Neural Network for Disease Classification

One hundred forty eight cases were considered in training and testing for the diagnosis of four diseases. The distribution of the database is shown in Table 4.1. Fully connected and feedforward networks with backpropagation learning were implemented for the study of the presence or absence of a particular disease. Training was made solely on selected HRV features. The complexity of the classification for a particular disease

was shown in the topology of the network implemented and the testing of performance of the network was made using standard measures.

Table 4.1. Database available

Diagnosis	Amount in No.	Source
Normal	50	Physionet and lab
CHF	29	Physionet
Controlled Epilepsy (EP)	16	AIIMS
Diabetes mellitus (DM)	30	AIIMS
Ulcerative colitis (UC)	23	AIIMS

After all the preprocessing techniques mentioned in the previous sections were applied, clean RR intervals were fed to the AR model developed. Different spectral and temporal features were computed and the statistical representation of the data is illustrated in Table 4.2 below.

Table 4.2 Ranges of spectral and temporal features for respective diseases (Mean ± SD)

Parameter	**Normal**	**CHF**	**DM**	**EP**	**UC**
Phf	0.0002 ± 0.0002	0.0000 ± 0.0000	0.0000 ± 0.0000	0.0004 ± 0.0003	0.0001 ± 0.0001
Plf	0.0005 ± 0.0004	0.0000 ± 0.0001	0.0000 ± 0.0000	0.0003 ± 0.0003	0.0001 ± 0.0001
Ptot	0.0013 ± 0.0010	0.0002 ± 0.0003	0.0001 ± 0.0001	0.0009 ± 0.0007	0.0004 ± 0.0004
Sympatho-vagal ratio	3.3200 ± 1.5200	0.715 ± 0.88500	2.1800 ± 1.2500	1.2100 ± 0.9800	2.6800 ± 2.1100
Hfcent	0.1560 ± 0.02500	0.1727 ± 0.0868	0.2600 ± 0.1100	0.2400 ± 0.0700	0.2200 ± 0.0720
Plfnorm	73.600 ± 10.3700	49.059 ± 19.003	63.3200 ± 15.40	47.8700 ± 17.9600	66.300 ± 13.750
Phfnorm	26.3300 ± 10.380	50.94 ± 19.0031	36.6800 ± 15.40	52.1200 ± 17.9500	33.7000 ± 13.75
SDNN	54.3700 ± 23.130	32.99 ± 23.7900	15.3700 ± 20.03	42.8800 ± 17.200	28.2700 ± 14.19
RMSSD	15.2200 ± 6.6670	15.72 ± 15.3500	3.9100 ± 1.9600	19.7200 ± 10.6900	9.9100 ± 7.1300
pNN50count	0.0110 ± 0.0119	0.0012 ± 0.0016	0.0001 ± 0.0004	0.0227 ± 0.0221	0.0055 ± 0.0114
SDSD	15.2190 ± 6.6670	15.721 ± 15.360	3.9100 ± 1.9600	19.7208 ± 10.6900	9.9100 ± 7.1280

Table 4.2 shows all features of HRV for short-term recording as per the standard guideline [1]. As can be seen clearly from table 4.2, diseases have different effects on different HRV features. For instance apart from Hfcent, reduced HRV features were observed on diabetes patients. However, all diseases cause the central frequency of high

frequency power to increase. All the diseases had also the effect of reducing the sympatho-vagal ratio, which may be associated with the dysfunction of sympathetic activities. Generally, UC patients had shown an increase in Phf. These variations were used as the indicatives for the possibility of diagnosis using HRV.

The correlation technique was employed to find out some redundancy in the feature vector, the result of which is shown in Table 4.3 below: The assumption was made that two features are correlated if the correlation coefficient between the two sets is found out to be greater than 0.75.

Table 4.3 Avoiding redundancy using correlation method

Parameters	**Corr.coefficient**	**Rejected parameter**
Plfnorm &Phfnorm	-0.99	Plfnorm
Ptot & plf	0.80	Ptot
SDSD & RMSSD	0.99	SDSD

Plfnorm, Ptot, and SDSD were rejected based on the correlation test shown in table 4.3. This results in the input vector having eight components; five spectral features and three temporal features. Rejection of redundant features is useful in reducing the number of cases needed for reliable training.

4.8.1 Scaling of Input Vector

The values of one feature may be orders of magnitude larger than that of another. This may cause biasing of the network learning towards a particular feature or even worse, may cause the hidden layer nodes to saturation. To reduce this risk, we implemented a statistical approach shown below:

$$\hat{\mu}_i = \frac{1}{n}\sum_{k=1}^{k=n} x_i^k ;$$

$$\hat{\sigma}_i^2 = \frac{\sum_{k=1}^{k=n}(x_i^k - \hat{\mu}_i)^2}{n-1}, \text{ then } x_i^k \leftarrow \frac{x_i^k - \hat{\mu}_i}{\hat{\sigma}_i}$$

where x_i^k is the kth component of the input vector x

4.8.2 Multiple Category classification

The problem defined here is a multiple category classification problem where there are five classes, four of which are pathological and one for Normal. In this case, there are two choices of implementations

1) Break the multicategory problem into a series of two-category problems

2) Construct a more complex mathematical structure for the decision function

The first approach was opted to be used here due to i) The main focus is to classify a case as either normal or pathological of a particular disease ii) the limitation of the database available.

4.8.3 Classification between Normal and Abnormal

We created two classes one for Normal and another for abnormal. In the abnormal category we took samples of data from each of the four diseases: diabetes mellitus(DM),Ulcerative colitis(UC), controlled Epilepsy(EP) and Congestive Heart Failure(CHF) . And we trained the network beginning from the simple architecture with one hidden layer and keep on increasing hidden nodes by experimenting with different learning rate, momentum, and epoch for each architecture. The final result is shown in Table 4.4

Table4.4 Results for Normal versus Abnormal (CHF, EP, UC and DM)

Diagnosis	Correctly classified	Incorrectly classified	Total
Normal	6	4	10
Abnormal	22	0	22
Total	28	4	32

Performance measures:

Sensitivity=22/22=1

Specificity=6/10=0.6

Accuracy=28/32=0.875

Positive Predictive Value=22/(22+4)=0.846

Topology: 8-16-16-2

Network parameters: Threshold, learning rate and momentum are set to 0.04, 0.1 and 0.8 respectively.

The input nodes being fixed to eight and the output to two nodes, the complexity of the relationship between classes is manifested as the number of hidden layers and number of hidden nodes used. We implemented the idea that the number of hidden nodes should be at least twice the number of input nodes [12]. And it works with a reasonable accuracy.

4.8.4 Classification between Normal and Diabetic patients

Table4.5 Results for Normal versus Diabetes

Diagnosis	Correctly classified	Incorrectly classified	Total
Normal	6	1	7
Diabetes	4	0	4
Total	10	1	11

Performance measures:

Sensitivity=4/4=1

Specificity=6/7=0.857

Accuracy=10/11=0.909

Positive Predictive Value=4/(4+1)=0.80

Topology: 8-5-2

Network parameters: Threshold, learning rate and momentum are set to 0.4, 0.04 and 0.5 respectively.

It is seen from the topology that HRV can easily differentiate normal and diabetic patients. It is only five hidden nodes with a single hidden layer that gives about 91 % of accuracy along with good sensitivity and specificity. This is in agreement with a wide variation in the ranges of HRV [as seen in table 4.2] between normal and DM patients.

4.8.5 Classification between Normal and UC patients

Table4.6 Results for Normal versus UC

Diagnosis	Correctly classified	Incorrectly classified	Total
Normal	14	2	16
UC	6	0	6
Total	20	2	22

Performance measures:

Sensitivity=6/6=1

Specificity=14/16=0.875

Accuracy=20/22=0.91

Positive Predictive Value=6/6+2=0.75

Topology: 8-5-5-2

Network parameters: Threshold, learning rate and momentum are set to 0.4, 0.05 and 0.5 respectively.

Here also, two hidden layers with five hidden nodes each, was sufficient to obtain 91 % accuracy. In this case, by increasing the number of hidden layer to two, we reduced the number of epochs needed to reach to the same performance level with the network having only single layer. This is also a promising result due to the fact that with a larger training dataset, the performance may easily be improved

4.8.6 Classification between Normal and CHF patients

Table4.7 Results for Normal versus CHF

Diagnosis	Correctly classified	Incorrectly classified	Total
Normal	4	1	5
CHF	6	2	8
Total	10	3	13

Performance measures:

Sensitivity=6/8=0.75

Specificity=4/5=0.8

Accuracy=10/13=0.77

Positive Predictive Value=8/(6+1)=1.14

Topology: 8-12-12-2

Network parameters: Threshold, learning rate and momentum are set to 0.3, 0.1 and 0.5 respectively.

The complexity between normal and CHF patients is seen from the topology with two hidden nodes having twelve hidden nodes each. And the accuracy is also only 77%. Because our database was limited we couldn't keep on increasing the hidden nodes and layers as it would result in over fitting. A larger dataset may give better results.

4.8.7 Classification between Normal and EP patients

Table4.8 Results for Normal versus EP

Diagnosis	Correctly classified	Incorrectly classified	Total
Normal	2	3	5
EP	7	0	7
Total	9	3	12

Performance measures:

Sensitivity=7/7=1

Specificity=2/5=0.4

Accuracy=9/12=0.75

Positive Predictive Value=7/(7+3)=0.70

Topology: 8-10-2

Network parameters: Threshold, learning rate and momentum are set to 0.4, 0.1and 0.6 respectively.

In this study, the best configuration was a single hidden layer with ten nodes, in which we obtained the accuracy of 75%. This is the minimum accuracy we obtained in the overall classification problems. Different configurations were tried and result in poorer accuracies.

4.8.8 Classification between UC and Diabetic patients

Table4.9 Results for UC versus Diabetes

Diagnosis	Correctly classified	Incorrectly classified	Total
Diabetes	4	0	4
UC	9	3	12
Total	13	3	16

The performance between the two diseases can be measured only using accuracy, as both diseases are positive in clinical sense. And the accuracy is 13/16=0.813

Classification between UC and diabetes patients was tried and gave a promising result with the accuracy of 81.3%. The network topology implemented was 8-7-7-2. This was done simply to highlight the fact that using HRV features of sufficiently much larger database than the one we used here, further classification was also possible.

4.9 Conclusion

In this chapter after brief introduction to the design issues in NN for classification, different configurations were developed for diagnosis of the four diseases under study, and we obtained good results, taking in to consideration the relatively small database we had. The complexity of the model, expressed in terms of the number of hidden nodes and number of hidden layers, depends on the type of disease under study. While diabetes diagnosis was made with simple model (1 hidden layer with 5 nodes), diagnosis of CHF needed a complicated model (2 hidden layers with 12 hidden nodes each). Complicated models means that the training database should be larger to obtain better results.

CHAPTER #5

CONCLUSIONS AND FUTURE SCOPE

5.1 Conclusion

In the first section of this study, quantification of HRV using AR modeling was made for R-R time series obtained from short-term (five minute) ECG recording. We tested our model first using known sinusoidal signal. A number of test signals were used repeatedly and the model gives very good spectrum estimation. It is only after this that we applied it to HRV modeling. For different diseases, we obtained different ranges for each features-an indicative of the possibility for classification of diseases using ANN.

In the second section of this study, ANN was developed based on HRV features for disease classification. Four diseases were considered: Diabetes mellitus, Ulcerative colitis, controlled Epilepsy and Congestive heart failure. The two main focuses of this study were i) to classify between normal and a particular disease and ii) to confirm whether the subject is normal or abnormal due to one of the four diseases. The network developed to classify between normal and abnormal classes where the abnormal class is made from the samples of the four diseases, performs well with sensitivity=1, specificity=0.6, accuracy=0.875, and positive predictive value=0.846. The network developed for diabetes diagnosis performs with sensitivity=1, specificity=0.857, accuracy=0.909, and positive predictive value=0.80. The third network developed for Ulcerative colitis diagnosis performs with sensitivity=1,specificity=0.93, accuracy=0.94, and positive predictive value=0.75. The fourth network developed for CHF diagnosis performed with specificity=0.8,accuracy=0.77,positive predictive value=1.14. And finally, the classification between normal and EP patients is done with sensitivity=1,specificity=0.4,accuracy=0.75,positive predictive value=7/(7+3)=0.70.

This thesis demonstrates the potential of short- term HRV, when integrated with neural networks, as a diagnosis tool for clinical applications. The model may substitute a number of tests that are currently in use for diagnosis. Its noninvasiveness and comfort

for patients may be the factors to see its breakthrough in clinical applications in short coming years.

5.2 Future scope

The work implemented in this thesis can be extended in the following areas:

1. By implementing another algorithm for automatic detection and correction of entopic beats, the whole system (from ECG recording to diagnosis) can be converted to a real time system.
2. The network performance can be enhanced further by:
   a) Modifying the network by increasing the input neurons using a combination of different basic features implemented in this study.
   b) By using different decision function for classification
   c) Training the network with a larger database
   d) Modifying the network parameters (like learning rate, number of epochs for training) in adaptive manner.

APPENDIX A

NEURAL NETWORK FUNDAMENTALS REVIEW

A.1 Artificial Neuron and Neural Network

To better understand how artificial neural network works, and to know when to use it, understanding of the defining characteristics of neural networks is needed.

A neural net consists of a large number of simple processing elements called neurons, units, cells, or nodes. Each neuron is connected to other neurons by means of directed communication links, each with an associated weight. The weights represent information being used by the net to solve a problem. Neural networks can be applied to a wide variety of problems, such as storing and recalling of data or patterns, classifying patterns, performing general mappings from input patterns to output patterns, grouping similar patterns, or finding solutions to constrained optimization problems.

Each neuron has an internal state, called its activation or activity level, which is a function of the inputs it has received. Typically, a neuron sends its activation as a signal to several other neurons. It is important to note that a neuron can send only one signal at a time, although that signal is broadcast to several other neurons.

For example, consider a neuron Y, shown in Figure A.1, that receives inputs from neurons X1, X2 and X3. The activations (output signals) of these neurons are x1, x2, and x3 respectively. The weights on the connections from X1, X2, and X3 to neuron Y are w1, w2, and w3, respectively. The net input Y_{in}, to neuron Y is the sum of the weighted signals from neurons X1, X2 and X3, i.e.,

$$Y_{in} = \sum_{i=1}^{3} x_i w_i ,$$

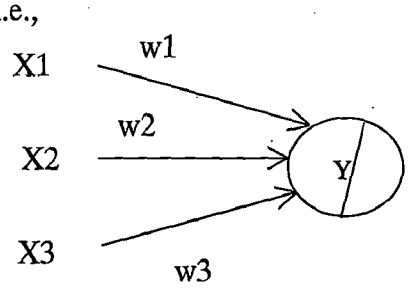


Figure A .1 A simple artificial neuron

The activation y of neuron Y is given by some function of its net input, $Y=f(y_{in})$. Different functions of neurons are discussed in the next sections. For a logistic sigmoid function:

$$f(x) = \frac{1}{1+\exp(-x)} \quad \text{----------(A.1)}$$

Now, suppose further that neuron Y is connected to neurons Z1 and Z2, with weights v1 and v2, respectively, as shown in Figure A.2. Neuron Y sends its signal y to each of these units. However, in general, the values received by neurons Z1 and Z2 will be different, because each signal is scaled by the appropriate weights v1 and v2. In atypical net, the activations z1 and z2 of neurons Z1 and Z2 would depend on inputs from several or even many neurons, not just one, as shown in Figure A.2. Although the neural network in Figure 4.2 is very simple, the presence of a hidden unit, together with a nonlinear activation function

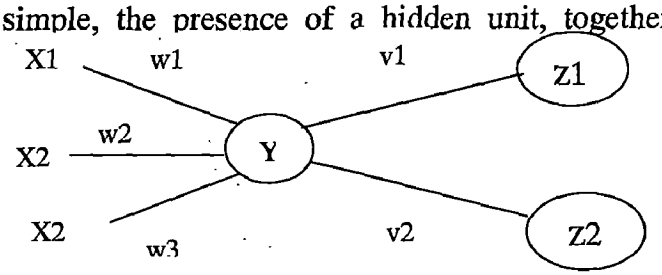


Figure A.2 Simple Neural Network

gives it the ability to solve many more problems than can be solved by a net with only input and output units. On the other hand, it is more difficult to train (i.e. to find optimal values for the weights) a net with hidden units.

A.2 Biological Neural Networks

The extent to which a neural network models a particular biological neural system varies. Though this is a concern for some, for others, the ability of the net to perform useful tasks (such as approximate or represent a function) is more important than the biological plausibility of the net. As our current definition of intelligence, or ability to learn, is based on the working of biological neurons, understanding the close analogy between the structure of the biological neuron and the processing element(or artificial neuron) is important as the basis for the definition of artificial intelligence.

A biological neuron has three types of components that are of a particular interest in understanding an artificial neuron: its dendrite, soma, and axon. The many dendrites

receive signals from other neurons. The signals are electric impulses that are transmitted across a synaptic gap by means of a chemical process. The action of a chemical transmitter modifies the incoming signal (typically, by scaling the frequency of the signals that are received) in a manner similar to the action of the weights in an artificial neural network.

The soma, or cell body, sums the incoming signals. When a sufficient input is received, the cell fires; that is, it transmits a signal over its axon to other cells. It is often supposed that a cell either fires or doesn't at any instant of time, so that transmitted signals can be transmitted as binary. However, the frequency of firing varies and can be viewed as a signal of either greater or lesser magnitude. This corresponds to looking at discrete time steps and summing all activity (signals received or signals sent) at a particular point in time.

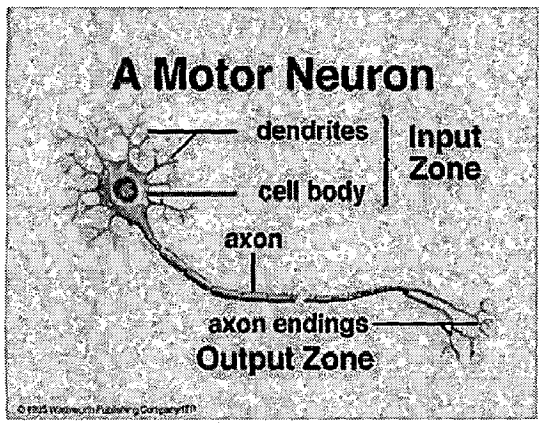


Figure A.3 Biological Neuron

The transmission of the signal from a particular neuron is accomplished by an action potential resulting from differential concentrations of ions on either side of the neuron's axon sheath (the brain's 'white matter').

A.3 Typical Architectures

It is often convenient to visualize neurons as arranged in layers. Typically, neurons in the same layer behave in the same manner. Key factors in determining the behavior of a neuron are its activation function and the pattern of weighted connections over which it sends and receives signals. Within each layer, neurons usually have the same activation function and the same pattern of connections to other neurons. To be more specific, in many neural networks, the neurons within a layer are either fully connected or not interconnected at all.

The arrangement of neurons into layers and the connection patterns within and between layers is called **the net architecture.** Many neural nets have an input layer in which the activation of each unit is equal to an external input signal.

Neural networks are often classified as single layer or multilayer. In determining the number of layers, the input units are not counted as a layer, because they perform no computation. Equivalently, the number of layers in the net can be defined to be to be the number of layers of weighted interconnect links between theslabs of neurons.

A.3.1 Single-Layer Net

A single layer net has one layer of connection weights. Often, the units can be distinguished as input units, which receive signals from the outside world, and output units, from which the response of the network is read. In the typical single layer net, as shown in Figure A.4, the input units are fully connected to output units but are not connected to other input units, and the output units are not connected to other output units.

For pattern classification, each output unit corresponds to a particular category to which an input vector may or may not belong. In a single layer net, the weights for one output unit do not influence the weights for other output units. For pattern association, the same architecture can be used, but now the overall pattern of the output signals give the response patterns associated with the input signal that caused it to be produced. One point may be noted here: it is possible that the same type of net can be used for different problems, depending on the interpretation of the response of the net. However, the limitation of single layer network is, they can't solve non-linearly separable problems.

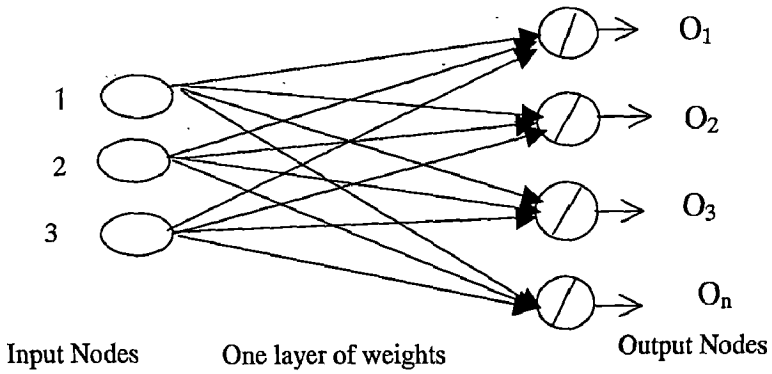


Figure A.4 Single layer network

A.3.2 Multilayer Network

A multiplayer net is a net with one or more layers (or levels) of nodes (called hidden units) between the input and output units (see Figure A.5). Typically, there is a layer of weights between two adjacent levels of units. Multilayer nets can solve more complicated problems than can single-layer nets, but training may be more difficult. However, in some cases, training may be more successful, because it is possible to solve a problem that a single-layer net cannot be trained to perform correctly at all.

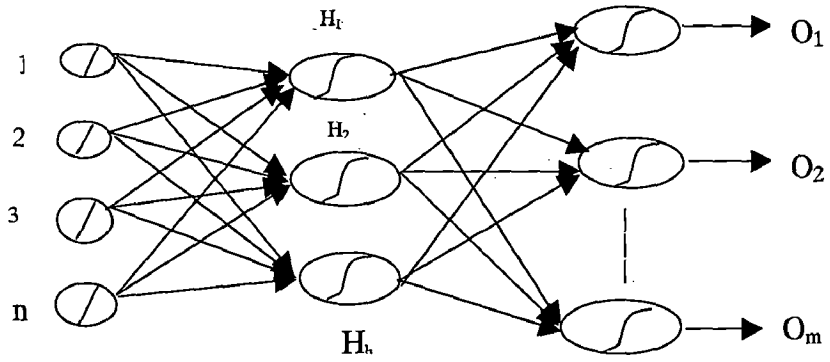


Figure A.5 Typical Multilayer network

A.3 Common Activation Functions

The basic operation of an artificial neuron involves summing its weighted input signal and applying an output, or activation function. For the input units, this function is used for all neurons in any particular layer of a neural net, although this is not required. In most cases, a nonlinear activation function is used. In order to achieve the advantages of multilayer nets, nonlinear functions are required (since the results of feeding a signal through two or more layers of linear processing elements are no different from what can be obtained using a single layer.

A.3.1 Identity Functions

$f(x) = x$ for all x

Identity functions are used in the input layer units where the network is interfaced to the external world. The nodes with this functions act as a relay, and their activation is equal to the external signal applied on them.

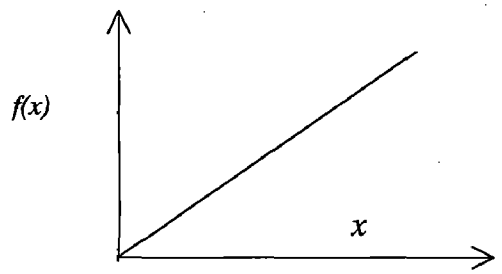


Figure A..6 Identity function

A.3.2 Binary Step Functions (with threshold θ)

Single-layer nets often use a step function to convert the net input, which is a continuously valued variable, to output unit that is a binary (1 or 0) or bipolar (1 or – 1)signal. The binary step function is also known as the threshold function or heavy side function.

$f(X)=1$ *if* $X>=\theta$

0 *if* $x<\theta$

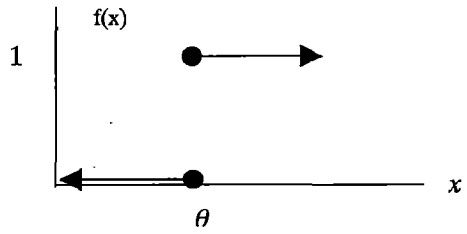


Figure A.7 Binary step function

A.3.3 Sigmoid Functions

Sigmoid functions (s-shaped curves) are useful activation functions. The logistic function and the hyperbolic tangent functions are the most common. They are especially advantageous for use in neural nets trained by backpropagation , because the simple relationship between the value of the function at a point and the value of the derivative at that point reduces the computational burden during training.

Depending on its range, sigmoid function may be classified as binary sigmoid (or logistic sigmoid) and bipolar sigmoid.

i) Binary sigmoid:

$$f(x) = \frac{1}{1+\exp(-x)}$$

$$f'(x) = \delta f(x)[1 - f(x)]$$

Note that, depending on the problem, the logistic sigmoid function can be scaled to have

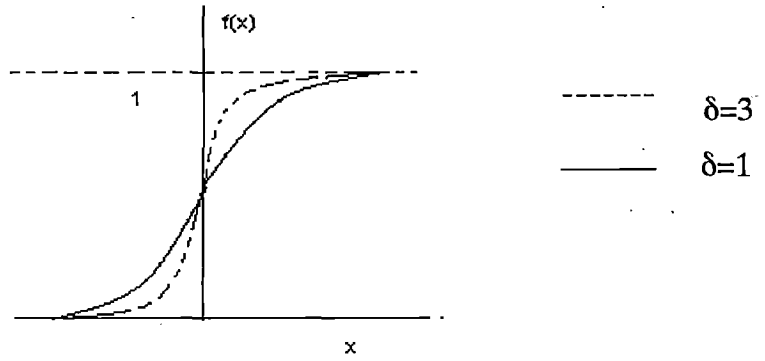


Figure A.8 Binary sigmoid. Steepness parameters δ=1 and δ=3

any range of values. This is a sigmoid function with range from 0 to 1. It is sometimes called logistic sigmoid. This function is often used as the activation function for neural nets in which the desired output value either are binary or are in the interval between 0 and 1.

ii) Bipolar sigmoid:

The bipolar sigmoid is closely related to the hyperbolic tangent function, which is also often used as the activation function when the desired range of output values is between –1 and 1. For a binary data, it is usually preferable to convert to bipolar form and use the bipolar sigmoid or hyperbolic tangents.

$$g(x) = 2f(x) - 1 = \frac{2}{1+\exp(-\delta x)} - 1$$

$$= \frac{1-\exp(-\delta x)}{1+\exp(-\delta x)}$$

$$g'(x) = \frac{\delta}{2}[1+g(x)][1-g(x)]$$

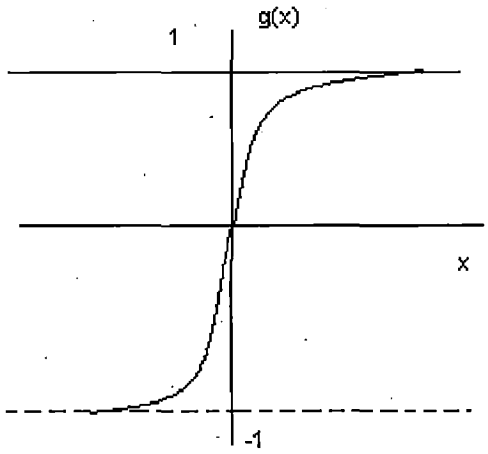


Figure A.9 Bipolar sigmoid

A.4 Neural Network Classification based on their Function

Neural networks can be classified in a number of ways depending on structure (as discussed in the previous section), function or objective. Based on their functions, neural networks may be divided in to four categories:

i) Classification models:

Classification models assign input data items to two or more categories. These may be supervised learning in which the categories are known or unsupervised learning in which the categories may not be known.

ii) Association Models:

The two types of association models are auto-association, which focuses on the retrieval of an object based on part of the object itself; and hetro-association, which focuses on the retrieval of an object in one set using an object in a different set.

iii) Optimization:

The objective of these systems is to find the best solution by minimizing a cost function or other measure.

iv) Self –organization:

This approach organizes information using adaptive learning facilities. It is similar to clustering algorithms, based on unsupervised learning.

APPENDIX B

GUI FOR AR MODELING AND DISEASE CLASSIFICATION

B.1 AR Modeling GUI

AR modeling of HRV is done by integrating Matlab and Labview softwares. For its better appearance and flexibility, Labview is used. The versions used are labview 6.1 and Matlab 6.1. In both softwares the upward compatibility is held, such that this program can be run efficiently in higher versions.

B.1.1 Inputs expected from the user

a) **Maximum order:** This is the maximum complexity of the model within which the best order is to be searched. Default is 30.

b) **Input file path:** This is the full path of the clean equi-spaced RR time series (after interpolation and ectopic beat correction)

C) **Sampling frequency:** The resampling frequency of RR time series

B.1.2 Outputs to the User

a) Plot of the power spectral density of the HRV signal on the front panel and matlab figure, and Matlab figure showing the validity of the Model if any of the autocorrelation values in the plot are significant (>0.5), it is not valid and try again using larger order but less than 30.

b) The best order of the model for the particular case

c) Model coefficients, which optimizes the estimation of the time series signal (i.e. HRV)

d) The temporal HRV measures: SDNN(standard deviation between two normal R-peaks) , RMSSD(root mean square value of successive differences between adjacent intervals) and pNN50count(the fraction of the number of successive R-R intervals whose difference is greater than 50ms).

e) Spectral HRV measures: PHF (The power spectral density (psd) of HRV in higher frequency region [0.15-0.5Hz]), PLF (The psd of HRV in higher frequency region [0.15-

0.5Hz]), Sympatho-vagal ratio (PLF/PHF), HF normalized (normalized HF power) and Central frequency of PHF.

Important Notes

1. The RR interval output from the QRS detection algorithm should be first run using ectopic correction algorithm (ectopiccorrection.m attached here or any other algorithm), and if there is any ectopic beats uncorrected using the algorithm, correct it manually).
2. The clean RR interval should be interpolated and resampled at low frequency (2-8Hz) using the attached program (interpolation.m)
3. Every time the program is run for a particular subject, it stores the features in a file 'features.txt' located in C:\MATLAB6\work directory. Therefore, rename 'features.txt' before running the program again. Otherwise, the file would be overwritten when the program is run again.

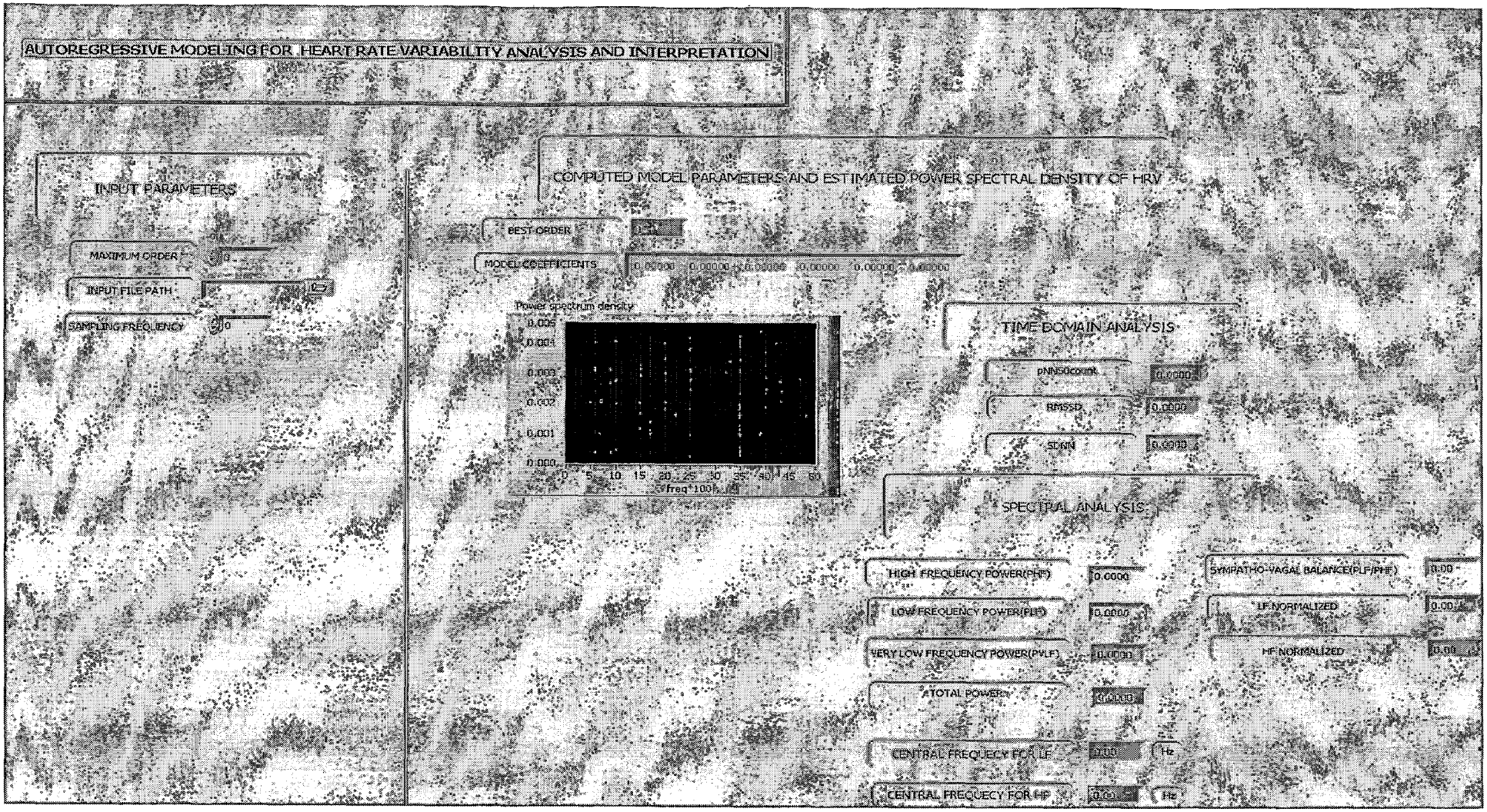


Figure B.1 GUI for AR modeling of HRV

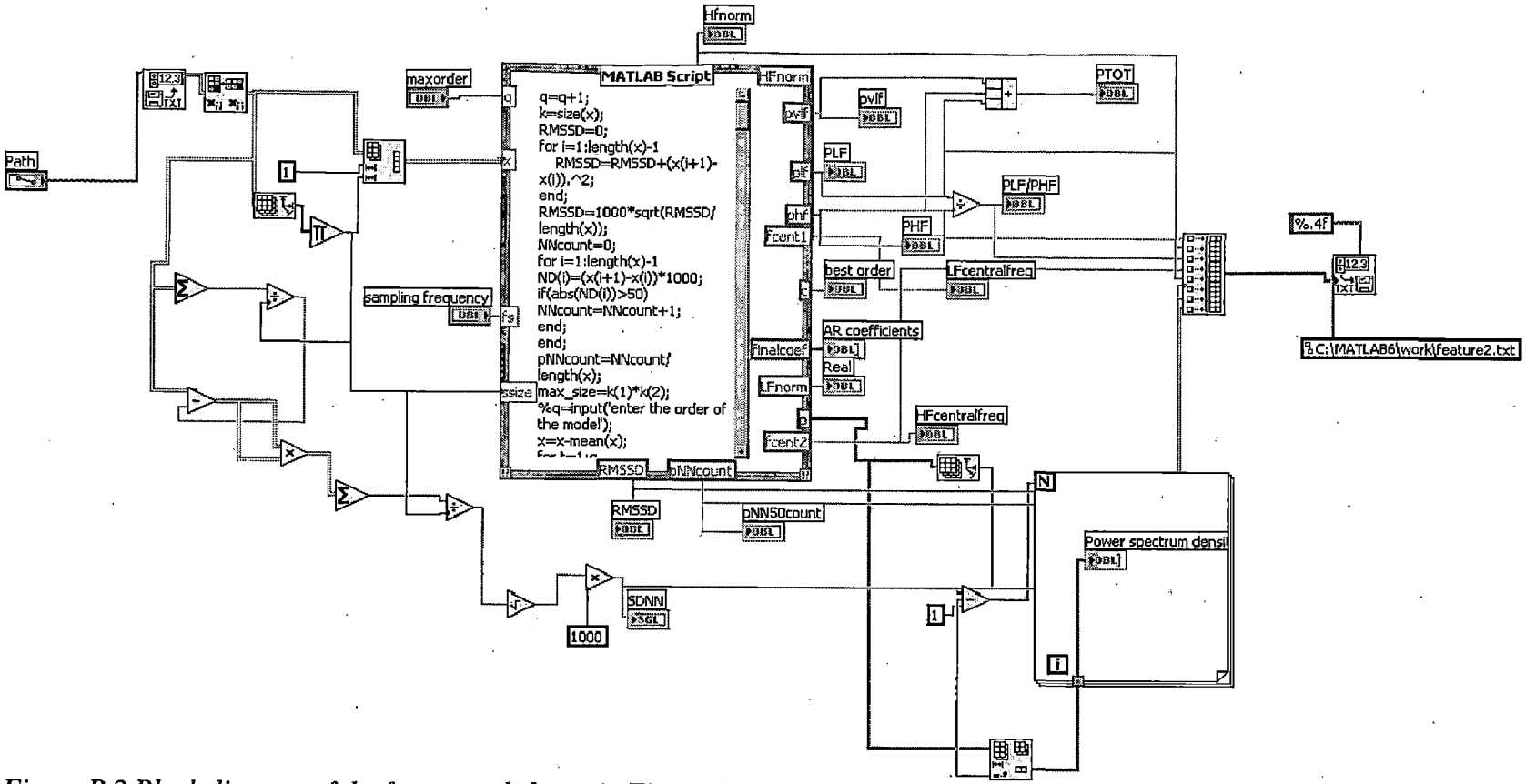
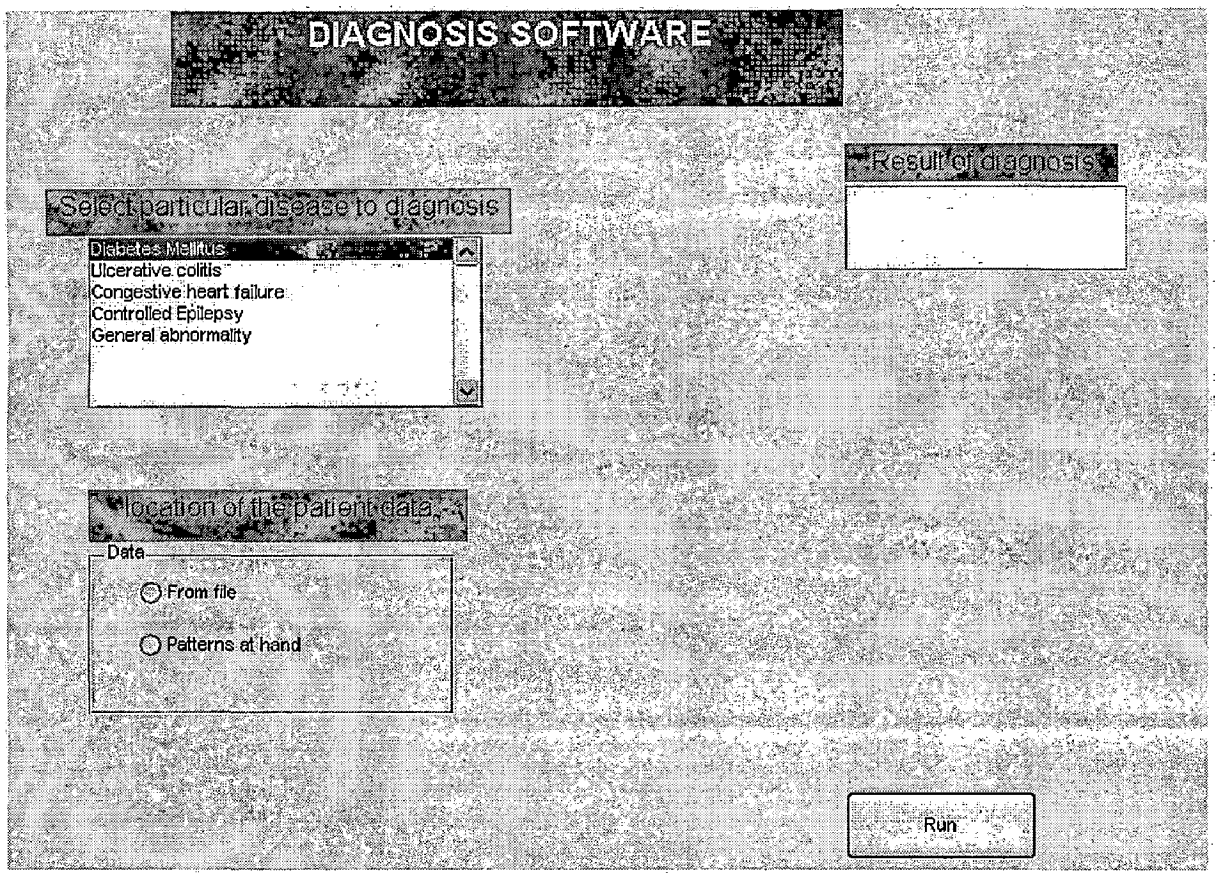


Figure B.2 Block diagram of the front panel shown in Figure B.1

GUI for ANN-Based diagnosis using HRV



B.2 ANN-Based Diagnosis GUI

The components included in this GUI are:

a) One list box containing:

i) Diabetic mellitus:

ii) Controlled Epilepsy:

iii) Ulcerative colitis

iv) Congestive heart failure

v) General abnormality

Selection of one of the lists by clicking on them sets the diagnosis algorithm for checking the presence or absence of that particular disease.

Important note

1. General abnormality option is selected when the doctor/physician needs a fast check on the presence of at least one of the diseases listed or if it is normal. This can be used as the first step before further diagnosis is made on a particular disease.
2. It is a general assumption here that the physician/ Doctor has a suspicious subject for a particular disease and the main objective is not to classify between different diseases but on the assurance of the presence of the suspected disease.

a) One panel labeled 'data' to locate the patient record containing two buttons:

i) From file

ii) Patterns at hand

b) One Edit box labeled 'Result of diagnosis': This is where the diagnosis result is displayed

c) A push button labeled 'Run': This is the only button, which triggers the diagnosis algorithm(by clicking on it)

If 'from file' is selected, dialogue box pops up giving the user the option to choose a file for diagnosis. Select file name and click OK, the diagnosis result would be displayed in the edit box .If 'patterns at hand' is selected, an input dialogue box pops waiting for the user to feed the features manually, enter the features one by one and click OK, the diagnosis result would be displayed in the edit box

Important Notes:

1. Since the ANN is trained by using the features obtained from the AR model we developed, evaluate the features for the new cases only using the same program, and not others.
2. The program can be run as many times as possible by clicking on the 'Run' button for different cases.

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