Acquisition and Classification of Heart Rate Variability Using Time-Frequency Representation

By

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Abstract

It has been shown that the heart rate varies not only in relation to the cardiac demand but is also affected by the presence of cardiac disease and diabetes. Furthermore, it has been shown that heart rate variability may be used as an early indicator of cardiac disease susceptibility and the presence of diabetes. Therefore, the heart rate variability may be used for early clinical screening of these diseases. In order to reliably assess the patient's condition, the heart rate variability information is determined from an electrocardiogram data acquisition system. Once collected, the heart rate variability signal is characterised and used as a basis for classification.

This study details the development of a heart rate variability data acquisition system, method of collecting known patient data, and design of a signal-processing algorithm that characterises heart rate variability information to be used as a basis for patient classification. Specifically, six sets of 5 minute electrocardiogram signals are collected by a personal computer based data acquisition system in a clinical setting. Consecutive R-wave deflections are detected from the electrocardiogram and used to determine the individual heart beat intervals. The outlying measurements are then removed and the remaining data is interpolated. The processed data is then characterised using time-frequency analysis and specific features are determined. Lastly, these features are used as a basis in a classification system. The results are then compared to the known patient conditions and the effectiveness of the screening procedure is determined.
Acknowledgements

The author would like to extend his appreciation to his supervisor Prof. A E A Almaini of the School of Engineering at Napier University. Though this study was carried out far from Edinburgh, Prof. Almaini was close by through his guidance and oversight. Furthermore, sincere gratitude is extended for Prof. Almaini's patience and willingness to travel to the United Arab Emirates in order to meet face to face and view the study first hand.

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Declaration

I declare that no material contained in this thesis has been used in any other submission for an academic award.

[Signature]

Mr. Michael Jacobson
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<th>Symbol</th>
<th>Description</th>
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<tbody>
<tr>
<td>$\Delta f$</td>
<td>Frequency Resolution</td>
</tr>
<tr>
<td>$\psi_{j,n}$</td>
<td>The mother wavelet at scale $j$ and location $n$.</td>
</tr>
<tr>
<td>$\phi_{j,n}$</td>
<td>The scaling function at scale $j$ and location $n$.</td>
</tr>
<tr>
<td>$\Delta t$</td>
<td>Time Resolution</td>
</tr>
<tr>
<td>ABP</td>
<td>Arterial Blood Pressure</td>
</tr>
<tr>
<td>AFT</td>
<td>Autonomic Function Tests</td>
</tr>
<tr>
<td>$A_j[n]$</td>
<td>The WT approximation coefficient at scale $j$ and location $n$.</td>
</tr>
<tr>
<td>ANS</td>
<td>Autonomic Nervous System</td>
</tr>
<tr>
<td>AR</td>
<td>Autoregressive</td>
</tr>
<tr>
<td>BR</td>
<td>Baroreceptor</td>
</tr>
<tr>
<td>CHD</td>
<td>Coronary Heart Disease</td>
</tr>
<tr>
<td>CHDD</td>
<td>Coronary Heart Disease with Diabetes Mellitus</td>
</tr>
<tr>
<td>CVD</td>
<td>Cardiovascular Disease</td>
</tr>
<tr>
<td>DAN</td>
<td>Diabetic Autonomic Neuropathy</td>
</tr>
<tr>
<td>DAQ</td>
<td>Data Acquisition</td>
</tr>
<tr>
<td>$D_j[n]$</td>
<td>The WT detail coefficient at scale $j$ and location $n$.</td>
</tr>
<tr>
<td>DM</td>
<td>Diabetes Mellitus</td>
</tr>
<tr>
<td>DWT</td>
<td>Discrete Wavelet Transform</td>
</tr>
<tr>
<td>ECG</td>
<td>Electrocardiogram</td>
</tr>
<tr>
<td>EEG</td>
<td>Electroencephalogram</td>
</tr>
<tr>
<td>FFT</td>
<td>Fast Fourier Transform</td>
</tr>
<tr>
<td>$F_s$</td>
<td>Sample rate ($F_s = 1/T_s$).</td>
</tr>
<tr>
<td>FT</td>
<td>Fourier Transform</td>
</tr>
<tr>
<td>FWT</td>
<td>Fast Wavelet Transform</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
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<tr>
<td>--------------</td>
<td>-------------</td>
</tr>
<tr>
<td>g, h</td>
<td>The high pass and low pass quadrature mirror filters.</td>
</tr>
<tr>
<td>HF</td>
<td>High Frequency Band of the HRV Signal</td>
</tr>
<tr>
<td>HP</td>
<td>Heart Period</td>
</tr>
<tr>
<td>HPF</td>
<td>High Pass Filter</td>
</tr>
<tr>
<td>HR</td>
<td>Heart Rate</td>
</tr>
<tr>
<td>HRV</td>
<td>Heart Rate Variability</td>
</tr>
<tr>
<td>IQRNN</td>
<td>Inter-Quartile Range of Normal-to-Normal Beat Intervals</td>
</tr>
<tr>
<td>K</td>
<td>The dimension of the response space (the number of classes).</td>
</tr>
<tr>
<td>L</td>
<td>The dimension of the reduced feature set.</td>
</tr>
<tr>
<td>LF</td>
<td>Low Frequency Band of the HRV Signal</td>
</tr>
<tr>
<td>LPF</td>
<td>Low Pass Filter</td>
</tr>
<tr>
<td>M</td>
<td>The dimension of the original feature set.</td>
</tr>
<tr>
<td>MAP</td>
<td>Mean-Average Pressure</td>
</tr>
<tr>
<td>N</td>
<td>The dimension of the measurement space (the length of the time series in samples). Also used to indicate the normal patient class.</td>
</tr>
<tr>
<td>NaN</td>
<td>Not a Number</td>
</tr>
<tr>
<td>PC</td>
<td>Personal Computer (IBM Compatible)</td>
</tr>
<tr>
<td>PS</td>
<td>Power Spectrum</td>
</tr>
<tr>
<td>PSA</td>
<td>Power Spectral Analysis</td>
</tr>
<tr>
<td>PSD</td>
<td>Power Spectral Density</td>
</tr>
<tr>
<td>PVC</td>
<td>Pre-Ventricular Contraction</td>
</tr>
<tr>
<td>QRS</td>
<td>Ventricular Beat Complex of the ECG</td>
</tr>
<tr>
<td>RMS</td>
<td>Root – Mean - Square</td>
</tr>
<tr>
<td>rMSSD</td>
<td>Root-Mean-Squared of Successive Difference</td>
</tr>
<tr>
<td>RR</td>
<td>Interval Time Between Consecutive ECG R-Waves</td>
</tr>
<tr>
<td>RSA</td>
<td>Respiratory Sinus Arrhythmia</td>
</tr>
<tr>
<td>SABP</td>
<td>Systolic Arterial Blood Pressure</td>
</tr>
</tbody>
</table>
SDANN Standard Deviation of 5 minute Normal-to-Normal Beat Interval Averages
SDNN Standard Deviation of Normal-to-Normal Beat Intervals
SDNNIDX Mean of the STD of Normal-to-Normal Beat Intervals
SDSABP STD of the SABP
STD Standard Deviation
STFT Short-Time Fourier Transform
UAE United Arab Emirates
VI Virtual Instrument (LabVIEW programme)
VLF Very Low Frequency Band
w_{j,k,n} WT or WPT basis vector at scale j, subband k, and location n.
WT (Discrete) Wavelet Transform
X The measurement space. This is a time series, such that x ∈ X ⊆ \mathbb{R}^N, where x = [x_1, x_2, ..., x_N]^T. This is equivalent to the expression x = \{x[1], x[2], ..., x[N]\}.
Y The response space. The output may be assigned to one of K classes, y ∈ Y = [y_1, y_2, ..., y_K].
ZC Zero Crossing
Chapter 1 - Introduction

1.1. Objectives

The primary objective of this work is to research the effectiveness of a clinical system for an expedient, non-invasive, screening of patient susceptibility to coronary heart disease (CHD) and the presence of diabetic mellitus (DM). Specifically, this work seeks to accomplish the following specific objectives.

- In order to research the effectiveness of the proposed screening system, a computer based, clinical data acquisition (DAQ) system for collecting electrocardiogram (ECG), respiration, and arterial blood pressure (ABP) data is designed and implemented. The system not only acquires the patient's physiological waveforms, but also stores the patient's physical dimensions, medical history, and laboratory results in order to confirm the patient's known condition and later assess the system's screening performance. The system also incorporates a clinical methodology in order to evoke a response from the patient's cardiac system, specifically, a change in the patient's heart rate (HR).

- Various signal processing algorithms are investigated and applied to the patient heart rate variability (HRV) signal, which is derived from the ECG signal. The objective is to research which algorithms best distinguish between diseased and normal patients. Furthermore, additional algorithms are investigated and applied to the patient respiration and ABP information in order to research if additional physiological information provides for enhanced patient screening for the presence of DM and CHD.
The effectiveness of the proposed screening system is researched by comparing the screening results to the known patient conditions. Specifically, the clinical screening system classifies a patient as normal (N) or having DM, CHD, or diabetic coronary heart disease (CHDD). The screening performance is assessed using the common medical statistics of sensitivity, specificity, positive predictive value and negative predictive value.

1.2. Thesis Outline

Chapter 1 presents the thesis objectives and provides a background of the physiological processes that regulate HRV. Current research related to HRV is also presented as well as analysis methods for characterising and classify physiological signals.

Chapter 2 provides details of the clinical DAQ system. Specifically, the clinical methodology for collecting the patient data is described. Additionally, the hardware components are explained and the custom-written DAQ and utility programmes are presented.

Chapter 3 discusses the bio-signal processing algorithm to extract HRV from ECG. In particular, the chapter presents the detection of the cardiac cycles in the ECG signal and the method of computing the HR for each beat. Considerations of removing possible outlier data are discussed as well as methods for removing the HRV signal trend.

Chapter 4 presents various methods and algorithms to analyse the HRV signal. Specifically, time domain based methods, frequency domain based methods, and time-frequency based methods are applied to the HRV signals of several sample patients and then compared. These analyses are later used as a basis for patient classification.
Chapter 5 presents the bio-signal processing algorithms for ABP analyses. The systolic and diastolic cyclic pressure limits are extracted from the ABP signal. Furthermore, the maximum change in pressure per cardiac cycle and the QA interval, which is an ABP-ECG data fusion algorithm, is presented and applied to several sample patients. Similar to HRV analyses, these analyses are later used as a basis for patient classification.

Chapter 6 compares the results of classification based upon various analyses features. In particular, patients with known conditions are used to train a classification system using supervised learning. The trained classification system is then tested on the patients and the classification error is compared for each set of features.

Chapter 7 provides a summary of the observations and conclusions of this research. Original contributions by the author are itemised and suggestions for future investigations are discussed.

1.3. Diabetes Mellitus

Diabetes Mellitus (DM) is characterised by abnormal, elevated blood glucose concentrations and is categorised into two types. Type I DM is a severe, chronic form of diabetes caused by insufficient production of insulin and resulting in abnormal metabolism of carbohydrates, fats, and proteins. Type I DM typically appears in childhood or adolescence, and is fatal if untreated. Type I DM is characterised by not only increased glucose levels in the blood and urine, but also excessive thirst, frequent urination, acidosis, and wasting. Type I DM is also called insulin-dependent diabetes. [1]
More common than Type I, is the Type II DM form of diabetes that typically appears in adulthood and also called non-insulin-dependent diabetes. In the United States of America (USA), there are over 10 million diagnosed cases with an estimated 5.9 million Americans who are unaware they are diabetic. Of the diagnosed cases of DM, 90% are Type II DM. [2] [3] In the United Arab Emirates (UAE) 19% of the people over 20 years of age is diabetic. Furthermore, 50% of all patients treated in hospitals of the UAE were unaware they were diabetic. [4] Also in the Arabian Gulf, it has been recorded that 15% of the Omani population is diabetic. [5] Beyond the Gulf, the World Health Organisation (WHO) estimates 135 million diabetics [6] and in the future, the US Centre for Disease Control (CDC) estimates an increase of Type II DM of 165% over the next 50 years. [7] The Emirates Medical Association's Diabetes Society estimates 50% of the UAE population will be diabetic within the next 25 years. [8]

Complications due to DM contribute to over 200,000 deaths in America per year. [9] Complications include blindness, kidney failure, retinopathy, neuropathy, and disability when amputation is necessary. Furthermore, DM is the leading cause of heart disease and stroke. In fact, diabetic cardiovascular disease (DCVD) is the leading cause of death for people with DM, who are 2 to 4 times more likely to suffer heart trouble than people without DM. Additionally, 70% of diabetic patients are more likely to die prematurely if they experience a heart attack. [10]

Common symptoms of DM include frequent urination, extreme thirst, unexplained weight loss, blurred vision, frequency or reoccurring skin, gum or bladder infections, unusual fatigue or drowsiness and occasionally, numbness or tingling in the hands and feet. However, many DM patients experience no symptoms at all. Traditional clinical diagnosis involves a routine of monitoring the blood glucose levels over several hours.
in response to glucose ingestion. Of course, this test does not indicate the progression of the disease or presence of diabetic complications. [11]

1.4. Diabetic Autonomic Neuropathy

Diabetic autonomic neuropathy (DAN), as defined by the 1988 San Antonio (Texas) consensus meeting, is a descriptive term restricted to disorders in the autonomic nervous system, manifesting as dysfunction of several organ systems. [12] Specifically, DAN is nerve damage caused by decreased blood flow and high blood-glucose levels. Autonomic neuropathies affect the nerves that regulate involuntary vital functions, such as the HR, digestion, and metabolism. The prevalence of observable neuropathy among diagnosed diabetics approaches 60%. [13]

DAN encompasses disturbances in reflex arcs involving one or more sensors, an afferent branch, a central processing unit, an efferent branch and neuromuscular junctions. [14] Symptoms of DAN are vague, non-specific and signs are difficult to detect, except in advanced stages of the disease. Even so, DAN is associated with increased morbidity and mortality with nephropathy, cardiac arrhythmias, myocardial ischaemia and sudden cardiac death all associated with DAN. [15] [16]

Diagnosis of DAN involves the Autonomic Function Tests (AFT) [17] recommended by the San Antonio (Texas 1988) consensus meeting. The tests include HR and Arterial Blood Pressure (ABP) responses to standing up, HR response to deep breathing, ABP response to sustained handgrip, HR response to Valsava manoeuvre, and spectral analysis of HR and ABP variability.
Success of a test in clinical practice depends on many factors that usually differ from accepted research tests. The clinical procedure must incorporate simplicity, which is a non-complex methodology that may be carried out by one person and requires minimal patient cooperation. The procedure must also be safe and entails no unnecessary risk to the patient. Lastly, the procedure must be cost effective, reproducible, time efficient, and have easily interpretable results.

When assessing DAN using the AFT HR response to sustained handgrip, the following methodology is used. First, the maximum patient handgrip contraction is determined and then the patient is requested to sustain a handgrip of 30% of maximum contraction for up to 5 minutes. ABP is measured every minute, and the difference between the diastolic blood pressure before the release of the handgrip and the start of the test is taken as the measure of the response. However, the response is related to the strength of contraction and has a strong gender influence. Moreover, adequate performance is beyond the ability of many diabetic and elderly subjects. [18] The test is cumbersome and of limited use in a practical clinical setting.

HR and ABP responses to Valsava manoeuvre are complex and difficult to perform in a clinical environment. The procedure consists of forced expiration to a set pressure against a closed expiratory route. There is an initial rise in the ABP and a baroreceptor reflex (BR) mediated decrease in HR. The BR refers to bio-sensors that detect pressure in the aortic arch and carotid arteries. With a decrease in HR, a fall in ABP occurs, followed by an increase in HR and thus a recovery of the ABP. Immediately after the termination of the test, there is a transient increase in ABP, leading to a fall in HR. Needless to say, this complex response is difficult to index and use as an assessment of DAN. Therefore, both the Valsava manoeuvre and ABP response to sustained handgrip were not considered in this study.
Requesting a patient to change from a horizontal (supine) position to a vertical (standing) position brings the influence of gravity on the circulatory system, and thus, a greater cardiac load. With an increased load, the ABP decreases which causes an increase in HR due to the BR reflex. Lastly, with an increase in HR, the ABP increases. This is then followed by a decrease in the HR, for normal patients. This AFT test is easily implemented by requesting the patient to lie quietly (supine) for at least 5 minutes, then stand up unaided as quickly as possible, and remain standing thereafter for another 5 minutes. The test is objective, reproducible and does not depend on age or resting HR. Furthermore, this test has been proven to detect the earliest physiological changes in approximately two thirds of DM patients. [19] [20]

The HR response to deep breathing is also used as an AFT, and is termed respiratory sinus arrhythmia (RSA). The RSA is measured by requiring the patient to lie quietly and breathe deeply at a specified rate, which produces maximum variations in HR. In most studies RSA is quantified as the mean ratio between the maximum and minimum HR during consecutive deep breaths (HRMAX / HRMIN). However, there is no consensus on the exact clinical method or how the response is quantified. [21]

1.5. Coronary Heart Disease

CHD and Cardiovascular Disease (CVD) include various dysfunctions of the circulatory system, and accounts, by far, for the greatest cause of morbidity in the USA, as shown in the 1996 morbidity statistics of Figure 1.1. [22] In the UAE, CVD mortality accounted for 25% of all deaths in the year 2000, and 49% of all non-communicable diseases. [23]
Figure 1.1 lists DM mortality separate from CVD mortality, and the number of CVD deaths with DM as the underlying cause is not recorded. [24] However, it is known that DM patients are 2 to 4 times more likely to develop CVD than non-DM patients. In the UAE, 43% of DM diagnosed patients are recorded in the CVD mortality statistics. [25] Similarly in the USA, CVD accounts for 65% of DM deaths. [26]

![USA Mortality in 1996](image)

Figure 1.1: USA Mortality in 1996.

Early detection of CHD prior to clinical events, coupled with implementations of preventive management strategies, can delay the progression of the disease. In fact, proper diet, physical exercise, cessation of smoking, control of blood pressure and reduced cholesterol lowers a patient's odds of myocardial infarction by 19 times, as shown in Figure 1.2. [27] [28]

Primary screening of CHD involves the Exercise ECG Test, which, if positive, is followed by coronary angiography to diagnose CHD. This test involves monitoring the
12-lead ECG signal while the patient is requested to perform an increasing physical activity, usually moderated by a treadmill. Specifically, the test begins with the patient at a slow anaerobic pace and ends with an aerobic run. Throughout the procedure, the clinical technician monitors the ECG morphology, checks for ectopic beats, and notes the presence of cardiac arrhythmia. Based upon the results, the patient is recommended for angiography in order to confirm the presence of CHD.

However, recent studies have shown the Exercise ECG Test to be a poor indicator of the presence of CHD in patients. A recent JAMA publication has shown that patients who receive angiography have far less incidents of myocardial infarction than those patients who pass the Exercise ECG Test. [29] [30] On a personal note, the author's father-in-law suffered a myocardial infarction five months after an Exercise ECG screening indicated no presence of CHD. Some have suggested augmenting the screening through analysis of the HRV for improved diagnosis. [31] Even so, many disabled, obese and

![Graph showing myocardial infarction risk given known patient condition.](image-url)
elderly patients are not able to perform the physical requirements of the Exercise ECG screening. Thus, another simple and low-cost clinical screening of CHD is required.

1.6. Non-Invasive Physiological Signals

With the development of cost-effective computers and DAQ systems, use of non-invasive physiological signals for clinical diagnosis and screening has increased greatly. [32] Physiological signals include mechanical measurements of ABP, respiratory pressure, bladder pressure, blood flow, heart sounds, and body temperature. Physiological signals also include electrical measurements of ECG, electroencephalogram (EEG), electromyogram (EMG), galvanic skin response (GSR), and many other electrical signals of the body. Beyond this, new systems are being developed for clinical chemical measurements of blood oxygen and carbon dioxide saturation through the use of infrared light reflection and absorption. [33] From these physiological measurements, secondary measurements are computed, such as respiration from the respiratory pressure and HR from ECG or ABP signals. Non-invasive measurements minimise risk of infection, require no analgesics, and reduce measurement artefact due to patient stress, such as adrenalin and hypertension.

Currently, most non-invasive physiological measurements are analysed directly by the clinical physician or technician. However, with the advancement of low-cost computational power, the clinical diagnosis may be efficiently automated in order to screen more patients in a workday, reduce the screening cost, and minimise the possibility of misdiagnosis due to human error.

The process of automating the clinical diagnosis involves acquisition of the physiological signal, characterisation of the signal through analysis and feature
extraction, and, lastly, classification of the patient condition, as displayed in Figure 1.3.

The type of signal analysis and feature selection employed depends empirically on which best highlights the differences between normal and diseased patients. Classification is implemented through traditional clustering based upon the Euclidean distance or by neural networks (NN), both of which are discussed later in this chapter.

**Figure 1.3: Algorithm for analysing and classifying a physiological signal.**

Signal analysis may be categorised into time-based analysis, frequency-based analysis, and time-frequency based analysis. Time-based analysis involves the application of mathematical procedures directly to the measured physiological samples. Frequency-based analysis involves first translating the measurements into the frequency domain where analysis of the power spectrum is performed. Time-Frequency analysis involves analysis of the power spectrum while preserving the time information of the physiological measurements. The best analysis method for characterising the signal is the one that provides the best classification.

### 1.6.1. Time-Based Analysis

Statistical analysis of the measured physiological signal is commonly used to characterise the signal for categorising the patient condition. The most common
statistical analysis algorithms are the mean and standard deviation (STD), as defined in Equation 1.1. The mean computation determines the average value while the STD determines the spread or breadth of the signal values. Since most physiological measurements are sampled and represented as numerical values in a computer, the sample mean and sample STD are used to provide an estimate of the mean and STD, as defined in Equation 1.2.

\[ \bar{x} = \frac{1}{T} \int_{0}^{T} x(t) \, dt \]
\[ \sigma = \sqrt{\frac{1}{T} \int_{0}^{T} x^2(t) \, dt - \bar{x}^2} \]

Equation 1.1: Mathematical definition of the mean and standard deviation for signal, \( x \), over period, \( T \).

\[ \bar{x} = \frac{1}{N} \sum_{n=0}^{N} x(n) \]
\[ \sigma = \sqrt{\frac{1}{N} \sum_{n=0}^{N} x^2(n) - \bar{x}^2} \]

Equation 1.2: Mathematical definition of the sample mean and sample standard deviation for signal, \( x \), with total number of samples, \( N \).

It has been noted that the sample mean and sample STD are sensitive to outlying samples since the entire sample set is used in their computation. An outlying sample is defined as a sample that differs significantly from the entire population, possibly due to measurement error. Including an outlier in the computation greatly affects the estimate of the mean and standard deviation. Therefore, it is suggested to estimate the mean and STD using the sample median and inter-quartile range. The median is defined as the 50% percentile of the sample set, and the inter-quartile range is defined as the difference between the 75% and 25% percentiles of the sample set, per Equation 1.3. Note that since the median and inter-quartile range both employ a sorting function, the outlying
samples are shifted above and below the upper and lower quartiles, respectively, and so, have little effect on the estimate of the mean and STD. [34]

\[
\bar{x} = S(x(I(0.5N))) \\
\sigma = S(x(I(0.75N))) - S(x(I(0.25N)))
\]

Equation 1.3: Mathematical definition of the sample median and inter-quartile range. N defines the total number of samples, I defines the greatest integer function, and S defines the sorting function.

Beyond the mean and standard deviation, time based analysis also includes histogram analysis, derivative analysis, and non-linear analyses. Each of these analyses performs mathematical operations on the physiological sample set in order to highlight differences in the patient condition before estimating the mean and STD.

1.6.2. Frequency-Based Analysis

In the early 1800s, while researching the effects of heat transfer, Fourier published a method to analyse a signal's frequency composition. In particular, if a signal meets certain criteria, he proved that the signal may be expressed as a sum of sine waves of various amplitudes and frequencies, per Equation 1.4, which is termed the Fourier Series (FS).
• X must be periodic: \( x(t) = x(t + T) \), where \( T \) is the signal period.

• X has a finite number of discontinuities in a period.

• X has a finite number of maxima and minima in a period.

• X may be integrated over a period \( \int_0^T |x(t)| \, dt < \infty \).

If all these conditions hold, then \( x(t) = \sum_{n=0}^{\infty} \left( a_n \cos(n\omega_0 t) + b_n \sin(n\omega_0 t) \right) \).

Equation 1.4: Conditions for the existence of the Fourier series.

Equation 1.5 displays a more generalised form of FS using the exponential sinusoidal equivalence. The Fourier coefficient, \( c_n \), is determined according to the second part of Equation 1.5. Note that the Fourier coefficient depends solely on the signal period and frequency, \( f_0 \), since the time is integrated out.

\[
x(t) = \sum_{n=-\infty}^{\infty} c_n e^{j2\pi nf_0 t}
\]

where, \( c_n = \frac{1}{T} \int_{-T/2}^{T/2} x(t) e^{-j2\pi nf_0 t} \, dt \)

Equation 1.5: Generalised Fourier series.

Frequency analysis of a signal involves computation of the Fourier coefficient for various frequencies. In particular, the signal period is taken to approach infinity, per the first line of Equation 1.6. The period of a signal is defined as the amount of time for one cycle, and frequency of a signal is defined as the number of cycles per second. Therefore, the period is the inverse of the signal frequency, per the second equation of Equation 1.6, which is then substituted into the third line. As the frequency limit approaches infinity, the integral is defined, per the last line of Equation 1.6. This line also defines the Fourier transform (FT), which computes the signal's magnitude as a function of frequency instead of time.
1. \[ x(t) = \lim_{T \to \infty} \frac{1}{T} \sum_{n=-\infty}^{\infty} X(nf_o) e^{j2\pi nf_o t} \]

2. Let \( \Delta f = \frac{1}{T} \)

3. \[ x(t) = \lim_{\Delta f \to 0} \sum_{n=-\infty}^{\infty} X(nf_o) e^{j2\pi nf_ot} \Delta f \]

4. \[ x(t) = \int_{-\infty}^{\infty} X(f) e^{j2\pi nf} df \quad X(f) = \int_{-\infty}^{\infty} x(t) e^{-j2\pi ft} dt \]

Equation 1.6: Derivation of the Fourier Transform.

The FT is then used to analyse a set of sample measurements by determining the most influential frequencies; specifically, which frequencies, \( f \), have the greatest magnitude, \( |X(f)| \). Once the FT is computed for a set of frequencies, the mean of the signal magnitude at various frequency ranges, or spectrum, is computed in order to characterise the signal for classification.

The time interval of the physiological measurement relates to the lowest resolvable frequency. Since the period (time interval) is inversely related to the frequency, the smallest measurable frequency is the maximum time interval. For example, if it is desired to analyse 0.05 Hz in a signal, then at least a 20-second \((1/0.05)\) measurement of the physiological signal is required. Similarly, higher frequencies require less measurement time.

The highest resolvable frequency of the FT is defined by the sampling rate of the signal. With use of computers and DAQ systems, most physiological signals are sampled at a particular rate. This rate defines the maximum resolvable frequency and is termed the Nyquist frequency. Specifically, Nyquist sampling theorem states that the largest frequency component of a measured signal must be at most half of the sampling frequency.
This may be easily shown by considering the chart in Figure 1.4. Given the original spectrum of the physiological signal, sampling has the effect of duplicating the spectrum about multiples of the sampling frequency. If the original spectrum of the physiological signal is greater than half of the sampling frequency, then upper frequencies of the physiological signal overlap, which is termed, aliasing. Aliasing appears as distortions in the signal after sampling, and so, must be avoided by a proper choice of the sampling frequency. In practice, the sampling frequency is set to a minimum of 2.5 times the largest frequency of interest in the physiological signal. For example, if the HRV physiological signal has frequency bandwidth less than 2 Hz, then the signal may be sampled at 2.5 times 2 Hz, or 5 Hz.

Figure 1.4: Pictorial explanation of Nyquist sampling theorem and the minimum allowable sampling frequency.

Use of the FT in signal analysis is common and often applied without considering the signal's parameters. Specifically, it is important to note that the conditions of existence for the FT are the same as the FS. Also, it is important to note that since time is integrated out, the time of events occurring in the signal is lost. Thus, if the signal is non-stationary, in other words, changes over time, the time information concerning
these events is lost. For example, consider stationary signal, X, and non-stationary signal, Y, of Figure 1.5. Both signals consist of three sine waves with different frequencies, 100 Hz, 200 Hz, and 300 Hz. Both signals are observable different, as one signal is the addition of three sine waves and the other consists of one sine wave for a time, a second sine wave for a time, and lastly, the third. The FT of both of these signals is displayed in Figure 1.6. Note that although both signals are observably different in time, the FT of each is essentially the same. This is due to the time-invariant requirements of the FT. Since time is integrated out, the FT only displays peaks at the three main frequencies of interests, whether or not the three frequencies are summed together or occur in separate time intervals.
Figure 1.5: Stationary signal, \( Y \), and non-stationary signal, \( X \), respectively.
In regards to physiological signals, most are considered time varying. In other words, the signal changes in shape, amplitude, and spectrum over time. At one time, certain frequencies of a signal peak, and at a later time, other frequencies of a signal dominate. For example, the surface electrical activity of the brain (EEG) is known to have a different frequency spectrum depending on whether the subject is awake or asleep. Therefore, if the FT is taken of the EEG over an entire day, the time of the awake and asleep period spectral differences is lost.

Even so, physiological signals are often considered to be 'wide-sense' time-invariant. That is to say, the signal is assumed to not change much over a certain time interval. In
relation to the previous EEG example, the signal may be considered time-invariant over short time periods, over which the patient's condition is known to change little.

1.6.3. Time-Frequency Analysis: Short Term Fourier Transform

In order to determine time of changes in the physiological signal spectrum, time-frequency analysis is performed. The short-term Fourier transform (STFT) corrects the loss of time indexing of FT by segmenting the signal into regular time intervals before computing the FT of each. Considering the previous example of stationary signal, X, and non-stationary signal, Y, of Figure 1.5. The STFT was computed for each of these signals and displayed in Figure 1.7. Specifically, the example signals were divided into three time intervals, 0-0.03 seconds, 0.03-0.06 seconds, and 0.06-0.09 seconds. The FT was then computed for each interval and normalised. Note that each example signal has a very different STFT with both the time and frequency information being preserved. Therefore, if the physiological signal requires information concerning the time of the spectral events, STFT analysis is appropriate. [35]

However, STFT analysis is deficient in being able to resolve both the time and frequency information. Recall that the FT requires longer time intervals in order to resolve lower frequencies. Thus, the minimum possible time interval, \( \Delta t \), is set by the lowest frequency of interest. Specifically, the time and frequency resolution is governed by the Heisenberg inequality, per Equation 1.7. In other words, the more precise the frequency analysis, the worse the time resolution is. And, the better the time resolution, the worse the frequency resolution is. This deficiency in the STFT has led to multidimensional signal analysis, whereby the resolution of the time and frequency are variable depending upon the range of the time and frequency measurements.
Figure 1.7: The short-term Fourier transform of signals Y and X, respectively, over the time intervals, 0-0.03 seconds, 0.03-0.06 seconds, and 0.06-0.09 seconds. The z-axes display the normalised magnitude.

\[
(\Delta f)(\Delta t) \geq \frac{1}{4\pi}
\]

Equation 1.7: Heisenberg inequality as it relates to the STFT time and frequency resolution.
1.6.4. Time-Frequency Analysis: Wavelet Transform

Similar to the STFT, the wavelet transform (WT) provides the decomposition of a signal over time and frequency. However, instead of decomposing the signal over sine waves, as is done with the STFT, the decomposition is carried out over another function, termed the 'mother wavelet,' as shown in Equation 1.8. The Heisenberg inequality for time and frequency resolution still applies to the mother wavelet, as it did to the STFT; however, the mother wavelet is then scaled and shifted in time in order to provide multiple time and frequency resolutions, which is also shown in Equation 1.8.

\[ f \in L^2(\mathbb{R}) \quad \text{if} \quad \int |f|^2 < \infty \]

\[ f = \sum \lambda c_\lambda \Psi_\lambda \]

\[ W_t f(x) = f(x) \ast \Psi_s(x) = \frac{1}{s} \int \hat{f}(t) \Psi \left( \frac{x-t}{s} \right) dt \]

\( \Psi = \) Mother Wavelet

\( s = \) Scale Factor (\( s = 2^i \), where I is an integer)

Equation 1.8: The wavelet transform and existence conditions.

The mother wavelet scaling (changes in the frequency resolution) and dilating (changes in the time resolution) are carried out in powers of two with low frequencies having longer time intervals than higher frequencies. This gives the WT a major advantage over the STFT by enabling multiple resolutions, as is shown in Figure 1.8.
The choice of the mother wavelet depends upon the signal being analysed. In particular, the mother wavelet is chosen to match, and thus, highlight the areas of interest in the signal. If the signal to be analysed is sampled, then the discrete wavelet transform (DWT) is used to perform the decomposition. For example, Figure 1.9 illustrates a sample DWT decomposition using a Haar mother wavelet. [36] The Haar mother wavelet is defined as $1$ over half the time interval and $-1$ over the remainder of the time interval, per Figure 1.9.

Similar to FT and FS, the decomposed signal may be reconstructed. In regards to Figure 1.9 the original function, $f_0$, is recoverable as the sum of $f_2$, $\theta_1$, and $\theta_2$. The function, $f_2$, is termed the 'approximation' and contains the lowest frequency information of the original signal, $f_0$. The $\theta_i$ signals are termed the 'details' and contain various frequency ranges of the original signal, $f_0$. Note that throughout the decomposition, the time information has been preserved.
The WT is applied to the previous example stationary signal, X, and non-stationary signal, Y, of Figure 1.5. Recall that each signal consists of the same three frequencies, 100 Hz, 200 Hz, and 300 Hz, but are noticeably different with signal Y consisting of the sum of the three frequencies and signal X being a single sine wave which has a different frequency over each time period, 0-0.03 seconds, 0.03-0.06 seconds, and 0.06-0.09 seconds. The Haar wavelet is employed and the WT decomposition for each signal is displayed in Figure 1.10. Specifically, the time, approximation and detail coefficients for the first six levels are displayed. In order to better display the signal power, the absolute value is taken of each coefficient. Also, note that the detail level correlates to frequency ranges, with the lowest detail corresponding to the greatest frequency range.
Figure 1.10: Wavelet transform of example signals, Y and X, respectively. The z-axes display the absolute wavelet detail coefficients.
Visual inspection of Figure 1.10 displays a marked difference between the two charts. The time-invariant signal, $Y$, exhibits a similar frequency structure over the entire time interval while the time-varying signal, $X$, displays significant changes in the frequency structure over each time each of the 0-0.03, 0.03-0.06, and 0.06-0.09 second time intervals. In particular, the time-varying signal, $X$, exhibits the lowest frequency power during the 0-0.03 second time interval and highest frequency power is displayed in the 0.06-0.09 second time interval.

According to FT identities, a periodic, sampled signal in the time domain becomes a periodic, sampled signal in the frequency domain. Using this fact, computer algorithms, termed the 'Fast Fourier Transform' (FFT) have been developed to efficiently compute the FT coefficients. Similarly, the 'Fast Wavelet Transform' (FWT) has been developed to efficiently compute the WT coefficients. With computational efficiency and better resolution, the WT is rapidly replacing the STFT for analysis of time-varying signal.

### 1.6.5. Euclidian Classification Techniques

Once a physiological signal has been analysed, the resulting features are used as a basis for classification. Classical classification methods involve computation of the Euclidian distance, as shown in Equation 1.9. The signal characterisation, $X$, may be multidimensional, and is assigned the class, $C$, to which $X$ is closest to the class centre, $c$.

\[
D = \sqrt{\sum_{i=1}^{N} (x_i - c_i)^2}
\]

Equation 1.9: Multidimensional distance formula between arrays $X$ and class centre, $c$. 

43
For example, it is desired to classify an unknown patient condition to one of four known conditions, as shown in Figure 1.11. This is accomplished by computing the Euclidian distance between the unknown condition and each of the four known patient conditions. The unknown condition is assigned to the condition which gives the minimum distance. This type of classification is termed a nearest-neighbour classifier and is implemented in Figure 1.12 by a MatLab m-file.

```matlab
Function [class]=class4data(data, c1, c2, c3, c4)
% CLASS4DATA Given an matrix of data, this function classifies the data
% according to the class centres, c1, c2, c3 and c4, using
% the nearest neighbour criteria.
% The data is organized into a matrix of column data sets and
% row features. A 1 indicates classification to class 1, 2 indicates class 2,

class=[]; Ld = size(data);
for i=1:Ld(2)
    t1 = sum((c1 - data(:,i)).^2).^(1/2);
    t2 = sum((c2 - data(:,i)).^2).^(1/2);
    t3 = sum((c3 - data(:,i)).^2).^(1/2);
    t4 = sum((c4 - data(:,i)).^2).^(1/2);
    if (t1 < t2) & (t1 < t3) & (t1 < t4)
        class = [class 1];
    else
        if (t2 < t1) & (t2 < t3) & (t1 < t4)
            class = [class 2];
        else
            if (t3 < t1) & (t3 < t2) & (t3 < t4)
                class = [class 3];
            else
                class = [class 4];
            end;
        end;
    end;
end;
```

Figure 1.12: Classification based upon the minimum Euclidian distance to the class centre.
Besides minimum distance, Euclidian classification may consider the probabilistic distribution of the known patient conditions. This type of classification is known as Bayesian classification, which provides a significant improvement in classification performance. Specifically, the condition decision is based upon discriminating functions, which are used to determine the classification, as shown in Figure 1.13.

![Figure 1.13: Classification into one of N conditions according to discriminating function, gj.](image)

The discriminating functions may be determined by either supervised or unsupervised learning. [37] Supervised learning has the advantage of training the classifier with known patient conditions and the associated probabilistic distributions. Unsupervised learning does not require a priori knowledge of the patient conditions and can even estimate the number of different patient conditions within a data set; however, this is often set as an input to the algorithm.

Figure 1.14 displays an algorithm flowchart that uses unsupervised learning and Euclidian minimum distance in order to determine N class centres. Specifically, the algorithm initialises by assigning the first N samples of the data to the N cluster centres, respectively. Then, these cluster centres are used as a basis for classification by assigning each sample to the nearest class centre. Once all the samples have been assigned to one of N classes, a new class centre is computed from the assigned class
members. Termination occurs when the new class centres do not change by $\delta$ from the previous class centres.

Figure 1.14: Flowchart of the unsupervised learning algorithm for $N$ clusters.

Figure 1.15 displays a MatLab m-file implementation of the flowchart in Figure 1.14 for computing four class centres using unsupervised learning. As with the flowchart, the algorithm begins by assigning the class centres to the first four samples. Then the entire sample set is classified using the minimum distance, or nearest neighbour, criteria. That is, each sample is assigned to the class which gives a minimum distance to that class's centre. Once all the entire data set has been classified, the class centres are re-computed...
as the sample mean of all the class members. Then, using the new centres, the entire sample set is again classified, and the class centres are again computed. The algorithm terminates when the Euclidian distance between the old class centres and the new class centres is less than a given value, δ. For robustness and to avoid oscillatory conditions, a maximum of 1000 iterations is allowed for the algorithm.

Supervised learning incorporates knowledge about the patient condition. Specifically, if the observations of the known patient conditions are normally distributed, then the observation mean and STD may be used to describe the class centre and distribution. Furthermore, the class may be described with more than one dimension. In other words, the class centre is a vector of values with each being the sample mean of that particular dimension, as shown in Equation 1.10. Similarly, the multidimensional class distribution is described by the covariance matrix, as shown in Equation 1.11. [38]

\[
c = (c_1, c_2, \ldots, c_M) \quad \text{where, } c_i = \frac{1}{N} \sum_{j=1}^{N} x_{ij}
\]

Equation 1.10: Class centre, c, with dimension, M, is determined from N observations, x.

\[
\Sigma = \frac{1}{N-1} \begin{bmatrix}
\sigma_{11}^2 & \cdots & \sigma_{1j}^2 & \cdots & \sigma_{1M}^2 \\
\vdots & \ddots & \vdots & \ddots & \vdots \\
\sigma_{ij}^2 & \cdots & \sigma_{jj}^2 & \cdots & \sigma_{jM}^2 \\
\vdots & \ddots & \vdots & \ddots & \vdots \\
\sigma_{M1}^2 & \cdots & \sigma_{Mj}^2 & \cdots & \sigma_{MM}^2
\end{bmatrix}
\]

where, \(\sigma_{ij} = \frac{1}{N} \sum_{j=1}^{N} (x_{ij} - c_i)(x_{ij} - c_j)\)

Equation 1.11: Class covariance, Σ, with dimension, M by M, is determined from N observations, x, and class centre, c.
Function \([c_1, c_2, c_3, c_4, \text{iter}]=\text{nfourclass}(\text{data}, \text{delta})\]

% FOURCLASS Given a matrix of data, this function determines the centres
% of four classes using unsupervised learning and nearest
% neighbor criteria. The total number of iterations used
% to find the class centres is also returned.
% The data is organized into a matrix of column sets and row features

\text{iter} = 0;
\text{c}_1=\text{data}(:,1); \text{lc}_1=\text{c}_1; \text{c}_2=\text{data}(:,2); \text{lc}_2=\text{c}_2; \text{c}_3=\text{data}(:,3); \text{lc}_3=\text{c}_3; \text{c}_4=\text{data}(:,4); \text{lc}_4=\text{c}_4;

\text{while} 1
\text{iter} = \text{iter} + 1;
\text{if} (\text{iter} > 1000) \% \text{CHECK FOR UNSTABLE SOLUTION
\text{return};
\text{end};
\text{class}_1=[]; \text{class}_2=[]; \text{class}_3=[]; \text{class}_4=[];

\text{for} \ i=1:\text{length(data)}
\text{t}_1 = \text{sum}((\text{c}_1 - \text{data}(:,i)).^2).^0.5; \text{t}_2 = \text{sum}((\text{c}_2 - \text{data}(:,i)).^2).^0.5; \text{t}_3 = \text{sum}((\text{c}_3 - \text{data}(:,i)).^2).^0.5; \text{t}_4 = \text{sum}((\text{c}_4 - \text{data}(:,i)).^2).^0.5;

\text{if} (\text{t}_1 < \text{t}_2) \& (\text{t}_1 < \text{t}_3) \& (\text{t}_1 < \text{t}_4)
\text{class}_1 = \text{[class}_1 \text{data}(:,i)];
\text{else}
\text{if} (\text{t}_2 < \text{t}_1) \& (\text{t}_2 < \text{t}_3) \& (\text{t}_2 < \text{t}_4)
\text{class}_2 = \text{[class}_2 \text{data}(:,i)];
\text{else}
\text{if} (\text{t}_3 < \text{t}_1) \& (\text{t}_3 < \text{t}_2) \& (\text{t}_3 < \text{t}_4)
\text{class}_3 = \text{[class}_3 \text{data}(:,i)];
\text{else}
\text{class}_4 = \text{[class}_4 \text{data}(:,i)];
\text{end};
\text{end};
\text{end};

\text{if} \neg\text{isempty(class}_1)
\text{Lc} = \text{size(class}_1);\text{if Lc}(2) > 1
\text{c}_1 = \text{mean(class}_1');\text{else}
\text{c}_1 = \text{class}_1;
\text{end};
\text{end};
\text{if} \neg\text{isempty(class}_2)
\text{Lc} = \text{size(class}_2);\text{if Lc}(2) > 1
\text{c}_2 = \text{mean(class}_2');\text{else}
\text{c}_2 = \text{class}_2;
\text{end};
\text{end};
\text{if} \neg\text{isempty(class}_3)
\text{Lc} = \text{size(class}_3);\text{if Lc}(2) > 1
\text{c}_3 = \text{mean(class}_3');\text{else}
\text{c}_3 = \text{class}_3;
\text{end};
\text{end};
\text{if} \neg\text{isempty(class}_4)
\text{Lc} = \text{size(class}_4);\text{if Lc}(2) > 1
\text{c}_4 = \text{mean(class}_4');\text{else}
\text{c}_4 = \text{class}_4;
\text{end};
\text{end};
\text{t}_1 = \text{sum}((\text{c}_1 - \text{lc}_1).^2).^0.5; \text{t}_2 = \text{sum}((\text{c}_2 - \text{lc}_2).^2).^0.5; \text{t}_3 = \text{sum}((\text{c}_3 - \text{lc}_3).^2).^0.5; \text{t}_4 = \text{sum}((\text{c}_4 - \text{lc}_4).^2).^0.5;
\text{if} (\text{t}_1 < \text{delta}) \& (\text{t}_2 < \text{delta}) \& (\text{t}_3 < \text{delta}) \& (\text{t}_4 < \text{delta})
\text{return};
\text{end};
\text{lc}_1 = \text{c}_1; \text{lc}_2 = \text{c}_2; \text{lc}_3 = \text{c}_3; \text{lc}_4 = \text{c}_4;
\text{end};

Figure 1.15: MatLab m-file algorithm to compute four cluster centres using unsupervised learning.
Given the multivariate class centre, $c$, and covariance, $\Sigma$, a new classifier is defined using the Mahalanobis distance equation, as shown in Equation 1.12. Similar to nearest-neighbour classification, the Mahalanobis distance is computed between the unknown patient condition and known class centres, with consideration of the class distributions. The unknown patient condition is then assigned to the class with the minimum distance.

Figure 1.16 displays a MatLab m-file implementation of this classification given two class centres and their associated covariance matrices.

$$D = \sqrt{(x - c)^T \Sigma^{-1} (x - c)}$$

Equation 1.12: Mahalanobis distance between sample vector, $x$, and class centre, $c$.

```matlab
Function [class]=class2data(data, c1, c2, s1, s2)
% CLASS2DATA Given an matrix of data, this function classifies the data
% according to the class centres, c1 and c2, give the associated covariance
% matrices, s1, and s2.
% The data is organized into a matrix of column data sets and
% row features. A 1 indicates classification to class 1, 2 indicates class 2.
class=[1]; Ld = size(data);
for i=1:Ld(2)
    d1 = (data(:,i) - c1)' * inv(c1) * (data(:,i) - c1);
    d2 = (data(:,i) - c2)' * inv(c2) * (data(:,i) - c2);
    if (d1 < d2)
        class = [class 1];
    else
        class = [class 2];
    end;
end;
```

Figure 1.16: Classification based upon the minimum Mahalanobis distance to the class centre.

**1.6.6. Neural Network Classification Techniques**

Recent developments in the field of neural networks (NN) have provided powerful tools for classification. This is especially true when the problem at hand is a complex one, with many interdependent variables. By simulating the behaviour of a biological neuron, a network capable of self-learning which of the signal features are important for classification. Many learning algorithms and network topologies have been developed.
It has also been shown that depending on the nature of the problem at hand, different network topologies perform differently. [40] [41]

For this study, the network training is carried out on a commercially available artificial neural network package, NeuroShell2 that is displayed in Figure 1.17. The package builds, trains, and applies Group Method of Data Handling (GMDH) polynomial networks. These networks are implemented using polynomial functions to model the functioning of individual neurons, as per the work of Prof. A. G. Ivakhnenko from the Institute of Cybernetics, Ukrainian Academy of Sciences. [42]

![Figure 1.17: Commercial neural network design and training package, NeuroShell2.](image)

The exact number of neurons and layers in the NN are determined by trial and observation. Once a specific architecture is chosen, it is trained on the known patient conditions. The trained NN is then applied to additional patients with known conditions in order to test the classification.
Specifically, in using the NeuroShell2 package, the design process involved assigning the training data, building the network, and then testing the network by applying it to sample sets, as per Figure 1.18. Once the network has been built, the neuron weights and network calculations are exported and integrated with other programming packages, such as MatLab. The polynomial calculations tend to be many and complex. Furthermore, it is often not clear upon what the NN is basing its classification. Even so, it has been shown that a NN is able to perform superior to that of classical classification.

[43]

1.6.7. Classification Assessment

Once a classification system has been designed, it is assessed to determine its ability to screen a patient for disease. In this study, the patient is screened for both DM and CHD. In medical practice, the effectiveness of a clinical screening is determined by computed

Figure 1.18: NeuroShell2 application for building and training neural networks.
the sensitivity, specificity, positive predictive value, and negative predictive value
statistics, according to Equation 1.13. [44] The sensitivity is the probability that a
diseased patient is correctly classified as having the disease. The specificity is the
probability that a normal patient is correctly classified as not having the disease. The
positive predictive value is the probability that a person has the disease given a positive
classification result, and the negative predictive value is the probability that a person
does not have the disease given a negative classification result.

<table>
<thead>
<tr>
<th>Known Patient Condition</th>
<th>Negative</th>
<th>Positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease Absent</td>
<td>A</td>
<td>B</td>
</tr>
<tr>
<td>Disease Present</td>
<td>C</td>
<td>D</td>
</tr>
</tbody>
</table>

Sensitivity = \( \frac{d}{c + d} \)  
Specificity = \( \frac{a}{a + b} \)

Positive Predictive Value = \( \frac{d}{b + d} \)  
Negative Predictive Value = \( \frac{a}{a + c} \)

Equation 1.13: Evaluating classification results by determining the sensitivity, specificity, positive predictive value and negative predictive value.

For example, a certain classifier is used to screen 10,000 patients for DM. 9,620 of the
patients are known to be non-diabetic and 380 are known to have DM. The results of the
classification are displayed in Figure 1.19. According to the results, the classifier has a
sensitivity of 0.895, which means that 89.5% of the time, the classifier correctly
detects a patient with DM. The specificity is 0.90, which means that 90% of the time,
the classifier correctly assigns a non-diabetic patient as free of DM. The negative
predictive value is 0.995, which means that if the classifier indicates the patient is free
of DM, then 99.5% of the time, the classifier is correct. The positive predictive value is
0.26, which means that if the classifier indicates that the patient is diabetic, then only
26% of time is the patient truly diabetic (a false positive). In other words, this example
classifier is good for screening patients for DM, but if it indicates a patient is positive for DM, then further testing is required in order to ensure the patient truly has DM. [45]

<table>
<thead>
<tr>
<th>Known Patient Condition</th>
<th>Negative for DM</th>
<th>Positive for DM</th>
</tr>
</thead>
<tbody>
<tr>
<td>DM Absent</td>
<td>8660</td>
<td>960</td>
</tr>
<tr>
<td>DM Present</td>
<td>40</td>
<td>340</td>
</tr>
</tbody>
</table>

Sensitivity = \frac{340}{40 + 340} = 0.895

Specificity = \frac{a}{a + b} = \frac{8660}{8660 + 960} = 0.90

+ Predictive Value = \frac{340}{960 + 340} = 0.26

- Predictive Value = \frac{8660}{8660 + 40} = 0.995

Figure 1.19: Example assessment of a DM classifier.

1.7. Heart Rate Variability

The HR is controlled by the sympathetic and parasympathetic branches of the autonomic nervous system (ANS). The parasympathetic nerves (Vagus) slow the HR through the release of acetylcholine. Sympathetic nerves accelerate the HR through the release of noradrenaline. The variability of the HR is the result of a balance between the sympathetic and parasympathetic nerves. These two branches of the ANS serve as a control system for the HR in order to respond to changing conditions of the cardiac load. [46]

The diagram in Figure 1.20 describes the basic circulatory system. The circulation and arterial blood pressure are affected by the cardiac output, specifically, the HR and stroke volume. The heart itself is control by the central nervous system, specifically, the ANS. Baroreceptors are sensors that detect pressure in the aortic arch and carotid arteries. These sensors serve as feedback for the HR control system. Additionally, chemoreceptors are sensors used to measure chemical variables, such as the pH sensors.
in the medulla, which in turn, also provides control of the respiration and HR through the release of adrenaline by the adrenal medulla.

Fluctuations in HR (and thus the ABP) are quasi-periodical, repeating with a period, which are not strictly constant, showing changes in morphology, amplitude and phase from one beat to the next. In steady state conditions, these oscillations are maintained around a certain mean value. For the human, with no ANS control, the heart beat is approximately 100 beats per minute (BPM). With ANS control and resting, the parasympathetic response dominates and the HR lowers to approximately 70 BPM. During exercise, the sympathetic response dominates and the HR increases accordingly.

The beat-to-beat variation in HR is the HRV, which may be easily monitored non-invasively in a clinical setting. Since the HR is controlled primarily by the ANS, measurement of the HRV provides information about the sympathetic and parasympathetic cardiovascular control mechanisms. [47] However, the HRV is also affected by respiration, mental stress, cardiovascular disease, drugs, ectopic beats and age.
In case of dysfunction, compensatory changes occur in order to keep the entire circulatory system within normal operating limits. [48] Specifically, reduced HRV may indicate the presence of DAN and that the sympathetic and parasympathetic nervous systems are not coordinating an appropriate HR response. Additionally, it has been shown that the HRV spectrum is affected by the presence of CHD and CVD. [49]

1.7.1. Time-Based Analysis of HRV

Analysis of the HRV has usually focused on the standard deviation of normal-to-normal (SDNN) beats in the ECG. Specifically, the STD of time between consecutive normal R-waves is computed. Since the STD computes a measure of the data range, the STD of the time intervals gives a measure of the HRV.

Traditionally, the HRV was measured over a 24-hour period. Specifically, the STD of 5 minute intervals (SDANN) were computed and then averaged. However, 24-hour measurements are not easy in a clinical setting. Therefore, in this study only short-term (30-minute) HRV analysis is used. [50]

Besides the STD, the root-mean-square of the difference between successive RR intervals (rMSSD) is used as an estimate of the HRV derivative. Similarly, with the trend removed, the number of zero crossings (ZC) serves as an indicator of highest frequency component within the HRV. Each of these analyses is discussed in detail in Chapter 4, HRV Analysis.

1.7.2. Frequency-Based Analysis of HRV

Since the early seventies, modern signal analysis techniques have been applied to the HRV and ABP. Helped by recent developments in computer hardware and software,
power spectral analysis (PSA) of cardiovascular signals assumed a prominent place as a simple, non-invasive tool in the armoury of cardiovascular system tests. Regrettably, the introduction of this test into clinical medicine has been slow, because the PSA is a difficult concept for many physicians. Moreover, a thorough comparison between PSA and classic diagnostic methods is not yet available. Also, diabetics have been unfortunately excluded from all studies investigating HRV and PSA in CHD. Obviously the cause is the complexities that arise in design, methodologies and analysis by compounding the effect of age, DAN and DM.

The power spectrum (PS) of the HRV consists of three major frequency bands ranging from 0 to 0.5 Hz. The boundaries of these bands are not strictly defined. The most commonly accepted bands are the very low frequency (VLF) band from 0.02-0.05 Hz, the low frequency (LF) band from 0.05-0.15 Hz, and the high frequency (HF) band from 0.15-0.5 Hz. Changes in each of these bands correspond to specific physiological changes.

Variations in the VLF band relate to temperature regulation of the body, the vasomotor control and the renin-angiotensin system, with a centre-of-frequency at 0.04 Hz. The rennin-angiotensin system refers to the hormone rennin which is released by the kidneys to catalyze the production of angiotensin and secretion of aldosterone, which regulates blood volume, and in turn, ABP and HR. An ultra low frequency band (ULF) from 0.01-0.04 Hz has also been described for long-term studies, but its exact physiological significance is not readily apparent and is not used for short-term HRV studies.

Variations in the LF band relate to the ABP control system. It has a centre-of-frequency at about 0.1 Hz and is called the Mayer band, corresponding to oscillations in blood pressure described by Mayer in 1874. It is influenced by parasympathetic and
sympathetic systems with an increase in vagal activity causing a spectral peak in this frequency range. Conversely parasympathetic blockade diminishes LF power, especially in the supine position.

Interventions that increase sympathetic activity include passive tilting, standing, mental and physical stress, sympathomimetic agents, baroreceptor unloading with nitroglycerine infusion and coronary occlusion. Thus, these are also known to increase the power in the LF band. However, the magnitude of the power in this band decreases monotonically with age. Breathing does not influence it, when the respiratory rate is above 9 BPM. In supine position, its magnitude is mainly dependent on parasympathetic system.

Variations in the HF band relate to respiration and are associated with parasympathetic activity with a centre-of-frequency at 0.25Hz, which varies with the respiratory rate. This band is mediated solely by the parasympathetic system. The magnitude of the power in this band is more in the supine than the standing position. There is a linear decline in the power of this band up to the age of 30 years, and does not change thereafter. [51]

1.7.3. HRV and Power Spectral Analysis Changes in Disease

Normal individuals show a progressive decrease of HRV with age with a loss of 4.6 beats per each decade of life. However, almost two-thirds of patients with clinically detectable peripheral neuropathy, such as burning feet, decreased knee and ankle reflexes, decreased pinprick, position and vibration sense, have significant changes in HRV. Furthermore, all patients with clinically detectable DAN have abnormal HRV. [52]
Additionally, CHD causes a reduction of HRV and a shifting of the LF and HF components. The reduction correlates well with the angiographic severity but not with other CHD features, including the presence of a previous myocardial infarction, location of diseased coronary arteries, and indices of left ventricular function. There is also reduction in the LF power which is attributed to the decrease in vagal out-flow, since there is no change in the LF/HF ratio, which suggests that the sympathetic cardiac function is not affected in CHD.

1.7.4. Time-Frequency Based Analysis of HRV

Although the time based and frequency based analyses are different, the results are comparable since SDNN is theoretically the same as the total spectral power of the HRV. Similarly, the rMSSD and ZC time analyses correlate well with the HF band.

However, the HR is dynamic, changing continually over time in response to various conditions and cardiac loads. This means the HRV signal is not stationary and additional information maybe found by analysing the HRV signal in response to various actions such as resting, standing, and controlled breathing. In order to best characterise the HRV signal, new analyses techniques are required which preserve both the time and frequency components of the signal. Time-frequency analysis allows the HRV spectral bands to be computed over time as the patient performs various actions in the clinical setting. It is hypothesised that the normal patient response differs from the diseased patients providing a low-cost, efficient screening for DM and CHD.
1.8. Summary

The world prevalence of DM is rising and projected to increase astronomically. DM is also a major health concern in the Middle East and especially in the UAE where surveys suggest that 20% of UAE citizens are diabetic.

A variety of health complications are associated with DM including DAN, retinopathy and amputations. However, CHD and CVD complications are the most common causes of morbidity and mortality in diabetic patients. In general, the severity of complications becomes worse as the disease progresses. Early detection of DM and CHD, combined with proper treatment, can delay the progression of the disease and rise of complications. Unfortunately, many DM and CHD patients are unaware they have the disease.

In the clinical setting, measurement of non-invasive physiological signals such as ECG, ABP, and respiration have become possible with the rise of low-cost computers and physiological acquisition system. Non-invasive screening greatly reduces the risks of infection and increased patient stress. From the ECG, the beat-to-beat HR may be extracted and analysed. Variations in the HR differ between normal patients and those with DM and CHD. These differences are apparent in both time and frequency analyses. Therefore, non-invasive physiological signals may be used in the clinical setting to efficiently screen patients for DM and CHD.

Specifically, the HRV signal may be extracted from the ECG and used as a means of patient screening. The HRV spectrum varies in response to specific actions such as resting, standing, and controlled breathing. Analysis of these HRV spectral over time may provide a suitable basis for classification of patients into N, DM, CHD, and CHDD.
classes, and thus, providing a quick, low-cost, and effective means for clinical screening.
Chapter 2 - Clinical Data Acquisition System

2.1. Introduction

In order to research the effectiveness of DM and CHD clinical screening based upon the HRV signal, a data acquisition system to collect the patient physiological data is required. This chapter details the clinical DAQ system and methodology of collecting the patient physiological data. Specifically, the required hardware components of the system and the routine a clinical technician used to screen a patient are presented. Furthermore, the custom developed software programmes used by the technician are introduced and explained.

The specific goal of the system is to record HRV physiological data as it changes over time in response to various patient activities. Although the HRV data is computed only from the ECG, the patient ABP and respiration are recorded and studied as possible additional indices to the patient's cardiac condition. Also, in order to determine the classification performance, the patient's medical history and laboratory results are recorded in order to assess the patient's current condition.

2.2. Methodology

The patient physiological data is collected by use of a personal computer (PC) and non-invasive DAQ system, as displayed in Figure 2.1. Use of a PC reduces the overall cost of the system and allows for a simplified user interface. Non-invasive physiological measurement allows for the patient to be screened in a clinical setting with reduced patient stress and little concern of infection.
As far as the screening procedure, the patient is initially connected to the physiological measurement equipment and requested to lie (supine) quietly on the examination table, as per the clinical procedure of Appendix E. Then, the patient's medical history and laboratory results are recorded. Specifically, the patient's name, telephone number, hospital number, sex, age, height, weight, hip circumference, waist circumference, and cigarette usage, treatment for diabetes, blood pressure, activity index, and anxiety index are recorded, per Appendix F. The activity and anxiety indices are determined according to questionnaires located in Appendix A and B, respectively. This data is taken for an associated study which correlates anxiety and activity to disease, specifically the presence of DM and CHD. The laboratory results focus on various tests, which are detailed in Appendix C. Besides completing the medical history and determining the patient's activity and anxiety indices, the interaction between the patient and technician allow for the patient to feel at ease with the connections to the physiological measurement equipment. This, in turn, lowers the patient's stress and reduces the hypertension artefact in the measurement of the physiological data.
Once it appears to the technician that the patient is at ease, 5 minutes of supine physiological data are collected, as per the clinical procedure of Appendix E. The average human heart rate is approximately 70 beats per minute, and so 5 minutes of electrocardiogram acquisition collects 350 beats, which subsequently gives 350 HRV samples. Similarly, the average human respiration is approximately 10 breaths per minute, and so 5 minutes of chest pressure data gives about 50 breath samples to base the respiration measurement.

The technician then requests the patient to stand and another 5 minutes of physiological data are immediately collected. Then, the patient is asked to sit/squat and another 5 minutes of physiological data are collected. Lastly, the patient is requested to breathe at 9, 12, and 15 breaths per minute, each for a 5-minute duration. During each of the patient controlled breathing durations, the patient's physiological data are again collected. In order to assist in timing their breaths, the patient is requested to breathe according to respiration timer programme. Therefore in summary, each patient action is characterised by approximately 350 cardiac beats and 50 breaths.

2.3. Hardware Requirements

Figure 2.2 summarises the clinical system to record the patient information. Besides the PC and DAQ board, three external devices are used to measure the patient respiration, ABP, and ECG. Each device outputs a voltage signal, which is calibrated to the respective physiological measurement. The DAQ digitises the relative voltage signal and the PC implements the calibration equation to determine the physiological measurement.
The DAQ board, which is installed in the PC, is the National Instruments' [53] PCI-6023E, 12-bit data acquisition board, as shown in Figure 2.3. The board is low-cost and may be configured to digitise various voltage ranges using 12 bits of resolution. For example, if the 0 to 10 V\textsubscript{DC} voltage range is chosen, then 0 V\textsubscript{DC} is assigned the value 0 and 10 V\textsubscript{DC} is assigned the value 4096. Using this voltage range, the resolution is computed as the voltage range per total DAQ-count (10 V\textsubscript{DC} / 4096), which, for this voltage range, is approximately 2.4 mV. Therefore, the least count (smallest measurable voltage) for this voltage range is 2.4 mV.

As far as sampling frequency, the National Instruments' PCI-6023E has a maximum rate of 200K Samples per second for a single data channel. Since the clinical system is collecting three channels of data (ECG, ABP and respiration), the maximum acquisition
rate is 200K / 3, or approximately 67K Samples per second. This limit far exceeds the sampling frequency requirements for ECG, ABP and respiration, and so, the DAQ board is acceptable for using the clinical system.

2.3.1. Electrocardiogram Acquisition

In order to best detect the ECG R-waves, the QRS complex of the ECG is maximised through placement of the patient electrodes in the Einthoven bipolar positions (Figure 2.4). With these electrode positions, Lead II ECG is acquired as per the guidelines of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. [54] Specifically, the ECG is amplified to the voltage range and sampled at 500 Hz.

![Image](image.png)

Figure 2.4: Electrocardiogram Lead II electrode connections and 1000x ECG pre-amplifier.

The Lead II electrode positions provide an ECG signal in the range of a few milli-Volts (mV). [55] In order to amplify the ECG signal for the DAQ, a battery-operated, 1000x pre-amplifier is employed. A gain of 1000x magnifies the mV ECG signal into the Volts range. Operating the pre-amplifier on battery power eliminates the need for an expensive and complex AC to DC power conversion circuit. All AC to DC power
conversion circuits leak AC ripple-voltage, which is usually in the mV range. However, since the ECG measurement is also in this range, it is common for the AC ripple-voltage to corrupt the ECG signal. This is especially a problem since the AC power operates at 50 Hz, which is in the midst of the known ECG spectrum. Utilising battery power for the pre-amplifier eliminates this concern of the AC ripple-voltage. Since the pre-amplifier draws little power, a single 9 V\textsubscript{DC} transistor battery provides more than 24 hours of operation.

Figure 2.5 summarises the ECG pre-amplifier circuit through use of a block diagram. The initial isolation-buffer amplifier provides high input impedance that is greater than 10 M\Omega. The second stage, differential amplifier allows for enhanced common mode rejection, which reduces interference common to both the right arm and left arm electrodes. The third stage is a 50 Hz low pass filter, which is used to suppress induced power-line noise. The final stage amplifier provides signal gain, which is adjusted to provide an overall amplification of 1000x.

![Figure 2.5: Electrocardiogram 1000x pre-amplifier block diagram.](image)

The details of the ECG pre-amplifier circuit are displayed in Figure 2.6. The circuit operates on a single 9 V\textsubscript{DC} battery and utilities LM358 operational amplifiers operating
on single-ended voltage rails (0 \text{V}_{\text{DC}} \text{ and } 9 \text{V}_{\text{DC}}). The ECG baseline is adjusted between the rails (~4.5 \text{V}_{\text{DC}}), which allows for a 4.5 \text{V}_{\text{DC}} \text{ maximum deflection.}
The pre-amplifier output signal is sampled (Fs) by the DAQ at a rate of 500 Hz, as per the guidelines of the European Society of Cardiology for determine HRV from ECG. Therefore, the detection time of the ECG R-wave has a resolution of $1/500$, or 2 ms, as shown in Equation 2.1.

$$\text{ECG Voltage} = (\text{DAQ Count}) \left( \frac{10\text{mV}}{4096} \right)$$

$$\text{Least Count} = \frac{10\text{mV}}{4096} = 2.4\mu\text{V}$$

$$\text{Resolution} = \frac{1}{500\text{Hz}} = 2\text{ms}$$

Equation 2.1: ECG DAQ calibration equation, least count, and time resolution calculations.

The DAQ board is configured to digitise the 0 to 10 V$_{DC}$ range. Therefore, the calibration of Equation 2.1 is used to determine the ECG physiological measurement of a given DAQ count. Note the units are in mV, considering the 1000x effect of the ECG pre-amplifier. Also displayed in Equation 2.1 is the least count of the ECG measurement. The least count defines the smallest resolvable voltage of the ECG.

### 2.3.2. Arterial Blood Pressure Acquisition

The patient's ABP is acquired using an Ohmeda Finapres 2300 [57] and finger cuff, as pictured in Figure 2.7 and Figure 2.8, respectively. The device uses the plethysmography of the index finger as a means to indirectly measure the ABP. Plethysmography is defined as measurements in the variation of the size of an organ or body part, based on the amount of blood passing through it. The Ohmeda clinical device inflates a cuff around the index finger and thus restricts the blood flow in the finger. It then releases the pressure in the cuff until variations in the pressure due to the ABP are detected. These variations are then automatically calibrated to the ABP by the device. In
order to ensure accurate measurements, the Ohmeda device automatically self-calibrates the ABP against the plethysmography variation of the index finger once every minute.

Figure 2.7: Ohmeda Finapres arterial blood pressure monitor.

Figure 2.8: Ohmeda Finapres finger transducer.
Besides measuring the ABP, the Ohmeda Finapres monitor provides an output port that generates 1 V$_{DC}$ for every 100 mmHg of ABP. A human has a positive ABP, which is normally less than 500 mmHg. Therefore, the DAQ board is configured to digitise the Ohmeda Finapres output voltage in the 0 to 5 V$_{DC}$ range. The sample frequency is set to 500 Hz in order correspond with the ECG acquisition. Given these settings, the ABP DAQ calibration and least count are displayed in Equation 2.2. Note the ABP units are in mmHg.

\[
\begin{align*}
\text{ABP Pressure} &= (\text{DAQ Count}) \left( \frac{5V_{DC}}{4096} \right) \left( \frac{100 \text{mmHg}}{1V_{DC}} \right) \\
\text{Least Count} &= \left( \frac{5V_{DC}}{4096} \right) \left( \frac{100 \text{mmHg}}{1V_{DC}} \right) = 0.12 \text{mmHg} \\
\text{Resolution} &= \frac{1}{500 \text{Hz}} = 2 \text{ms}
\end{align*}
\]

Equation 2.2: ABP DAQ calibration equation, least count, and time resolution calculations.

![Respiration monitor and placement of pressure transducer.](image)

2.3.3. Respiration Acquisition

The patient respiration is acquired by using a custom built clinical device [58] that outputs a voltage corresponding to changes in a pressure transducer strapped to the
patient's diaphragm, as shown in Figure 2.9. Specifically, an elastic band is strapped around the patient and a pressure transducer is placed in the mid-chest region. As the patient inhales, the patient's lungs expand and cause an increase in pressure upon the transducer. Similarly, as the patient exhales, the lungs reduce in size and the transducer experiences a reduced pressure. The device reads the differences in pressure and outputs a corresponding voltage in the range of 0 to 5 V. Since the time between the pressure peaks are used to determine the rate of respiration, the output voltage is not calibrated to the actual pressure. The output voltage is over-sampled at 500 Hz in order to use the same data structure as the ECG and ABP and ease computer storage of the information.

Once acquired, the respiration is determined as the sampling period multiplied by number of samples between two consecutive chest pressure peaks, as per Equation 2.3. Note that $p_i$ is the sample-number a detected peak in the chest pressure waveform, and so, $(p_i - p_{i-1})$ is the number of samples between two pressure peaks which corresponds to one full breath-cycle. The units of respiration are breaths per minute.

$$\text{Respiration} = \left\lfloor \frac{1 \text{ Breath}}{(p_i - p_{i-1}) \text{ sec}} \right\rfloor \left(\frac{500 \text{ Samples}}{60 \text{ sec}}\right) \left(\frac{60 \text{ sec}}{\text{min}}\right)$$

Equation 2.3: Computation of patient respiration.

2.4. Software Requirements

The software developed for the study is classified into two categories: DAQ and utilities. All programmes were developed using the LabVIEW application development package and consist of the Patient Data Collection, Patient Data Review, Patient Laboratory Editor, and Patient Data Extraction programmes.
2.4.1. National Instruments' LabVIEW

LabVIEW is an acronym for Laboratory Virtual Instrument Engineering Workbench. This application development package features a graphical programming environment with tools necessary for DAQ, data analysis, and graphical presentation. Recent years has seen an increasing use of LabVIEW in both industry and scientific research. This is largely due to the ease of writing complicated applications without the requirement of compilers and rigid English-based code.

LabVIEW programmes are called Virtual Instruments (VIs) because the user interface resembles an instrument with buttons, switches, and graphical output. A VI consists of a front panel and a block diagram. The front panel specifies the inputs and outputs of user interface. It consists of digital controls for user input and digital indicators for output display, as shown in the example programme of Figure 2.10. The block diagram consists of icons, which represent input, output, operations, structures, and subroutines. The block diagram contains the VI programming instructions. The programme is defined through wiring connections between the controls, indicators, and icons, which represent mathematical functions, constants, and programme control structures, as shown in the example VI of Figure 2.12.

![Figure 2.10: Front panel of an example LabVIEW programme to compute distance.](image-url)
LabVIEW departs from traditional English-based coding. The coding is termed 'G' for graphical-based coding and requires a new way of thinking about programme construction. Instead of writing lines of code and calling subroutines, a VI employs wires connecting icons together. The icons may represent operations such as multiplication, programme flow structures, such as loops, or subroutines. The wires represent the flow of the variables through these operations.

As with any programming language, LabVIEW includes looping, ordering of operations, and decision making. These items are termed 'structures' in LabVIEW and are implemented visually, as displayed in Figure 2.12. For example, a while loop is implemented by a rectangular icon. Inside the rectangle represents operations done inside the loop. Operations placed outside the rectangle are done either before or after the loop, depending upon the wire connections.
While Loop Structure

Items inside the structure are repeated until the loop is terminated by a 'False' value.

Index,
\[ i = 0, 1, \ldots \]
Termination

Sequence Structure

Structure contains several frames. The structure executes the operations in each frame in order.

Icon Based

All operations, structures, and subroutines are displayed as icons with wire connections.

Sequence Structure

Structure contains several frames (True/False default). The selector chooses the frame to execute.

Figure 2.12: Sample LabVIEW programme structures.

With the advancement of PC processing power, LabVIEW is able to perform with a run-time library. In other words, similar to Microsoft Visual Basic, LabVIEW does not require compilation and linking steps before programme execution. That allows for faster programme debugging and development. It also allows for on-location editing and programming; that is, the clinical technician himself may edit the VI and adjust it as necessary, without requiring the presence of the developer.

2.4.2. Patient Data Collection Programme

The Patient Data Collection programme stores the patient's contact information, medical history, physical characteristics, and the three physiological waveforms: respiration, ECG, and ABP.
Figure 2.13: Patient data collection programme user interface. The lower three charts display the raw data (in DAQ counts) during physiological acquisition.

The programme user interface is displayed in Figure 2.13. The digital controls (user inputs) are located above the three charts. The input is organised into patient information, physical characteristics, and results of the laboratory tests, which are categorised into glycaemia, lipid, and angiography. Once the information is entered, the technician chooses 'Begin Sampling' and the 5 minutes of physiological data is saved to the PC disk. During the 5 minute sampling, raw data is displayed in lower strip charts of Figure 2.13. These charts allow the technician to ensure the instruments are properly connected, operational, and collecting data as expected. Once the programme has collected the 5 minutes of the supine data, the technician requests the patient to stand and chooses the associated data type (standing), and again selects 'Begin Sampling.'

If the technician notices a problem with the data stream from one of the instruments, the 'Abort Sampling' command may be used to discontinue sampling. After fixing the
problem, the 'Begin Sampling' command may be used again to take 5 minutes of data, which automatically replaces the corrupted data.

The basic sampling procedure of the Patient Data Collection programme is displayed in Figure 2.14. Specifically, once the clinic technician selects the 'Begin Sampling' option, a data file on the computer hard disk is opened and the patient's history, patient's laboratory results, and calibration parameters are written to the file. Then the DAQ board is configured for direct memory access (DMA) sampling. This allows the DAQ board to write the DAQ counts of the physiological measurements directly to a block of the PC memory without requiring communication with the PC microprocessor. That frees the PC microprocessor to perform other programming tasks, such as displaying the collected data and saving it to disk.

Due to the physical configuration of the PC compatible memory, the maximum DMA memory size is 64 KBytes. Since each DAQ count consists of two bytes, and three channels of data are sampled, the DMA block memory size is set to 10,000 samples, which gives a total memory size of approximately 60 KBytes (2 Byte DAQ count x 3 Data Channels x 10,000 samples). However, that does not limit the total sampling time, as the DMA may be repeatedly configured to fill as many 60 KBytes memory blocks as needed.
Begin Sampling

Open Data File

Write Patient Information and Channel Calibrations

Configure DAQ Board for DMA of Acquisition of 10,000 Samples

Wait for DMA Buffer to Fill

Write DMA to Disk

Display ECG, ABP and Respiration Charts

150,000 Samples?

No

Yes

End Sampling and Close Data File

Figure 2.14: Patient data collection programme sampling procedure.

Specifically, once the DMA memory buffer is filled, the programme writes the DAQ counts of the DMA memory buffer to the opened data file and then displays the DAQ counts in three strip charts: ECG, ABP, and Respiration. Since 5 minutes of physiological data is required and since the data is sampled at 500 Hz, the total number of required samples per data channel is 150,000 samples, according to Equation 2.4. Therefore, the DMA memory buffer reinitialized and set to automatically fill with additional samples. Once the desired number of samples has been taken, the DAQ board sampling is halted and the data file is closed.

\[
\text{Total Samples} = (5 \text{ min}) \left( \frac{60 \text{ sec}}{\text{min}} \right) \left( \frac{500 \text{ Samples}}{\text{sec}} \right) = 150,000 \text{ Samples}
\]

Equation 2.4: Total samples per channel in 5 minute sampling.
The sampling procedure of Figure 2.14 is coded using National Instruments' LabVIEW. The VI block diagram (code) is best viewed on a large screen computer monitor as it is quite detailed. In accordance with the sampling procedure, the VI first opens a disk file based on the patient's name and the patient information is organised into an array structure and written to the file, as per the block diagram displayed in Figure 2.15. The details of the file structure may be viewed in Appendix D.
After writing the patient information to the disk file, the Patient Collection programme configures the DAQ to collect ECG, ABP, and respiration waveforms using DMA transfer, as per the display in Figure 2.16. Specifically, 10,000 DAQ counts are taken from each of the three channels and stored in a 10,000 x 3 dimensioned matrix. The DAQ count is stored instead of the physiological measurement in order to increase the

Figure 2.15: Patient collection VI block diagram for file creation and data storage of the patient hospital number, telephone, physical characteristics, and laboratory results.
computer speed for real-time measurement and reduce the size of the data file since the DAQ counts consist of 2 byte integers and the physiological measurements consist of 4-byte, floating-point decimals.

The 10,000 DAQ counts are continually written to the data file until a total of 150,000 samples have been saved. The DAQ counts are written for the respiration, ABP, and ECG, respectively. Since the each DAQ count consists of a two-byte integer, the total file size for the 5 minute sampling is 900 KBytes, per Equation 2.5. The initial patient information and laboratory results add less than 1 KByte to the data file, and so, are ignored in the file size calculation.

\[
\text{File Size} = (3 \text{ Channels}) \left( \frac{150\text{K Samples}}{\text{Channel}} \right) \left( \frac{2 \text{ Bytes}}{\text{Sample}} \right) = 900\text{K Bytes}
\]

Equation 2.5: Data file size for one 5 minute sampling.

Per the clinical procedure, each patient has six 5 minute data files taken; one for supine, standing, and sitting and 3 for breathing rates at 9, 12, and 15 breaths per minute.
Therefore, each patient requires approximately 5.4 MBytes (6 x 900 KBytes) of disk space. The clinic-based computer contains a 40 GByte hard disk, of which the operating system and LabVIEW take approximately 1 GByte of disk space. That allows for approximately 7,400 (39 GByte / 5.4 MByte) patients to be screened and stored.

2.4.3. Patient Data Review Programme

Once the 6 sets of physiological data have been collected, the technician may review the data using the 'Data Display' programme as shown in Figure 2.17. This allows the technician to quickly determine if any acquisition problems occurred during the session, by glancing through the physiological waveforms. If a problem is noted, the technician has the patient immediately available to re-takes the affected 5 minute set. Requesting patients to return to the clinic for further tests is often problematic.

Each 5 minute data set is stored in a separate file. The technician opens one of the 6 data sets: supine, standing, sitting, and sitting at 9, 12, and 15 breaths per minute and views the physiological waveforms. Due to limitations in the chart structure, only 3000 samples are displayed at a time. And so, the technician steps through the entire data set by selecting 'Next Set' until the end of the data set is reached.
The Patient Data review VI block diagram is partially displayed in Figure 2.18. The VI queries the user’s choice of filename and disk location. Then the VI computes the number of bytes in the patient’s history in order to skip to the physiological waveform data. Before displaying the physiological data, the VI uses the calibration information to compute the physiological measurement from the stored DAQ counts, per Figure 2.18. Lastly, the VI displays 3000 samples of each physiological waveform for the technician to review. A sequence structure is used as the first frame reads the physiological data from the file and the second frame waits for the user to review the data before reading, calibrating, and displaying the next 3000 samples.
2.4.4. Patient Laboratory Data Edit Programme

Occasionally, the patient's laboratory results are not available at the time of the physiological acquisition in clinic. Instead of requiring the patient to wait for the results before collecting the physiological waveforms, the Patient Edit VI allows the technician to open a saved data set and edit the non-physiological measurement data. Figure 2.19 displays the user interface of the VI. Note that the technician is not allowed to edit the patient's name and telephone number.

The main structure used in the Patient Edit VI block diagram is a sequence structure. The first frame opens the data file and reads the patient name, telephone number, and information concerning the patient's history, characteristics, and laboratory results, as shown in Figure 2.20. The VI also allows the calibration coefficients and sampling frequency to be edited.
Once the technician has completed the necessary changes, the 'Save Info' command is selected and the second frame of the sequence then executed, as shown in Figure 2.21.
Here, the control values are combine into an array and written to the same file, thus overwriting the old information with the new.

![Figure 2.21: Patient Edit VI block diagram, sequence 1.](image)

### 2.4.5. Patient Data Extraction Programme for MathWorks' MatLab

MathWorks' mathematical programme, MatLab [59], is used to develop and test the signal-processing algorithm for extracting and analyzing the HRV from the ECG. Therefore, a custom utility was developed to read the patient's six data sets and create waveform files that are MatLab compatible. Once the best analysis algorithm has been developed, it may be easily implemented by LabVIEW.
The VI user interface is displayed in Figure 2.22. When executed, the VI first queries the user to select the patient data to process. The technician may select any of the six 5 minute data sets, as the utility is able to determine all the data set file names from any one data set. Once the utility has determined the patient's name, it processes all the data sets. Once a patient is selected, the VI creates a new directory using the patient's name.
and then creates a file entitled 'LD' which contains the patient's information and laboratory results, as seen in Figure 2.23.

Next the VI, reads each of the six data sets and creates corresponding, calibrated, MatLab compatible files entitled: SP, SD, ST, S9, S12, and S15. The determination of the calibration equations is seen in Figure 2.23 and Figure 2.24 displays the calibration implementation. Note the text file icon, which is used to save the data sets in a MatLab compatible file.

![VI block diagram](image)

Figure 2.24: Patient data extract VI block diagram which reads 3000 samples from the data set, applies the calibration equations, and then saves the physiological measurements to a MatLab compatible file.
2.4.6. Patient Respiration Timer Programme

Three of the acquisition sets require the patient to breathe at a particular rate. In order to accomplish this, a 'Respiration Timer' VI was written to guide the patient's breathing rate. The VI user interface is displayed in Figure 2.25 and allows the technician to set the respiration at 9, 12, or 15 breaths per minute. The patient is guided by following the red and blue bars, which either indicate the patient to breathe in or out, accordingly. The VI uses five colour bars so that the patient can better gauge their breathing and knows approximately how much time remains to the end of the breath cycle.

![Figure 2.25: Breath timer VI user interface used to guide the patient in breathing 9, 12, or 15 breaths per minute. The 'BREATH IN' bar is red and the 'BREATH OUT' bar is blue.](image)

The Breath Timer was easily implemented in LabVIEW. The VI block diagram may be viewed in Figure 2.26. The VI employs a continuous while loop and Boolean shift-register. The red 'BREATH IN' and blue 'BREATH OUT' bars are Boolean lights that are toggled by True and False values, respectively. Each iteration of the loop shifts either a True or False value, and so, the VI either turns on all the 'BREATH IN' or
'BREATH OUT' bars after five iterations. Therefore, one full breath occurs after 10 loop iterations. The loop timing is set according to the selection of the constant value in the Case structure. The timer setting in Figure 2.26 is for 9 breaths per minute, as per the calculation in Equation 2.6. The timer values for 12 and 15 breaths per minute are displayed in Equation 2.7.

Figure 2.26: Breath timer VI block diagram.

\[
\text{Respiration} = \frac{1 \text{ Loop}}{667 \text{ ms}} \times \frac{1 \text{ Breath}}{10 \text{ Loops}} \times \frac{1000 \text{ ms}}{\text{sec}} \times \frac{60 \text{ sec}}{\text{min}} = 9 \frac{\text{Breaths}}{\text{min}}
\]

Equation 2.6: Respiration computation based upon the timer value.

\[
\text{Timer}_{12} = \left( \frac{\text{min}}{12 \text{ Breaths}} \right) \times \left( \frac{1 \text{ Breath}}{10 \text{ Loops}} \right) \times \left( \frac{1000 \text{ ms}}{\text{sec}} \right) \times \left( \frac{60 \text{ sec}}{\text{min}} \right) = 500 \text{ ms}
\]

\[
\text{Timer}_{15} = \left( \frac{\text{min}}{15 \text{ Breaths}} \right) \times \left( \frac{1 \text{ Breath}}{10 \text{ Loops}} \right) \times \left( \frac{1000 \text{ ms}}{\text{sec}} \right) \times \left( \frac{60 \text{ sec}}{\text{min}} \right) = 400 \text{ ms}
\]

Equation 2.7: Timer computation for 12 and 15 breaths per minutes.
2.5. System Observations

Note the physiological waveforms displayed in the Patient Data Review VI of Figure 2.17. The top chart displays the voltage of the respiration monitor. In comparison to the other charts, it is easily observable that the respiration frequency is far less than the ABP or ECG. Specifically, the number of samples between the respiration voltage peaks, as viewed in the top chart of Figure 2.17, is approximately 2000. Therefore, considering the sampling frequency and according to Equation 2.8, the patient respiration is about 15 breaths per minute, which is reasonable for humans.

\[
\text{Respiration} \approx \left( \frac{1 \text{ Breath}}{2000 \text{ Samples}} \right) \left( \frac{500 \text{ Samples}}{\text{sec}} \right) \left( \frac{60 \text{ sec}}{\text{min}} \right) = 15 \text{ breaths/min}
\]

Equation 2.8: Computation of approximate respiration from patient data.

The middle chart of Figure 2.17 displays ABP with a normal morphology. Besides regular systolic and diastolic pressure, the diacritic notch is observable. From the chart, the systolic pressure is approximately 140 mmHg, the diastolic pressure is approximately 75 mmHg and mean average pressure is approximately 120 mmHg. These results are reasonable for a human. As far as the heart rate, the number of samples per ABP cycle and Equation 2.9 are used to compute the rate to be approximately 70 BPM, which is also reasonable.

\[
\text{Heart Rate} \approx \left( \frac{7 \text{ ABP Cycles}}{3000 \text{ Samples}} \right) \left( \frac{500 \text{ Samples}}{\text{sec}} \right) \left( \frac{60 \text{ sec}}{\text{min}} \right) = 70 \text{ beats/min}
\]

Equation 2.9: Computation of heart rate from ABP.

The bottom chart of Figure 2.17 displays normal ECG. The characteristics of the ECG are explained in the next chapter. In brief, the ECG consists of three wavelets, termed the P-wave, QRS complex, and T-wave, respectively. In observing the collected ECG, the QRS complex and T-wave are easily observable. Furthermore, the subtle P-wave is
observable. The P-wave occurs prior to the QRS complex and after diastole, the cardiac rest period, which is defined as beginning after completion of the T-wave. Similar to the ABP, the heart rate (Equation 2.10) is computed to be approximately 70 BPM.

\[
\text{Heart Rate} \approx \left( \frac{7 \text{ECC Cycles}}{3000 \text{Samples}} \right) \left( \frac{500 \text{Samples}}{\text{sec}} \right) \left( \frac{60 \text{sec}}{\text{min}} \right) = 70 \text{ Beats/min}
\]

Equation 2.10: Computation of heart rate from ECG.

Lastly, in relation to the ABP and ECG charts of Figure 2.17, note that the ABP cycle lags the ECG QRS cycle. This is reasonable, considering human physiology, as the cardiac ventricles are first depolarised during the QRS complex of the ECG. Once depolarised, the cardiac muscle responds by contracting and initiates an increase in BP. Furthermore, the ABP is measured at the extremity (index finger) and so there is transit time between the heart and finger for the pressure wave to travel.

2.6. Summary

The goal of the research is to study the effectiveness of using external physiological data to assess the patient's DM and CHD condition. In order to enable this research, a clinical data acquisition is designed and implemented. Specifically, the DAQ system acquires respiration, ABP, and ECG non-invasively from the patient in a clinical setting. Furthermore, the system is based on a low-cost PC that employs the graphical coding development package LabVIEW, for configuring the DAQ, storing the data, and executing utility programmes.

Use of LabVIEW frees dependence upon rigid, English-based code and enables visual coding through the use of wires and symbolic icons. Also, considering the computational power of today's PCs, LabVIEW is able to operate through run-time
libraries, which eliminated the need for compiling and linking of modules. Instead, the VI may be easily changed in the clinical setting and executed directed.

Besides DAQ and data storage operations, LabVIEW includes the necessary operations and subroutines for implementation of complex data analysis routines. That enables future version of the Patient Collection VI to not only acquire the patient's physiological data, but also analyse and diagnose the condition. Furthermore, LabVIEW contains advanced communication subroutines that allow future versions of the Patient Collection VI to not only store the patient data remotely via the internet but also be remotely monitored and accessed by the doctoral staff and maintenance engineer.
Chapter 3 - HRV Extraction from Electrocardiogram

3.1. Introduction

The electro-physiological ECG signal is acquired from the patient; however it is the HRV signal that is used to assess the patient condition. Therefore, the HRV information must be extracted from the ECG signal. Specifically, the ECG QRS complexes are detected and the individual beat, heart periods are determined. Since beat heart period (HP) varies in time, the resulting data is interpolated for equal spacing in time. Lastly, the trend is removed in order to highlight the variability in the signal, as per the algorithm in Figure 3.1.

![Algorithm to process HRV from ECG](image)

3.2. ECG Characteristics

Before processing algorithms are developed, the general characteristics of the physiological signal are investigated in order to make use of *a priori* information. This knowledge enables the designer to produce more robust algorithms. This is particularly true for algorithms that incorporate peak detection.
The ECG signal is assumed to be semi-periodic and wide-sense stationary. That is to say, the peak event occurs on a regular based interval and, although there may be time dependant wavelets in the signal, as a whole, the signal is time-invariant. For example, the ECG signal consists of P-QRS-T wavelets (see Figure 3.2), which are time-dependent as far as their shape and duration, but for a 5 minute ECG signal, the individual complexes are viewed as stationary events in a periodic signal. Although this is generally true for most physiological signals, some have suggested that parameters estimated from the signal are not necessary periodic or time-invariant. [60]

![Figure 3.2: ECG beat with labelled wavelets.](image)

Beyond these characteristics, it is assumed that the ECG spectrum is band-limited, which means the signal information consists of a limited range of frequencies. For example, it has been shown that most of the ECG information is in the range of 0.05 Hz to 100 Hz. [61] Note that these spectral limits are set for human ECG and different species have different spectral bands.
In order to improve detection of the QRS complex, the maximum slope of the R-wave is used as a detection point instead of the maximum R-wave deflection. Consider the two ECG beats cycles in Figure 3.3. The individual samples are plotted in order to highlight the fact that the R-wave peaks are clipped due to either saturation of the pre-amplifier output or maximum quantisation of the analogue to digital converter. Either way, the R-wave peak is detected with at best ±5 sample resolution, which gives a measurement error of ±10 msec, since the sample period is 2 msec. However, the maximum slope of the R-wave is detected within ±1 sample, also shown in Figure 3.3, which gives a resolution of ±2 msec. Therefore, use of the maximum slope of the R-wave enhances the precision in determining the associated heart period. [62] [63]

![QRS Peak and Leading Edge Detection Comparison](image)

Figure 3.3: ECG with saturated peaks and marked maximum slope.

Besides problems of peak saturation, detection of the leading edge eliminates the need to account for baseline offset and baseline wander, where the ECG baseline slowly
increases or decreases over time. This is due to the fact that the baseline shift and slow baseline wander are approximately constant and, therefore, approach zero during differentiation.

In order to detect the leading edge of the R-Wave, the ECG differential is computed according to the difference equation, as shown in Equation 3.1. The time difference between the samples is not considered in the difference equation since it is constant for all samples of the ECG.

\[ y_i = x_i - x_{i-1} \]

Equation 3.1: Sample difference equation, which approximates the differential.

However, the differential approximation of Equation 3.1 also magnifies high frequency components in the ECG, such as the myoelectric (EMG) interference (muscle artefact). *A priori* considerations of the ECG spectrum (0.05 to 100 Hz), allow for use of another function that approximates the differential in the frequencies of interest and then approaches zero for higher frequencies. One such function is a 5-point secant (Equation 3.2), which approximates the ECG differential without amplifying the signal noise, as seen in Figure 3.4.

\[ y_i = 2x_i + 1x_{i+1} + 0x_{i+2} - 1x_{i-3} - 2x_{i-4} \]

Equation 3.2: 5-point secant difference equation used to approximate the differential.
Specifically, note that less than 0.2 Hz of the normalized frequency, the secant function is virtually identical to the differential. With a sampling frequency of 500 Hz, this means that frequencies less than 20% of 500 Hz (100 Hz) are, in effect, differentiated while frequencies greater than 100 Hz are reduced; effectively, low pass filtering the data and reducing the higher frequency noise. Therefore, not only is the approximate differential computed in order to use the peak detection algorithm to determine the maximum slope, but also any higher frequency noise is reduced to ensure more robust detection. Figure 3.5 displays the positive, 5-point secant of an ECG. Since the secant was taken in order to detect the leading edge of the R-wave, the negative values are discarded. Note the enhancement of the peaks in relation to the high frequency noise at the baseline. These peaks are then used to detect the leading edge of the R-wave and, subsequently, the time between sequential R-waves, which is the HR.
3.3. Peak Detection

Todd and Andrews have gone far in describing physiological signals as they relate to peak detection. [64] In summary, a physiological signal is comprised of a sequential data series of numbers. A peak is defined as any element in the data series that dominates both a preceding element and a subsequent element.

In mathematical terms, peaks are defined as local maxima. Specifically, a peak is a maximum value between two consecutive local minima. Similarly, a trough is a minimum value between two consecutive local maxima. To be considered a peak, a sample value must be at least $\delta$ greater than a trough. This threshold value, $\delta$, is also used to define a trough as the minimum value less than $\delta$ between two consecutive local maxima, per Equation 3.3.
\[ x_p = x_{T_i} + \delta \leq x_p \bigcap x_{T_{p-i}} + \delta \leq x_p \\
 x_r = x_{p_i} - \delta \geq x_r \bigcap x_{p_{p-i}} - \delta \geq x_r \]

Equation 3.3: Mathematical definition of a local maximum and minimum.

The Matlab [65], m-file algorithm of Figure 1.12 implements the above peak and trough definition. The operation of the algorithm depends upon the value chosen for the threshold. Visual inspection of the data allows for easy threshold selection. However, this requires supplemental training of clinical staff acquiring the data and additional time with the patient. Automated threshold estimation greatly improves the heart rate algorithm and simplifies the clinical procedure.

```matlab
function [P,T] = PIDetect(x, E)
    P = []; T = []; a = 1; b = 1; i = 0; d = 0;
    xL = length(x);
    while (i < xL)
        i = i + 1;
        if (d == 0)
            if (x(a) >= (x(i) + E))
                d = 2;
            elseif (x(i) >= x(b) + E))
                d = 1;
            end;
            if (x(a) <= x(i))
                a = i;
            elseif (x(i) <= x(b))
                b = i;
            end;
        elseif (d == 1)
            if (x(a) <= x(i))
                a = i;
            elseif (x(a) >= (x(i) + E))
                P = [P a]; b = i; d = 2;
            end;
        elseif (d == 2)
            if (x(i) <= x(b))
                b = i;
            elseif (x(i) >= (x(b) + E))
                T = [T b]; a = i; d = 1;
            end;
        end;
    end;
end;
```

Figure 3.6: Peak detection algorithm.

Since the leading edge of the R-wave is being detected, only positive slopes of the ECG are estimated. These slope values are then divided into two clusters. One cluster consists of the peaks, which are known to refer to the ECG R-wave. The other cluster consists of the positive slope values near zero.
In order to separate the positive slope values into two clusters, unsupervised learning, nearest neighbour criteria clustering is used. Unsupervised learning may be used since it is known that two clusters are desired. The nearest neighbour criterion is chosen since it requires far less calculation than sum-of-squared-error or Bayesian maximum likelihood criteria. [66]

The nearest neighbour criterion is implemented as the absolute difference between a sample and cluster means. The sample is assigned to the cluster mean with smallest difference. Once all the samples have been assigned, new cluster means are determined and samples are again classified to the nearest cluster mean. Algorithm termination occurs when the change in the cluster means is less than $e$. Figure 3.7 displays the Matlab m-file implementation of the unsupervised learning, two cluster classifier.

```matlab
function [c1, c2]=twoclass(x, e)
c1=x(1); lastc1=c1; c2=x(2); lastc2=c2;
while 1
    class1=[]; class2=[];
    for i=1:length(x)
        if (abs(cl-x(i)) < abs(c2-x(i)))
            class1 = [class1 x(i)];
        else
            class2 = [class2 x(i)];
        end;
    end;
    c2=mean(class2); cl=mean(classl);
    if (abs(lastc2-c2) < e) & (abs(lastcl-cl) < e)
        return;
    end;
    lastc2 = c2; lastcl = cl;
end
```

Figure 3.7: Two class clustering algorithm.

Once the cluster means are determined, the larger cluster mean is the centre of the peak data and used as the threshold for the peak detection algorithm.

Figure 3.8 displays the results of the peak detection algorithm with auto-threshold setting. Specifically, the secant-estimated derivative of 12 consecutive QRS complexes.
is displayed with the threshold marked as a straight line and the peaks marked with circles.

Figure 3.8: ECG secant estimate of the derivative with marked threshold and peak detections.

3.3.1. Peak Detection Enhancement - Linear Filtering

Since the ECG spectrum is assumed to be band-limited to the range 0.5 to 100 Hz, low pass filtering may be used to reduce noise above 100 Hz. Noise above 100 Hz is often associated with EMG interference and harmonics of $220 \, V_{\text{RMS}}$ power. Linear filtering, Finite Impulse Filtering (FIR), may be used to implement a low pass filter effect on the samples while maintaining a linear phase delay between samples. In other words, the higher frequency data is reduced in magnitude, but the same relative time delay between samples is preserved. [67] [68]
Equation 3.4 displays the filtering equation for a 10th order FIR filter, where the \( b_i \) coefficients are the filter coefficients. The coefficients are chosen in order to reduce the amplitudes of frequencies greater than 150 Hz, which implies a low pass filter (LPF) implementation.

\[
y_i = b_0x_i + b_1x_{i-1} + b_2x_{i-2} + b_3x_{i-3} + b_4x_{i-4} + b_5x_{i-5} + b_6x_{i-6} + b_7x_{i-7} + b_8x_{i-8} + b_9x_{i-9}
\]

Equation 3.4: 10th order FIR filter difference equation.

Since the filter of Equation 3.4 consists of only ten coefficients, the filter tends to unevenly reduce the higher amplitudes. This is due to the implication that the filter is multiplied by a square wave, which gives rise to a sinc function in the frequency domain. Hamming, and others, have shown that the sinc function side-lobes may be significantly reduced if the filter coefficients, \( b_i \), are adjusted by a windowing operation, as show in Equation 3.5.

\[
b_{wi} = b_i (0.54 - 0.46 \cos(\frac{2\pi i}{N-1}))
\]

Equation 3.5: Hamming window implementation.

In Equation 3.5, \( N \) is the filter order and \( i \) ranges from 0 to \( N-1 \). As an example application, typical ECG is corrupted with normal random noise and displayed in Figure 3.9. The \textit{a priori} spectral information and LPF are applied to the noisy ECG signal and result is displayed in Figure 3.10. Note the evident reduction in the high frequency noise at the baseline.
3.3.2. Peak Detection Enhancement - Refractory

Once a peak has been detected, a refractory or blanking time may be employed in order to ensure against false, early detection. Specifically, refractory halts possible peak
detection until such a time that a peak may be possible. The time of blanking is set using
\textit{a priori} information of the physiological data. Figure 3.11 displays the Matlab
implementation of the modified peak detection algorithm. The additional input defines
the number samples that must pass before a new peak may be detected.

In relation to the ECG signal, occasionally the cardiac re-polarisation, T-wave, is large
enough to be detected as an R-wave, as shown in Figure 3.12. Needless to say, this
misdetection would greatly affect the HRV.

\begin{verbatim}
function [P,T] = PTRDetect(Q, E, R)
P = []; T = []; a = 1; b = 1;
Rp = -R+1; Rt = -R+1;
i = 0; d = 0;
QL = length(Q);

while (i <= QL)
i = i + 1;
if (d == 0)
  if (Q(a) >= (Q(i) + E))
    d = 2;
  elseif (Q(i) >= (Q(b) + E))
    d = 1;
  end;
  if (Q(a) <= Q(i))
    a = i;
  elseif (Q(i) <= Q(b))
    b = i;
  end;
elseif (d==1)
  if (Q(a) <= Q(i))
    a = i;
  elseif (Q(a) >= (Q(i) + E))
    if (a > Rp+R)
      P = [P a]; Rp = a;
    end;
    b = i; d = 2;
  end;
elseif (d==2)
  if (Q(i) <= Q(b))
    b = i;
  elseif (Q(i) >= (Q(b) + E))
    if (b > Rt+R)
      T = [T b]; Rt = b;
    end;
    a = i; d = 1;
  end;
end;
end;

Figure 3.11: Refractory modified peak detection algorithm.
\end{verbatim}

Since it is known that the ECG signal is from a human, the maximum expected heart
rate in a clinical screening session is approximately 150 BPM. [69] Therefore, a
refractory of 400 msec may be used to safely avoid the secondary peak. Using the
modified peak detection algorithm and a known sampling frequency of 500 Hz, the refractory tuning is computed according to Equation 3.6.

\[
\text{Refractory} = \left( \frac{500 \text{ samples}}{\text{sec}} \right) \left( \frac{400 \text{ msec}}{\text{sec}} \right) \left( \frac{\text{sec}}{1000 \text{ msec}} \right) = 200 \text{ Samples}
\]

Equation 3.6: Computation of sample refractory based upon human physiology.

The modified peak detection with refractory algorithm is to the ECG signal with high T-wave deflections of Figure 3.12. Specifically, the ECG secant derivative estimate is shown and it is noted that the T-wave approaches the height of the R-wave. The peak detection algorithm output is also marked on the chart and is successful in avoiding the T-wave deflections.

![Figure 3.12: ECG derivative estimate with detected R-wave peaks and T-wave peaks avoided using refractory.](image-url)
3.4. HRV Computation

Once the ECG QRS complexes have been detected, the individual beat periods are computed as the difference between the time indexes of consequent R-wave, as shown in Figure 3.13. Since the period changes from one beat to the next, both the period and the time of the start of the period are recorded. As a convention, the beat period is assigned to the time index of the initial R-wave.

![Figure 3.13: Two ECG beats with individual periods marked.](image)

The HR is defined with units of beats per minute. Therefore, if the HP for one beat is 650 ms, then the HR for one beat is 92 Beats/min, per Equation 3.7. Note that the HR and HP are inversely proportional to one another and, though they contain the same information, give reciprocal distributions. That is, as the HP increases, the HR decreases, and visa versa.
\[
HR = \left( \frac{1 \text{ Beat}}{650 \text{ ms}} \right) \left( \frac{1000 \text{ ms}}{\text{sec}} \right) \left( \frac{60 \text{ sec}}{\text{min}} \right) = 92 \text{ Beats/ min}
\]

Equation 3.7: Computation of the HR for one beat, given HP for one beat.

Although the HP and HR are related, the HP is preferred for the HRV signal as it has been shown to give linear response to vagal stimulation, which slows the rate of cardiac contractions, while the HP gives a hyperbolic response. [70] Some have proved that logarithmic HP and HR give the same distribution, as shown in Equation 3.8, which eliminates concerns over which to use for the HRV signal. [71]

\[
HR \propto \left( \frac{1}{\text{HP}} \right) \\
\log(HR) \propto \log\left( \frac{1}{\text{HP}} \right) = -\log(\text{HP})
\]

Equation 3.8: Comparison of logarithmic HR and HP.

Even so, the goal of this study is to determine the best analyses to highlight differences between the patient conditions. The larger the difference, the better the classifier is able to assess the patient. For this reason, the author has chosen to focus on use of the HP per beat for the HRV signal.

### 3.5. Outlier Removal

Ectopic beats and skipped beats by the patient's heart give rise to discontinuities in the HRV signal. Ectopic beats are often premature ventricular contractions (PVC), shown in Figure 3.14, which, although do not resemble the typical P-QRS-T beat, are detected by the algorithm and significantly disrupt the HRV signal. In order to analyse the HRV signal, these discontinuities, termed outliers, are removed.
Outlying HR values differ statistically from the HRV signal as a whole. Traditionally, outliers are defined as samples that are more than 3 standard deviations from the sample mean, as shown in Equation 3.9. [72]

\[
\text{Outlier}_i = \begin{cases} 
  x_i > \bar{x} + 3\sigma_x \\
  x_i < \bar{x} + 3\sigma_x 
\end{cases}
\]

where, \( \bar{x} = \frac{1}{N} \sum_{i=1}^{N} x_i \), and \( \sigma_x = \sqrt{\frac{N \sum_{i=1}^{N} x_i^2 - (\sum_{i=1}^{N} x_i)^2}{N^2}} \)

Equation 3.9: Traditional outlier limits based upon sample mean and standard deviation.
For example, Figure 3.15 displays the HRV waveform for a 5 minute ECG. It is suspected that sample 162 is an outlying sample since it differs from the remainder of the data set. The set is approximately normal in its distribution, as shown in Figure 3.16, and the following statistics are computed in Figure 3.17. According to the statistics, sample 162 is less than outlier limit, and so, is marked as an outlier. Once the outlying sample is removed, interpolation is used to complete the data set and account for the missing sample. [73]
Histogram of Heart Periods

Figure 3.16: HRV sample distribution.

<table>
<thead>
<tr>
<th>Statistic</th>
<th>Units in msec</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample mean</td>
<td>850</td>
</tr>
<tr>
<td>Sample standard deviation</td>
<td>33</td>
</tr>
<tr>
<td>Upper outlier limit</td>
<td>949</td>
</tr>
<tr>
<td>Lower outlier limit</td>
<td>751</td>
</tr>
<tr>
<td>Sample_{162} value</td>
<td>720</td>
</tr>
</tbody>
</table>

Figure 3.17: HRV statistics for determining outlier conditions.

In recent years, it has been noted that outlier identification based upon the sample mean and standard deviation has the intrinsic problem of using the outlier values in computing the upper and lower limits. [74] Instead, the sample median and inter-quartile range are used as estimates for the sample mean and standard deviation. The median is defined as the 50% percentile of the sample values. The inter-quartile range is defined as the difference between the 25% and 75% percentiles of the sample values. Using these
definitions, an outlier is defined as any sample values outside the following limits of Equation 3.10, [75]

\[
\text{Outlier}_i = \begin{cases} 
    x_i > \text{median}(X) + 3\{(\text{range}(X)\} \\
    x_i < \text{median}(X) - 3\{(\text{range}(X)\} 
\end{cases}
\]

Equation 3.10: Outlier limits defined by the sample median and inter-quartile range.

In Equation 3.10, X is the set of all the sample values. This outlier definition has the strong advantage of not using any possible outlier values in computing the upper and lower limit. Considering the previous HRV signal, sample 162 is again suspected as corrupt due to an ectopic or skipped beat, since the following statistics are computed in Figure 3.18, and sample 162 is less than the lower outlier limit.

<table>
<thead>
<tr>
<th>Statistic</th>
<th>Units in msec</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample median</td>
<td>848</td>
</tr>
<tr>
<td>Sample inter-quartile range</td>
<td>38</td>
</tr>
<tr>
<td>Upper outlier limit</td>
<td>962</td>
</tr>
<tr>
<td>Lower outlier limit</td>
<td>734</td>
</tr>
<tr>
<td>Sample\text{162} value</td>
<td>720</td>
</tr>
</tbody>
</table>

Figure 3.18: HRV statistics for determining outlier conditions.

However, upon careful inspection of the ECG QRS detection algorithm, it was determined that no ectopic or skipped beats occurred. Also, it was confirmed that the previously introduced algorithm detected all the QRS complexes correctly and that the HRV signal was physiologically correct. Specifically, the observable difference in sample 162 is due to a sudden change in the cardiac rhythm, which is normal.
These statistical based outlier definitions assume time-invariant data. That is, that the sample statistics do not change with time. Over the 5 minutes of ECG collection, it was noted that the patient's heart rate continuously adjusted for the cardiac load, which is a normal physiological response. Therefore, most statistical based methods for outlier identification are not valid and instead *a priori* information is used in order to determine appropriate limits.

Specifically, human physiology is considered for determining the upper and lower limits of acceptable HRV samples. It is assumed that the HR does not increase or decrease by 50% over a 5 minute period while the patient is resting. [76] Using this *a priori* information, the following limits are computed and displayed in Figure 3.19. As per these calculations, it is determined that sample 162 is not an outlying sample and this outlier removal definition is implemented in the algorithm to extract the HRV information from the ECG signal.

<table>
<thead>
<tr>
<th>Statistic</th>
<th>Units in msec</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample median</td>
<td>848</td>
</tr>
<tr>
<td>Upper outlier limit (50% above median)</td>
<td>1270</td>
</tr>
<tr>
<td>Lower outlier limit (50% below median)</td>
<td>424</td>
</tr>
<tr>
<td>Sample162 value</td>
<td>720</td>
</tr>
</tbody>
</table>

Figure 3.19: HRV statistics for determining outlier conditions.

### 3.6. Interpolation

Most digital signal processing routines assume the data is equally spaced in time. As previously mentioned, the initial HRV data set consists of both time and period information. In order to produce equally spaced data, mathematical interpolation is
used. Also, since the maximum frequency of interest is less than 2.5 Hz, a sampling frequency of 5 Hz is chosen, as per the Nyquist sampling theorem.

Interpolation is accomplished by fitting a function to known data points, termed 'knots', and then using the function to compute the equally spaced data points. There are many interpolation algorithms such as the Lagrange polynomial interpolators. The author chose to use a cubic spline implementation as it minimizes overshoot and ringing associated with polynomial functions. Figure 3.20 displays 10 seconds of the original HP data computed from the ECG and equally spaced, interpolated HP data.

![Graph](image.png)

**Figure 3.20:** ECG HP data overlaid with 5 Hz interpolated HP.

### 3.7. Trend Removal

The average of the HRV signal corresponds to the average heart rate, which has been shown to be of little interest in classifying the patient condition. In order to better analyse the HRV signal, the trend is removed. Specifically, HRV signal information near 0 Hz is removed.
There are many methods of removing the signal trend. A quick and common one is to subtract the sample mean (or median) from each sample, as per Equation 3.11. A more generalised form is to subtract the best straight line determined by least squares, per Equation 3.12.

\[ y_i = x_i - \bar{x} \quad \text{where} \quad \bar{x} = \frac{1}{N} \sum_{i=1}^{N} x_i \]

Equation 3.11: Trend removal via subtraction of the sample mean.

\[ y_i = x_i - (mx_i + b) \]

where

\[
\begin{align*}
  m &= \frac{N \left( \sum_{i=1}^{N} x_i y_i \right) \left( \sum_{i=1}^{N} x_i^2 \right) \left( \sum_{i=1}^{N} y_i \right) - \left( \sum_{i=1}^{N} x_i \right) \left( \sum_{i=1}^{N} x_i y_i \right)}{N \left( \sum_{i=1}^{N} x_i^2 \right) - \left( \sum_{i=1}^{N} x_i \right)^2} \\
  b &= \frac{\left( \sum_{i=1}^{N} y_i \right) \left( \sum_{i=1}^{N} x_i^2 \right) - \left( \sum_{i=1}^{N} x_i \right) \left( \sum_{i=1}^{N} x_i y_i \right)}{N \left( \sum_{i=1}^{N} x_i^2 \right) - \left( \sum_{i=1}^{N} x_i \right)^2}
\end{align*}
\]

Equation 3.12: Trend removal via subtraction of the best straight line.

However, considering the HRV frequencies of interest, which is approximately 0.01Hz and greater, a moving average subtraction, or a high pass filter (HPF), may be used to remove the unwanted HRV information. Filtering allows for the selection of the desired signal information and removal of noise. In this case, a HPF is used to pass the desired HRV signal information and reduce the low frequency HRV trend, per Figure 3.21. [77]

![Figure 3.21: HRV trend removal via a HPF.](image)
A simple implementation of HPF of this technique may be done using the application of the WT. [78] The wavelet decomposition is implemented using a matched HPF and LPF, per Figure 3.22. At each level of the decomposition, the HPF successively reduces the passed HRV spectrum. Considering the implementation in Figure 3.22, the decomposition is carried out to level 7, since at that level, detail frequency range would be approximately 0.02 to 0.04 Hz, and the approximation would be from 0 to 0.02 Hz. The approximation coefficients are then discarded, and thus, the HRV signal trend is removed.

The advantage of wavelet based, HRV trend removal lies in the reduction of signal processing complexity. Instead of processing the HRV signal to remove the trend, the wavelet decomposition may be used to analyse the HRV signal and remove the trend in the same step. Further application of the WT to the HRV signal may be found in Chapter 4.
3.8. Summary

It has been shown that HRV may be extracted from ECG. A priori information of the ECG characteristics and human physiology are used to enhance QRS detection, and thus, computation of the HRV signal. Outlier analysis is used for correction of ectopic and missing beats. Although traditional and median based outlier removal was investigated, neither proved satisfactory due to the time-variant nature of the HRV signal. Instead, human physiology is used to compute acceptable outlier limits. Once outlying samples are removed, spline based interpolation is used to increase the sampling frequency and to equally space the data in time. Each of these steps of the algorithm to determine HRV from the ECG is implemented using MatLab, as shown in Figure 3.23.
function hp = hrvecg(ecg);
% Extract equally spaced heart period data from ECG
% usage hp = hrvecg(ecg)
% ecg = electrocardiogram data, 500 Hz sampling assumed
% hp = heart period, 5 Hz sampling frequency
% 5 point secant based peak detector used. The empty set is returned for an error.
hp = [];
% DETERMINE THE R-WAVE SLOPE
secg = secant(ecg, 0.002);
% DETERMINE PEAK THRESHOLD BASED UPON TWO-CLASS UNSUPERVISED CLASS SEPARATION
asecg = secg(asecg>15);
[cl c2 it]=twoclass(asecg, 10);
% DETERMINE MAXIMUM SLOPE LOCATION
[Peaks, V] = PTRDetect(secg, 2*abs(cl-c2), 200);
Peaks = Peaks';
pklen = length(Peaks);
if pklen > 2
  % SET THE TIME INDEX
  hpx = zeros(pklen-1, 2);
  hpx(:,1) = Peaks(1:pklen-1);
  % DETERMINE THE BEAT HEART PERIODS
  hpx(:,2) = Peaks(2:pklen) - Peaks(1:pklen-1);
  % REMOVE OUTLYING SAMPLES
  hpx = HRVoutlier(hpx);
  % INTERPOLATE TO 5Hz SAMPLING
  i = 0:100:(150000-100);
  hp = spline(hpx(:,1), hpx(:,2), i);
end;

Figure 3.23: MatLab algorithm to determine the HRV signal from ECG.

Lastly, in order to enhance the analysis of the signal variability and reduce algorithm complexity, the HRV signal trend is removed. Although linear regression or a HPF may be used to remove the trend, wavelet decomposition allows for easy trend removal and characterisation of the HRV signal in the same step. Therefore, the MatLab algorithm of Figure 3.23 does not include trend removal as this step is integrated with the HRV analysis of Chapter 4.
Chapter 4 – HRV Analysis

4.1. Introduction

The major goal of this research is to determine the effectiveness of using the HRV signal as a basis for screening patients for DM and CHD. The HRV signal is extracted from the ECG signal and consists of approximately \(350\) samples for each patient action, as explained in Chapter 2. In order to enhance the effectiveness of the screening, various features are computed from the HRV signal. Specifically, features are computed that best distinguish between diseased and non-diseased patients.

The type features computed are categorised into those extracted from the HRV time domain information, those from the HRV frequency domain information, and those from the HRV time-frequency domain information, as per the discussions in Chapter 1. The extracted features are correlated in order to determine which provide redundant information.

4.2. Time Domain Analysis

Time domain analyses of the HRV signal includes STD, rMSSD, ZC, histogram and phase analysis. [79] [80] [81] These various analyses are applied to sample HRV signals from N, DM, CHD, and CHDD patients as displayed in Figure 4.1, Figure 4.2, Figure 4.3, and Figure 4.4, respectively. For each data set, the trend (information less than 0.02 Hz) has been removed, and thus, the signals vary about the x-axis. In order to visually compare the data sets, the same y-axis units and scale are used.
In an initial inspection, it is noted that the N patient has the widest HRV range, spanning from -100 to 100 ms. The DM and CHDD patient HRV signals display reduced HRV range, which in all likelihood, is due to the presence of DAN. Although the CHD patient has a wide HRV range that approaches the N patient range, it is obvious that higher frequencies are missing from the signal. Each of these initial observations corresponds to the HRV diagnoses discussed in Chapter 1.

![Figure 4.1: Normal (N) HRV signal.](image)

![Figure 4.2: Diabetic (DM) HRV signal.](image)
4.2.1. Standard Deviation of Normal-to-Normal (SDNN)

The standard deviation of the 30 minute HRV gives an index to the overall variability of the signal, regardless of the patient's actions. 'Normal-to-Normal' refers the requirement of having the HRV signal computed from normal QRS complexes within the ECG signal, with ectopic and missing beats accounted for and corrected.
Since the signal average is known to be zero, then the modified sample STD is defined in Equation 4.1, which provides a measure of the data's variability. Specifically, with the mean HRV being zero, then 66% of the HRV signal samples are within \( \pm \sigma_x \), the sample STD.

\[
\sigma_x = \sqrt{\frac{1}{N} \sum_{i=1}^{N} x_i^2} \quad \text{if } x = 0
\]

Equation 4.1: Sample STD, given the sample mean is zero and \( N \) is the total number of samples.

The SDNN is computed for the four sample HRV signals and displayed in Figure 4.5. As expected from the initial inspection, the SDNN of the N patient has the largest SDNN result since the N patient's HR has the greatest amount of variability. Similarly, as expected, the diabetic patients (DM and CHDD) score lower SDNN results, likely due to the presence of DAN.

<table>
<thead>
<tr>
<th></th>
<th>Normal (msec)</th>
<th>DM (msec)</th>
<th>CHD (msec)</th>
<th>CHDD (msec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SDNN</td>
<td>86</td>
<td>18</td>
<td>36</td>
<td>17</td>
</tr>
</tbody>
</table>

Figure 4.5: Standard deviation results for 30-minute HRV signals of N, DM, CHD, and CHDD patients.

4.2.2. Mean of the Standard Deviation of Normal-to-Normal (SDNNIDX)

The mean of the STD of normal-to-normal (SDNNIDX) is computed as the sample mean of the SDNN of each 5 minute intervals. Specifically, the SDNN is computed for each of the patient actions during the clinical procedure, according to Equation 4.1. Then, the sample mean is computed of from each 5-minute SDNN result for the patient. Therefore, this analysis quantifies the variability within each of the patient actions.
The SDNN is computed for each of the sample patient HRV signals and is displayed graphically in Figure 4.6 and numerically in Figure 4.7. The SDNNIDX is then computed as the average of the SDNN for each action, as is also shown in Figure 4.7. As expected, the SDNNIDX results are very similar to the SDNN results, with the N patient giving the largest value and the diabetic patients (DM and CHDD) giving the lowest values due to the likely presence of DAN.

![SDNN of 5 Minute Actions](image)

Figure 4.6: SDNN for various patients and required actions.

<table>
<thead>
<tr>
<th>Action</th>
<th>Normal (msec)</th>
<th>DM (msec)</th>
<th>CHD (msec)</th>
<th>CHDD (msec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Supine</td>
<td>36</td>
<td>28</td>
<td>35</td>
<td>4</td>
</tr>
<tr>
<td>Standing</td>
<td>95</td>
<td>21</td>
<td>34</td>
<td>10</td>
</tr>
<tr>
<td>Sitting</td>
<td>90</td>
<td>10</td>
<td>30</td>
<td>16</td>
</tr>
<tr>
<td>Sitting 9</td>
<td>118</td>
<td>20</td>
<td>30</td>
<td>13</td>
</tr>
<tr>
<td>Sitting 12</td>
<td>76</td>
<td>8</td>
<td>39</td>
<td>20</td>
</tr>
<tr>
<td>Sitting 15</td>
<td>80</td>
<td>13</td>
<td>52</td>
<td>27</td>
</tr>
<tr>
<td>SDNNIDX</td>
<td>82</td>
<td>17</td>
<td>37</td>
<td>15</td>
</tr>
</tbody>
</table>

Figure 4.7: Sample mean of 5 minute SDNN.
4.2.3. Standard Deviation of the Mean of Normal-to-Normal (SDANN)

SDANN is the STD of the 5 minute interval sample means. In other words, instead of computing the mean of the 5 minute STD, the STD of the 5 minute means is computed. Considering that sample mean is a linear operation, it is expected that SDANN results correlate strongly with the SDNNIDX results.

In order to compute the SDANN, the trend is not removed from the sample HRV signals. First, 5 minute sample averages are computed for each of the patient actions, and then, the STD is computed from the interval averages, per the results in Figure 4.8. As expected, the N patient again scores the highest value, with the diabetic patients scoring the lowest.

<table>
<thead>
<tr>
<th>Action</th>
<th>Normal Average (msec)</th>
<th>DM Average (msec)</th>
<th>CHD Average (msec)</th>
<th>CHDD Average (msec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Supine</td>
<td>525</td>
<td>491</td>
<td>890</td>
<td>547</td>
</tr>
<tr>
<td>Standing</td>
<td>592</td>
<td>484</td>
<td>807</td>
<td>527</td>
</tr>
<tr>
<td>Sitting</td>
<td>580</td>
<td>465</td>
<td>869</td>
<td>550</td>
</tr>
<tr>
<td>Sitting 9</td>
<td>619</td>
<td>477</td>
<td>853</td>
<td>556</td>
</tr>
<tr>
<td>Sitting 12</td>
<td>563</td>
<td>465</td>
<td>853</td>
<td>555</td>
</tr>
<tr>
<td>Sitting 15</td>
<td>565</td>
<td>468</td>
<td>846</td>
<td>548</td>
</tr>
<tr>
<td>SDANN</td>
<td>32</td>
<td>11</td>
<td>27</td>
<td>10</td>
</tr>
</tbody>
</table>

Figure 4.8: Standard deviation of 5 minute HRV averages.

4.2.4. Histogram Analysis

A histogram displays the range of data over a set of predetermined bins. For the sample HRV signals, the bins are 100 ms wide and span the range -300 ms to 300 ms. The HRV signal data, for each patient, is then sorted and filled in the appropriate bin. The chart in Figure 4.9 displays the histogram of HRV signal for the sample N, DM, CHD, and CHDD patients. In agreement with earlier observations, the normal HRV signal has the
widest distribution while the diabetic patients have the narrowest distributions with tall central tendencies.

![Histogram Analysis](image)

Figure 4.9: Histogram analysis of the HRV signal for N, DM, CHD, and CHDD patients.

The inter-quartile range may be used to index the spread of the data in the histogram. The inter-quartile range is defined as the difference between the 75% percentile and 25% percentile of the sorted data, per the discussion in Chapter 1. Using this definition, the inter-quartile range of the sample HRV signals (IQRNN) is computed and displayed in Figure 4.10. In agreement with our previous results, the IQRNN indicates the normal HRV has the greatest range and that the diabetic patients have a much smaller range.

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>DM</th>
<th>CHD</th>
<th>CHDD</th>
</tr>
</thead>
<tbody>
<tr>
<td>IQRNN</td>
<td>111</td>
<td>20</td>
<td>46</td>
<td>14</td>
</tr>
</tbody>
</table>

Figure 4.10: Inter-quartile range of the HRV signal for N, DM, CHD, and CHDD patients.
4.2.5. Root Mean Square Successive Difference (rMSSD)

The successive difference estimates the sample derivative and indexes the change in the HR per cardiac cycle. In order to account for either an increase or decrease in the HR, the root-mean-square (RMS) is taken of the successive difference values, in accordance with Equation 4.2. Therefore, the rMSSD gives a measure of change in the HR per time. It is expected that the N patient exhibits the greatest rMSSD since, physiologically, the N patient has the best cardiac system that is able to change the HR quickly in response to changes in the cardiac load.

\[
X_{\text{RMS}} = \sqrt{\frac{1}{N} \sum_{i=1}^{N-1} (x_{i+1} - x_i)^2}
\]

Equation 4.2: Root-mean-squared value of the successive heart period differences.

The rMSSD is computed for each of the sample HRV patients and displayed in Figure 4.11. As expected, the N patient rMSSD result was much greater than that for the diseased patients, where the effect is due to the presence of CHD or DM.

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>DM</th>
<th>CHD</th>
<th>CHDD</th>
</tr>
</thead>
<tbody>
<tr>
<td>rMSSD</td>
<td>52</td>
<td>11</td>
<td>5</td>
<td>8</td>
</tr>
</tbody>
</table>

Figure 4.11: rMSSD for 30-minute HRV signals of N, DM, CHD, and CHDD patients.

4.2.6. Zero Crossings (ZC)

The number of times a signal crosses the x-axis, or zero crossings (ZC), may be used to estimate the higher frequency components of a signal, if that signal's trend has been removed. This time-based approximation does not account for changes in the sign of the signal's slope that do not cross the x-axis, and so, in no way does it give an exact measure of the high frequency components. The Matlab m-file algorithm in Figure 4.12...
is used to compute the ZC for the sample HRV patients. Note that the algorithm assumes that signal's trend was previously removed.

```matlab
function ZC = ZeroCount(R)
ZC = 0;
s1 = (R(1) > 0);
LR = length(R);
for i = 2:LR
    s2 = (R(i) > 0);
    if (s1 == s2)
        s = s2;
    end;
    ZC = ZC + 1;
end;
```

Figure 4.12: Algorithm to determine the number of zero crossings of a data set.

The ZC results may be viewed in Figure 4.13. In keeping with initial observations, the ZC results indicate that the CHD patient has reduced higher frequency components in comparison to the N and diabetic patients.

<table>
<thead>
<tr>
<th>Action</th>
<th>Normal</th>
<th>DM</th>
<th>CHD</th>
<th>CHDD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Supine</td>
<td>257</td>
<td>284</td>
<td>78</td>
<td>225</td>
</tr>
<tr>
<td>Standing</td>
<td>277</td>
<td>289</td>
<td>56</td>
<td>318</td>
</tr>
<tr>
<td>Sitting</td>
<td>249</td>
<td>162</td>
<td>87</td>
<td>215</td>
</tr>
<tr>
<td>Sitting 9</td>
<td>299</td>
<td>244</td>
<td>72</td>
<td>207</td>
</tr>
<tr>
<td>Sitting 12</td>
<td>237</td>
<td>159</td>
<td>70</td>
<td>204</td>
</tr>
<tr>
<td>Sitting 15</td>
<td>242</td>
<td>206</td>
<td>52</td>
<td>216</td>
</tr>
<tr>
<td>Average ZC</td>
<td><strong>260</strong></td>
<td><strong>224</strong></td>
<td><strong>69</strong></td>
<td><strong>231</strong></td>
</tr>
</tbody>
</table>

Figure 4.13: Average zero count results for N, DM, CHD, and CHDD patients.

### 4.2.7. Lorenz Plots

Lorenz Plots, also termed Poincare Plots, display changes per sample by charting successive samples, x(i) by x(i+1), for all X in the sample set. Similar to the rMSSD, the Lorenz Plot highlights the changes in HR per cardiac cycle. However, unlike the rMSSD, the Lorenz Plots displays both increases and decreases in HR. The changes in the HR per cardiac cycle are reflected in the Lorenz Plot as deviations along the negative xy-axis of Figure 4.14. The overall range of the HRV signal is reflected in the Lorenz Plot as deviations along the positive xy-axis, also shown in Figure 4.14.
The Lorenz Plots of N, DM, CHD, and CHDD patients are displayed in Figure 4.15, Figure 4.16, Figure 4.17, and Figure 4.18 respectively. In comparing the plots to previous results, the normal patient displays the greatest sample range and change per cardiac cycle. Similarly, the diabetic patients display reduced range and the CHD patient displays reduced changes per cardiac cycle.

Figure 4.15: Lorenz Plot of a sample normal patient.
Figure 4.16: Lorenz Plot of a sample DM patient.

Figure 4.17: Lorenz Plot of a sample CHD patient.
The Lorenz Plots do well in displaying the HRV range and changes per cardiac cycle, and provide a means for quick clinical assessment. Even so, other time based analysis tools, such as SDNN and rMSSD, better quantify the HRV signal numerically. Therefore, though the Lorenz Plot may be used for an immediate visual assessment of the HRV signal, it is not pursued further as a basis for patient classification.

4.2.8. Inter-Breath Pattern Analysis

It has been shown that HR varies in relation to the respiration. Specifically, normal HR decreases between maximum inhalations in response to baroreflex receptors. [82] Therefore, inter-breath pattern analysis was developed and applied to the sample patients in order to assess its use as a basis for classification.

The analysis is performed according to the algorithm in Figure 4.19. Specifically, the peak detection algorithm is used to determine the time index of the maximum inhalations. Then the corresponding ECG signal is used to determine the HRV signal. In
accordance with the HRV processing discussion of Chapter 3, the signal is QRS complexes of ECG are detected and ectopic beats are removed.

In order to compare the change in the HR between multiple maximum inhalations, the HRV signal is normalised and stretched to a standardised time interval. Lastly, the average pattern is determined from 5 minute individual HRV patterns. The average pattern and STD from the average are plotted in Figure 4.20.
The average HRV pattern displayed in Figure 4.20 follows the expectation in that the HR decreased between maximum inhalations. However, the STD of all the inter-breath HRV patterns implies a high measurement error in the average HRV pattern. Measurement error may be estimated by the STD divided by the average, per Equation 4.3. From the chart in Figure 4.20, though the average value changes, the STD is approximately 0.35 for each value. In accordance with Equation 4.3, the best approximate error would result from the greatest measurement. Using 0.65, the best approximate error is 54%, which is unacceptably high.

\[
\text{Approximate Error} = \frac{\sigma}{\mu} \\
\text{HRV Pattern Error} = \frac{\sim 0.35}{\sim 0.65} \equiv 0.54 = 54\%
\]

Equation 4.3: Estimate of measurement error and application to HRV pattern analysis.
The inter-breath HRV pattern analysis was applied to other normal and diabetic patients. Similar results to that of Figure 4.20 were obtained. Also, similar high measurement error was recorded which implies the analysis is not sufficient as a basis for classification.

### 4.2.9. Time Based Feature Comparisons

The time domain based features are compared, excluding the Lorenz Plots and inter-breath HRV pattern analysis. Specifically, each of the features is applied to sample N, DM, CHD, and CHDD patients and then normalised, as displayed in Figure 4.21 and Figure 4.22. Upon initial inspection, each of the analyses scored highest for the normal patient and significantly less for the diseased patients.

<table>
<thead>
<tr>
<th>Action</th>
<th>Normal</th>
<th>DM</th>
<th>CHD</th>
<th>CHDD</th>
</tr>
</thead>
<tbody>
<tr>
<td>SDNN</td>
<td>1.00</td>
<td>0.02</td>
<td>0.28</td>
<td>0.00</td>
</tr>
<tr>
<td>SDANN</td>
<td>1.00</td>
<td>0.02</td>
<td>0.79</td>
<td>0.00</td>
</tr>
<tr>
<td>SDNNIDX</td>
<td>1.00</td>
<td>0.02</td>
<td>0.32</td>
<td>0.00</td>
</tr>
<tr>
<td>IRQNN</td>
<td>1.00</td>
<td>0.06</td>
<td>0.33</td>
<td>0.00</td>
</tr>
<tr>
<td>RMSSD</td>
<td>1.00</td>
<td>0.11</td>
<td>0.00</td>
<td>0.06</td>
</tr>
<tr>
<td>ZC</td>
<td>1.00</td>
<td>0.81</td>
<td>0.00</td>
<td>0.85</td>
</tr>
</tbody>
</table>

Figure 4.21: Normalised, time-based feature results.
The normalised feature results are then correlated against one another in order to determine dependency. The correlation coefficient is computed according to Equation 4.4 and provides a measure of dependency between two data sets. A coefficient close to one indicates a close relationship between two data sets, and, therefore, dependency. As the coefficient becomes less than 1, a more distant relationship between the two data sets.

\[
\rho_{XY} = \frac{\sum_{i=1}^{N}(x_i - \bar{x})(y_i - \bar{y})}{\sigma_x \sigma_y}
\]

Equation 4.4: Correlation coefficient between arrays X and Y.

Dependent features provide redundant information to the classifier, and thus, do not improve classification. Independent features provide additional information, and thus, allow for better classification of the patient condition. The correlation coefficient between each of the time-based features is computed and displayed in Figure 4.23.
<table>
<thead>
<tr>
<th></th>
<th>SDNN</th>
<th>SDANN</th>
<th>SDNNIDX</th>
<th>IRQNN</th>
<th>rMSSD</th>
</tr>
</thead>
<tbody>
<tr>
<td>SDANN</td>
<td>0.87</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SDNNIDX</td>
<td>1.00</td>
<td>0.89</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IRQNN</td>
<td>1.00</td>
<td>0.89</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>rMSSD</td>
<td>0.94</td>
<td>0.64</td>
<td>0.92</td>
<td>0.92</td>
<td></td>
</tr>
<tr>
<td>ZC</td>
<td>0.24</td>
<td>0.27</td>
<td>0.20</td>
<td>0.20</td>
<td>0.57</td>
</tr>
</tbody>
</table>

Figure 4.23: Correlation coefficient between each time-based feature.

As expected, the STD features (SDNN, SDANN, and SDNNIDX) and inter-quartile range (IRQNN) are highly correlated as each gives a similar measure of the HRV. The change in HR per cardiac cycle (rMSSD) also displays some dependency with these features. However, the ZC feature displays marked independence from the rest of the features, and thus, additional information for better classification.

4.3. Frequency Domain Analysis

Frequency domain analysis of the HRV signal includes analysis of total signal power and comparisons between the signal power of various frequency bands. [83] [84] [85] [86] These various analysis procedures are applied to sample HRV signals from N, DM, CHD, and CHDD patients displayed in Figure 4.1, Figure 4.2, Figure 4.3, and Figure 4.4, respectively.

4.3.1. FFT-Based PSD Estimation

The PSD is estimated using the Fourier transform. Before computing the transform, the HRV signals are filtered using a Hamming window in order to limit the signal bandwidth and reduce spectral leakage, which leads to the rise of side-lobes and aliasing, as discussed in Chapter 1. The PSD estimate is computed according to Equation 4.5, according to the Welch periodogram, where $x_i$ is the HRV signal sample, $N$ is the number of samples, and $F_S$ is sampling frequency. In order to quickly estimate the PSD, the fast Fourier transform (FFT) is used, which is represented as $X(f)$ in Equation 4.5. [87]
The FFT is used to estimate the PSD for each of the patients. The frequencies of interest, 0.04 to 0.40 Hz, are displayed in Figure 4.24. Although the chart is somewhat difficult to read, it is observed that the normal patient exhibits the greatest power in the frequencies of interest. Furthermore, the CHD patient exhibits a reduction for frequencies near 0.2 Hz and 0.4 Hz.

Equation 4.5: FFT based PSD estimation.

\[
P(f) = \frac{F_s}{N} \left| \frac{1}{N} \sum_{i=0}^{N-1} X_i e^{-j2\pi if_i/N} \right|^2 = \frac{F_s}{N} |X(f)|^2
\]

4.3.2. Autoregressive Based PSD Estimation

The PSD may also be estimated using an autoregressive (AR) model of the time-based signal. The AR coefficients, \(a_i\), and number of coefficients (order), \(p\), are chosen to best model the time-based signal, \(X\), as shown by Equation 4.6. Once the AR coefficients are
determined, the PSD is estimated according to Equation 4.7. Although the AR-based PSD estimation involves the complexity of first determining the AR coefficients, the PSD has the advantage of a smoother PSD with sharper spectral peaks.

\[
\hat{x}(k) = -\sum_{i=1}^{p} a_i x(k-i)
\]

Equation 4.6: AR model, order p, of signal X.

\[
P(f) = \frac{\lambda^2}{F_s \left| 1 + \sum_{i=1}^{p} a_i z^{-i} \right|^2}
\]

where, \( z = e^{j2\pi f/F_s} \)

Equation 4.7: AR-based PSD estimation, where \( \lambda^2 \) represents the variance of the process.

There are many different algorithms used to determine the AR coefficients. The sample HRV signals are modelled using the Burg maximal entropy method. [88] The AR coefficients are then used to estimate the PSD of each sample patient, which is charted in Figure 4.25. Although the AR-based PSD estimate is smoother than the FFT-based PSD estimate, the average spectrum of each patient is similar. Specifically, the N patient exhibits the greatest amount of power and the CHD patient exhibits a reduction for frequencies near 0.2 Hz and 0.4 Hz.
Once the PSD is estimated, spectral features are determined in order to characterize the HRV signals. Specifically, the total spectral power and the ratio between the HRV high frequency (HF) band and HRV low frequency (LF) band are commonly used as a classification basis. [89] LF is defined as the frequency band from 0.05 to 0.15 Hz and HF is defined as the frequency band from 0.15 to 0.5 Hz, as per the discussions in Chapter 1. The total PSD and LF/HF ratio is computed for each for each of the sample patients and normalised for comparison. The results are displayed in Figure 4.26.

<table>
<thead>
<tr>
<th></th>
<th>PSD - FFT</th>
<th>PSD - AR</th>
<th>LF/HF - FFT</th>
<th>LF/HF - AR</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>1.00</td>
<td>1.00</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>DM</td>
<td>0.00</td>
<td>0.00</td>
<td>0.03</td>
<td>0.00</td>
</tr>
<tr>
<td>CHD</td>
<td>0.25</td>
<td>0.37</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>CHDD</td>
<td>0.01</td>
<td>0.03</td>
<td>0.11</td>
<td>0.06</td>
</tr>
</tbody>
</table>

Figure 4.26: Normalised, frequency-based feature results.

As an initial inspection, it is observed that the normal patient had the greatest total spectral power in the 0.05 to 0.50 Hz frequency band. Also, the CHD patient had the
greatest difference between the spectral power in the LF and HF frequency bands. These results are correlated against the SDNN and ZC time-based features and shown in Figure 4.27. As expected, the FFT and AR estimates of the total PSD and LF/HF ratios are highly correlated, since both seek to estimate the same values. Also, the PSD feature is highly correlated with the SDNN. This is also expected since, theoretically, the variance of a signal gives the same result as the total spectral power of a signal. Lastly, since the ZC estimates the fundamental frequency of a signal, it correlates well with the LF/HF ratio frequency since the higher frequency and ratio are both lower for the CHD patient.

<table>
<thead>
<tr>
<th></th>
<th>SDNN</th>
<th>ZC</th>
<th>PSD - FFT</th>
<th>PSD - AR</th>
<th>LF/HF - FFT</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSD - FFT</td>
<td>1.00</td>
<td>0.27</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PSD - AR</td>
<td>1.00</td>
<td>0.15</td>
<td>0.99</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LF/HF - FFT</td>
<td>0.13</td>
<td>0.99</td>
<td>0.16</td>
<td>0.04</td>
<td></td>
</tr>
<tr>
<td>LF/HF - AR</td>
<td>0.10</td>
<td>0.99</td>
<td>0.12</td>
<td>0.00</td>
<td>1.00</td>
</tr>
</tbody>
</table>

Figure 4.27: Correlation coefficient between each frequency-based feature.

4.4. Time-Frequency Analysis

As discussed in the introduction of Chapter 1, the HRV signal is time-varying. In other words, as time passes, the signal varies in its shape and spectral power. In regards to the clinical procedure the patient is required to perform a different action every 5 minutes. These actions give rise to different responses for each of the patient types: N, DM, CHD, and CHDD. Therefore, it is advantageous to characterise the HRV signal for each 5 minute interval in order to account for the HRV response to the actions. Therefore, time-frequency analysis is required, such as the short-term Fourier transform (STFT) or wavelet transform (WT).
4.4.1. Short-Term Fourier Transform Analysis

The STFT is used to compute the PSD for each 5 minute interval. The AR-based PSD estimate, per Equation 4.6, gives a similar result to the FFT-based estimate and provides a smoother PSD with sharper spectral peaks. The sample normal patient HRV signal is used and the PSD by time is displayed in Figure 4.28. Note that the PSD changes over time in response to patients actions.

![Short Term Fourier Transform - AR Estimated PSD](image)

Figure 4.28: STFT of a normal patient using the AR estimate of the PSD.

In order to create a basis for classification, the total PSD is computed as well as the power in the LF and HF bands. Lastly, the LF/HF ratio is computed for each 5 minute action. As a matter of example, these features are computed for a sample normal patient and displayed in the table of Figure 4.29. Of particular interest is the change in the LF/HF ratio from supine to patient activity.
<table>
<thead>
<tr>
<th></th>
<th>0 – 5 (min)</th>
<th>5 – 10 (min)</th>
<th>10 – 15 (min)</th>
<th>15 – 20 (min)</th>
<th>20 – 25 (min)</th>
<th>25 – 30 (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total PSD</td>
<td>97149</td>
<td>68650</td>
<td>37952</td>
<td>68290</td>
<td>106110</td>
<td>56341</td>
</tr>
<tr>
<td>LF</td>
<td>26941</td>
<td>57014</td>
<td>31148</td>
<td>32095</td>
<td>77430</td>
<td>41176</td>
</tr>
<tr>
<td>HF</td>
<td>57556</td>
<td>10522</td>
<td>6328</td>
<td>22627</td>
<td>26980</td>
<td>14163</td>
</tr>
<tr>
<td>LF/HF</td>
<td>0.468</td>
<td>5.419</td>
<td>4.922</td>
<td>1.419</td>
<td>2.870</td>
<td>2.907</td>
</tr>
</tbody>
</table>

Figure 4.29: AR-estimated PSD, LF, HF, and LF/HF ratio for each HRV action interval.

4.4.2. Wavelet Transform Analysis

Similar to the STFT, the WT provides both frequency and time information from the HRV signal. Specifically, the HRV signal is decomposed using the Dabachies, 12th order, wavelet, which is displayed in Figure 4.30. Previous research has shown that this wavelet highlight changes in the HRV signal due to the presence of DM and CHD. [90]

Per the discussions in Chapter 1, the wavelet is implemented through the means of mirrored quadrature, low pass and high pass filters, as shown previously in Figure 3.22. The specific filter coefficients for the Dabachies, 12th order, wavelet are displayed in Figure 4.31.

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Figure 4.31: Dabachies, 12th order wavelet decomposition implementation via low and high pass filters.

Since wavelet analysis provides multi-resolution time and frequency estimates of the PSD, each detail must be interpolated in order to plot the scaled details together on the same axes, as is shown in Figure 4.32. Note that the detail scales correspond to ranges of frequencies. In accordance with the application of the filter, the following detail coefficients represent the following frequency ranges: detail 3 represents the frequency range 0.31 to 0.63 Hz, detail 4 represents the frequency range 0.16 to 0.31 Hz, detail 5 represents the frequency range 0.08 to 0.16 Hz, and detail 6 represents the frequency range 0.04 to 0.08 Hz. Note that these bands do not exactly align with the STFT since the wavelet employs power of 2 resolutions.
Figure 4.32: Decomposition of a sample normal HRV signal using a 12th order, Daubichies wavelet. The RMS values of the wavelet coefficients are displayed.

Once the HRV signal is decomposed over time and frequency, the RMS values of the wavelet coefficients \([91]\) are computed in order to compare the signal strength of each detail. Then, the sample mean of a particular time interval for each detail is computed in order to determine a basis for characterising the signal. Since the patient is requested to perform a different action every 5 minutes, the averaging time interval of the wavelet coefficients is chosen to be 5 minutes.

Mathematically, the sample mean of individual RMS values correlates well to the sample STD of a particular time interval, per Equation 4.8. The two values are not the same since the sum of the absolute value does not equal the root of the sum of squares. However, each gives a comparable result and so is highly correlated. Considering the outlier discussions of Chapter 2, these methods of estimating the signal strength in each detail are very susceptible to the influence of outlying values since all the wavelet coefficients of the detail are used in the computation. Therefore, the author proposes the
use of the inter-quartile range to estimate the signal strength over each time interval of each detail level. As previously mentioned, the inter-quartile range estimates the sample deviation, and thus the signal power, without being affected by outlying samples. Thus, the inter-quartile range gives a more robust estimate of the signal power.

\[
\bar{w}_{\text{rearr}} = \frac{1}{M} \sum_{i=1}^{M-1} \sqrt{|w_i|^2} = \frac{1}{M} \sum_{i=1}^{M-1} |w_i|
\]

\[
\sigma_w = \sqrt{\frac{1}{M} \sum_{i=1}^{M-1} (w_i)^2}
\]

Equation 4.8: Comparison of the RMS sample mean and the sample STD over the time interval, \(M\).

The inter-quartile range is computed for 5 minute intervals for the last six detail levels and displayed in Figure 4.33. These range-based features compare well with the graphical wavelet decomposition of Figure 4.32. Detail level 2 has the smallest range values, which is also true for the graphical decomposition. Furthermore, both the table and the chart display similar time characteristics in detail level 6. Specifically, the detail peaks during the middle fifteen minutes of the 30 minute patient screening. Similar to other analyses, the diseased patients displayed different HRV signal characterisations than the normal patients.

<table>
<thead>
<tr>
<th></th>
<th>0 - 5 (min)</th>
<th>5 - 10 (min)</th>
<th>10 - 15 (min)</th>
<th>15 - 20 (min)</th>
<th>20 - 25 (min)</th>
<th>25 - 30 (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(D2) (0.63 - 1.25 Hz)</td>
<td>5.03</td>
<td>5.28</td>
<td>4.89</td>
<td>4.74</td>
<td>5.01</td>
<td>4.71</td>
</tr>
<tr>
<td>(D3) (0.31 - 0.63 Hz)</td>
<td>13.98</td>
<td>14.09</td>
<td>11.50</td>
<td>15.83</td>
<td>17.71</td>
<td>16.89</td>
</tr>
<tr>
<td>(D4) (0.16 - 0.31 Hz)</td>
<td>57.74</td>
<td>60.37</td>
<td>58.71</td>
<td>48.33</td>
<td>39.54</td>
<td>33.42</td>
</tr>
<tr>
<td>(D5) (0.08 - 0.16 Hz)</td>
<td>53.01</td>
<td>39.31</td>
<td>35.60</td>
<td>51.43</td>
<td>53.78</td>
<td>35.11</td>
</tr>
<tr>
<td>(D6) (0.04 - 0.08 Hz)</td>
<td>15.80</td>
<td>77.12</td>
<td>55.50</td>
<td>74.52</td>
<td>20.92</td>
<td>26.08</td>
</tr>
</tbody>
</table>

Figure 4.33: Inter-quartile range of 5 minute time intervals for each detail level of interest.
4.5. Summary

In order to research the effectiveness of screening patients for DM and CHD, various features are computed in order to characterise the HRV signal and determine a basis for patient classification, and thus diagnostic of the probable patient condition. The features may be time based, frequency based, or time-frequency based. The best feature to use is the one that gives the best classification.

The time based features are highly correlated and tend to give redundant information. The frequency based features give insight to the signal spectrum, but lose the time information of specific events such as the patient actions. Time-frequency based features, such as the STFT and WT, give insight to the signal spectrum and preserve the time of specific events.

It is common to use the magnitude of the WT coefficients as a measure of the signal power at each detail level. However, outlying samples can greatly affect the estimation of the average signal power over a certain time interval. The range also estimates the signal power over a certain time interval, but is not as susceptible to the effects of outlying samples.
Chapter 5 - Arterial Blood Pressure Processing

5.1. Introduction

As the HR varies in time, so does the ABP. Therefore, the ABP also gives information of the cardiac control systems and is an indicator of DM and CHD. Specifically, a drop in ABP is sensed by the baroreceptor, which triggers an increase in the HR, as per the discussions of Chapter 1. With an increase in the HR, the ABP then increases. This then mediates a decrease in HR. In other words, the HRV and variations in the ABP are highly correlated in normal patients and may provide additional information to better screen between normal and diseased patients.

As per the discussions in Chapter 2, the ABP signal is acquired non-invasively from the patient's finger. Similar to the HRV analyses, various characteristics are extracted from the ABP signal. Specifically, the individual cardiac cycles are detected and the mean-average, systolic, and diastolic pressures are determined. Also, the cyclic maximum change in pressure and the onset of systole is correlated to the ECG signal in order to provide additional insight to the patient cardiac condition. As with the HR, these ABP characteristics are interpolated to equal spacing in time for use with time based, frequency based, and time-frequency based analyses, as per the algorithm in Figure 5.1.

Figure 5.1: Algorithm to extract pressure characteristics from ABP.
5.2. ABP Characteristics

Similar to ECG processing, the general characteristics of the ABP signal are investigated in order to make use of a priori information. This knowledge enables the design of a robust algorithm with better detection of the signal characteristics.

The ABP signal is considered to be wide-sense stationary since the peak events occur in regular intervals and, although there may be time dependant wavelets within the signal, especially during diastole, as a whole, the signal is time-invariant. The ABP signal characteristics are displayed in Figure 5.2. Systole refers to the cardiac contraction and the systolic pressure is the peak pressure in the cycle. Similarly, the diastole is the cardiac rest interval and the diastolic pressure is the lowest pressure reached before systole. The maximum slope of the ABP signal has units of change in pressure (mmHg) per time and has been shown to correlate well with the cardiac contractility. The dicrotic notch, also displayed in Figure 5.2, is due to contraction of the aorta. Specifically, the aorta performs as a passive pump as it stretches during cardiac systole and then contracts during cardiac diastole, causing a small increase in ABP. In recent years, the slope of the ABP diastole and dicrotic notch are being investigated as indices to the cardiac condition and the compliance of the aorta and arteries.
5.3. Detection of ABP Characteristics

The ABP signal is acquired from the Ohmeda Finapres 2300 clinical device and a few ABP cycles are displayed in Figure 5.3. For non-diseased ABP, the systolic pressure is approximately 120 mmHg and the difference between the systolic pressure and diastolic pressure is approximately 35 mmHg. In the figure, the systolic pressure is less than 120 mmHg and the range is approximately 40 mmHg, which are within the normal ABP parameters.
Upon further inspection of the normal ABP signal in Figure 5.3, noise is seen in the diastole of the cardiac cycle. This noise and the dicrotic notch often hinder peak detection of the systolic and diastolic pressure. Therefore, in order to improve peak detection, linear FIR, low pass filtering is applied in order to remove frequencies above 200 Hz, which has been shown not to contain ABP information. The result of the filtering and removal of the noise are shown in Figure 5.4. The reduction in noise is readily apparent, and the systolic and diastolic pressure values are unchanged, and thus, the ABP information has been preserved. Furthermore, since linear phase filtering is used, the relative time information is unaffected.
In order to avoid falsely detecting the dicrotic notch as systolic pressure, peak detection with refractory is employed. As previously discussed in Chapter 3, the refractory is a blanking time in which detection is prevented. Since the ABP signal is from a human, it is expected that the maximum expected heart rate is 150 BPM. Therefore, a refractory of 400 msec may be used to safely avoid the secondary peak of the dicrotic notch. Considering \textit{a priori} human physiology, the dicrotic notch always follows the systolic pressure and occurs during diastole. However, after the detection of the diastolic pressure, no refractory is required since the systolic pressure follows immediately. With this \textit{a priori} information of the ABP characteristics, the peak detection with refractory algorithm of Chapter 3 is again modified for use with detection of ABP features, as seen in Figure 3.11. Using the peak and trough definitions of Chapter 3, the algorithm alternately searches for peaks (systolic pressure) and troughs (diastolic pressure) that are $\delta$ greater or $\delta$ less than the neighbouring data. The algorithm in Figure 3.11, is implemented as a Matlab m-file and the $\delta$ threshold value is input as 'E'. 'Q' is the data being searched and 'R' is the refractory input with units of sample number.
function \[P, T) = \text{ABPPTRDetect}(Q, E, R)\]
\[P = \{\}; T = \{\}; a = 1; b = 1;\]
\[R_t = R + 1;\]
\[i = 0; d = 0;\]
\[Q_L = \text{length}(Q);\]

while \((i \leq Q_L)\)
\[i = i + 1;\]
if \((d = 0)\)
if \((Q(a) \geq (Q(i) + E))\)
\[d = 2;\]
\[P = [P a];\]
\[b = i;\]
\[d = 1;\]
end;
if \((Q(a) < Q(i))\)
\[a = i;\]
\[d = 1;\]
elseif \((Q(i) < Q(b))\)
\[b = i;\]
elseif \((d = 1)\)
\[a = i;\]
elseif \((Q(a) > (Q(i) + E))\)
\[P = [P a];\]
\[b = i;\]
\[d = 2;\]
eleseif \((d = 2)\)
if \((Q(i) < Q(b))\)
\[b = i;\]
elesiseif \((Q(i) > (Q(b) + E))\)
\[if (b > R_t + R)\]
\[T = [T b]; R_t = b;\]
end;
\[a = i;\]
end;
eleseif \((d = 1)\)
\[a = i;\]
eleseif \((d = 2)\)
\[if (Q(i) > (Q(b) + E))\]
\[\text{end};\]
en;\]
end;
end;

Figure 5.5: ABP systolic and diastolic detection algorithm with diastole refractory.

Since the ABP signal is sampled at 500 Hz, a 400 ms refractory is computed to be 200 samples, per Equation 5.1.

| Refractory \(= \left[ \begin{array}{c} 500 \text{ samples per sec} \end{array} \right] \left[ \begin{array}{c} 400 \text{ msec} \end{array} \right] \left[ \begin{array}{c} \frac{\text{sec}}{1000 \text{ msec}} \end{array} \right] = 200 \text{ Samples} \end{array} \right) |

Equation 5.1: Computation of sample refractory based upon human physiology.

5.3.1. Alternative Algorithm

By experience, it was found that a slower HR often allows for misdetection of the dicrotic notch as systolic pressure. In order to avoid the misdetection, the refractory input value required continual adjustment. Therefore, an alternative systolic and diastolic pressure detection algorithm was developed in order to avoid the dicrotic notch with improved robustness. This new algorithm was based on searching for the first
derivative of the ABP signal. Specifically, the ABP derivative was estimated using the 5-point secant estimator of Chapter 3 and displayed in Figure 5.6. Then, the ABP derivative peaks are detected, which correspond to the maximum slope of the ABP signal. In accordance with human physiology, this maximum slope occurs during cardiac systole with the diastolic pressure and systolic pressure occurring before and after, respectively, per Figure 5.2. Therefore, once the maximum slope is detected, the algorithm searches forward for the systolic pressure peak and backwards for the diastolic pressure peak. Specifically, the algorithm searches for the values near zero which indicate a peak or trough, per the Matlab m-file in Figure 5.7.

![ABP Estimated Derivative](image)

**Figure 5.6:** ABP derivative estimated by a 5-point secant.

Note that the algorithm in Figure 5.7 returns the indices of the maximum slope, peak, and trough for each cycle, which corresponds to the ABP maximum change in pressure, systolic pressure, and diastolic pressure. The algorithm input is the ABP data set and the $\delta$ threshold, which defines a peak. Similar to the discussions of derivate estimation in Chapter 3, the ABP derivative is estimated by a 5-point secant in order to reduce higher frequency noise. The $\delta$ threshold is used to define a peak in the ABP. Considering
human ABP, an appropriate δ threshold value is 10 mmHg. The algorithm of Figure 5.7 uses the δ threshold value to define both a peak in the ABP and the derivative of the ABP. Experimentally, it was determined that the ABP derivate is approximately one hundred times greater than the ABP values. Using this information and the fact the sampling frequency is 500 Hz, the 5-point secant is determined with a rate of 100 (1/500) or 0.2 seconds.

```
function [S,P,T] = SPTDetect(Q, E)
% SECANT WITH 0.2 IN ORDER TO USE SAME E
x = secant(Q, 0.2);
S = []; P = []; T = []; a = 1; b = 1; i = 0; d = 0;
xL = length(x);
while (i < xL)
i = i + 1;
    if (d == 0)
        if (x(a) > (x(i) + E))
            d = 2;
        elseif (x(i) > (x(b) + E))
            d = 1;
        end;
        if (x(a) <= x(i))
            a = i;
        elseif (x(i) <= x(b))
            b = i;
        end;
        elseif (d == 1)
            if (x(a) <= x(i))
                a = i;
            elseif (x(a) > (x(i) + E))
                S = [S a]; b = i; d = 2;
            end;
        end;
    elseif (d == 2)
        if (x(i) <= x(b))
            b = i;
        elseif (x(i) > (x(b) + E))
            a = i; d = 1;
        end;
    end;
end;

% BEGIN SEARCH FORWARD FOR SYSTOLIC PRESSURE
f = a; fi = a;
while (fi < xL)
    if (Q(f) <= Q(fi))
        f = fi;
    elseif (Q(f) > (Q(fi) + E))
        P = [P fi]; fi = xL;
    end;
    fi = fi + 1;
end;

% BEGIN SEARCH BACK FOR DIASTOLIC PRESSURE
f = a; fi = a;
while (fi > 0)
    if (Q(f) >= Q(fi))
        f = fi;
    elseif (Q(fi) > (Q(f) + E))
        T = [T fi]; fi = 0;
    end;
    fi = fi - 1;
end;
end;
```

Figure 5.7: ABP systolic and diastolic detection algorithm based upon initial maximum slope detection.
5.4. ABP Feature Extraction

The detection algorithm of Figure 5.7 is used on a sample ABP signal. The first 10 seconds are displayed in Figure 5.8, along with the results of the detection algorithm. In particular, the figure displays the ABP signal along with the Ohmeda Finapres 2300 self-calibration interval, which occurs for a few seconds each minute. Note that the systolic, diastolic, and maximum change in pressure are detected without false detections during the calibration interval.

![Figure 5.8: ABP with marked detection points. Note the Ohmeda Finapres calibration interval.](image)

5.4.1. Maximum Change in Pressure

It has been shown that the cyclic, maximum change in pressure \( \frac{dp}{dt}_{\text{MAX}} \) of the ABP signal is an index to the cardiac contractility, and thus, the cardiac condition. As with
the HR, the heart contractility responds to changes in the cardiac load. Therefore, $\frac{d}{dt}$ \text{MAX} is acquired as a possible index for patient classification and assessment of cardiac condition.

![ABP Maximum Change in Pressure](image)

**Figure 5.9:** ABP cyclic maximum change in pressure over 5 minutes.

Figure 5.9 displays the $\frac{d}{dt}$ \text{MAX} of a normal ABP signal over 5 minutes. As expected, the $\frac{d}{dt}$ \text{MAX} varies with time with an average value of approximately 1100 mmHg/sec and a STD of approximately 110mmHg/sec. These values are later assessed as to their usefulness in patient screening.

### 5.4.2. Diastolic, Mean-Average, and Systolic Pressure

The mean-average pressure (MAP) is defined in several ways. Some have defined it as the average of the systolic and diastolic pressure over one cycle while others define it as
the average of all the ABP samples over one cycle. Figure 5.10 displays the cyclic diastolic, MAP, and systolic pressure of the ABP signal over a five minute period.

![ABP Pressure Measurements](image)

*Figure 5.10: ABP signal with systolic, mean-average, and diastolic pressure measurements.*

In comparing \( \frac{dP}{dt}_{\text{MAX}} \) and pressure features of Figure 5.9 and Figure 5.10, respectively, it is noted that the features correspond well. Specifically, just as \( \frac{dP}{dt}_{\text{MAX}} \) noticeably decreases just after 150 seconds, and thus an implied reducing in cardiac contraction, so the diastolic, MAP, and systolic pressures drop.

### 5.4.3. QA Interval

Besides the cyclic, maximum change in pressure of the ABP, it has been shown that the cardiac contractility may be indexed by comparing the time interval between the Q-point of the QRS complex of the ECG and systole onset. [92] This transit time is termed the QA interval and is specifically defined as the time between the Q-point of the ECG QRS complex and following diastolic pressure, termed the 'A' point. It has been shown that this transit time is an index for cardiac contractility, [93] and thus, a
measure of the cardiac condition. Physiologically, this measurement is the transit time from depolarisation of the ventricles and initial rise in pressure of the ABP, as shown in Figure 5.11. The QA interval measurement relates the electrical and mechanical properties of the cardiac system and has been shown to index the cardiac contractility. However, others have noted that the transit time is also dependant upon the arterial compliance and cardiac load. Even so, since the ECG and ABP are acquired at virtually the same time, the QA interval may be computed to a 2 msec resolution, in accordance with the sampling period.

![Figure 5.11: ABP and ECG signals plotted on one chart with QA interval indicated.](image)

In order to compute the QA interval, the time index of the ECG Q-point must be detected. The Q-point is displayed in Figure 3.2 and defined as the onset of the ECG QRS complex. Considering the morphology of the QRS complex, the R-wave gives the maximum slope and most robust feature for detection, per the discussion of Chapter 3. The Q-point is defined as the first positive slope, closest to zero that immediately precedes a local maximum slope of the R-wave, as displayed in Figure 5.12.
Furthermore, as previously discussed in Chapter 3, the maximum slope of the T-wave can approach the value of the R-wave maximum slope, as shown in Figure 5.12. In order to avoid this false detection, the refractory is employed to prevent search of a local maximum until the T-wave has passed.

![Estimated ECG Derivative](image)

Figure 5.12: ECG derivative estimated by a 5-point secant, per the discussion in Chapter 3.

Given the previous Q-point definition and refractory requirement, the Q-point detection algorithm of Figure 5.13 was developed. Specifically, the algorithm first estimates the derivative of the ECG signal using a 5-point secant. Then the algorithm searches for a local maximum, which is defined as a derivative value that is $\delta$ greater than its neighbouring samples. This $\delta$ threshold value is input as 'E' to the algorithm. Once a local maximum has been detected, the algorithm begins a search back for the first derivative value greater than zero, which indicated the onset of the QRS complex.
Lastly, a refractory is imposed to prevent possible false T-wave detections before the algorithm begins to search for the next local maximum.

```matlab
function [P] = QECGDetect(Q, E, R)
Q = secant(Q, 0.002);
P = [ ]; a = 1; b = 1;
Rp = -R+1; Rt = -R+1;
i = 0; d = 0;
QL = length(Q);
while (i <= QL)
i = i + 1;
if (d == 0)
    if (Q(a) >= (Q(i) + E))
        d = 2;
        elseif (Q(i) >= (Q(b) + E))
            d = 1;
        end;
    if (Q(a) <= Q(i))
        a = i;
    elseif (Q(i) <= Q(b))
        b = i;
    end;
    elseif (d == 1)
        if (Q(a) <= Q(i))
            a = i;
        elseif (Q(a) >= (Q(i) + E))
            if (a > Rp+R)
                Rp = a;
            % BEGIN SEARCH BACK FOR ECG Q POINT
            f = a;
            while (f > 0)
                if (Q(f) < 0)
                    P = [P (f+1)]; E = 0;
                end;
                f = f - 1;
            end;
            b = i; d = 2;
        end;
    elseif (d == 2)
        if (Q(i) <= Q(b))
            b = i;
        elseif (Q(i) >= (Q(b) + E))
            if (b > Rt+R)
                Rt = b;
            end;
            a = i; d = 1;
        end;
end;
end;
```

Figure 5.13: ECG Q-point detection algorithm based upon detection of R-wave slope.

The Q-point detection algorithm of Figure 5.13 was applied to sample, normal ECG. As previously mentioned in Chapter 3, the refractory was set to 200 samples and the threshold value was set to 100 mV/s, per inspection of the data. The results for the first few QRS complexes are displayed in Figure 5.14, along with the associated Q-point detections. Note the correct detections without false, T-wave detections.
Once the time indices of the ECG Q-points and the time indices diastolic pressure are identified, then the QA interval may be computed. Specifically, the algorithm of Figure 5.15 is used. Since the QA interval is a time measurement, its value must be greater than zero. Also, since the QA interval is a measurement of the transit time between the QRS complex and pressure increase, it must be less than the period for one cardiac cycle. Using the a priori information, the algorithm of Figure 5.15 compares the Q-point time indices and diastolic pressure time indices in order to determine reasonable QA interval values. Each QA interval calculation is assigned the Q-point time index as a matter of convenience and for interpolation to equally spaced data.
function [QA]=QA Detect(a, q, maxqa)
N = length(q); M = length(a); QA = [] ; i = 1; j = 1;
if ((N > 2) & (N > 2))
while ((i < N) & (j < M))
    if ((a(i)-q(j)) <= 0)
        i = i + 1;
    else
        if ((a(i)-q(j)) > maxqa)
            j = j + 1;
        else
            QA = [QA; (q(j) (a(i) - q(j)))];
            j = j + 1;
        end;
    end;
end;
end;
end;
end;

Figure 5.15: Algorithm to determine QA interval from ABP and ECG.

The algorithm of Figure 5.15 is applied to the diastolic pressure and Q-point indices of a sample, normal patient. The results are displayed in Figure 5.16 over a 5 minute period. The average QA interval time is approximately 330 msec with a 12 msec standard deviation.

Figure 5.16: QA Interval time between ECG Q-point and onset of systole.

In comparing to the $\frac{dP}{dt_{\text{MAX}}}$ cardiac contractility index, of Figure 5.9, there is no apparent change in the QA interval after the 150 second time index. Furthermore, the two feature
signal shapes are different, and so, there is little observable correlation between the two indexes for cardiac contractility.

5.5. Summary

The ABP is processed in order to determine the diastolic, mean-average, and systolic pressures. Furthermore, the maximum change in pressure and cardiac transit time are determined as possible indices to the cardiac contractility. For robustness and minimisation of false detections, linear FIR low pass filtering and detection of the maximum pressure slope are used. Also, the \textit{a priori} information of the ABP signal morphology is used in order to best detect the diastolic and systolic pressure, given the location of the maximum pressure slope.

Once processed, these ABP characteristics are analysed by time, frequency, and time-frequency based methods in order to determine which parameters are best for patient screening and classification.
Chapter 6 – Classification Results

6.1. Introduction

The analyses of HRV and ABP of Chapters 4 and 5 are used as a basis for classification and screening of DM and CHD in patients. In order to limit the scope of this initial study, the screened patients are limited to males between the ages of 44 and 59 years. Within this group, patients are known to be N, DM, CHD, or CHDD, in accordance with their medical history and clinical laboratory results.

The study planned to assess the classification results with at least 50 patients from each class (N, DM, CHD, and CHDD), with a total of 200 patients; however clinical operations provided complete data on only 17 total patients. Many more patients have been tested, however many patients did not have their condition confirmed by laboratory testing. Thus, even though the proposed screening process was able to screen many patients, most were not included in the testing as their conditions were not confirmed by traditional laboratory tests. Complete testing of a patient was not only tiring but complex, which further highlights the need for new, non-complex clinical screening methodologies. Therefore, due to the limited number of patients with known conditions, this pilot study focuses on assessment of the proposed screening methodology and the analyses which best highlight the differences between the patient conditions.

Figure 6.1 displays the relative HRV signals for the 17 patients. Specifically, five N, two CHD, five DM, and five CHDD patients are used for assessment of the classification results. Upon visual inspection, it is noted that, in general, the N and CHD patients display a greater range and higher spectral components.
The systolic ABP (SABP) and diastolic ABP (DABP) signals for each of the 17 patients are displayed in Figure 6.2 and Figure 6.3, respectively. Again, the y-axis of the charts are fixed in order to display relative changes between the patients. Upon visual inspection of these SABP signals, there does not appear to be any significant differences between the patient classes. Similarly, the DABP signals do not display any significant differences between the patient classes.
Figure 6.2: Systolic ABP signal of 17 patients with known conditions.

Figure 6.3: Diastolic ABP signal of 17 patients with known conditions.
6.2. Clinical Screening of DM

The HRV and ABP analyses tests of Chapters 4 and 5 are used as feature bases for classification of DM and non-DM patients. Specifically, a minimum distance classifier is built using supervised learning and then applied to each patient. The classification results, sensitivity, specificity, positive predictive value, and negative predictive values are then determined, per the MatLab m-file of Figure 6.4.

```
function [sn, sp, pvp, nvp, class] = TestDMAnalyses(features);
% Test Results
% sn = sensitivity, sp = specificity,
% pvp = positive predictive value, nvp = negative predictive value

% USE SUPERVISED LEARNING CLASSIFICATION
ndm = features(:,1:7);
dm = features(:,8:17);
undm = mean(ndm')';
udm = mean(dm')';
cndm = inv(cov(ndm'));
cdm = inv(cov(dm'));

% CLASSIFY
class = zeros(1,17);
for i=1:17;
    d1 = (features(:,i)-undm)'*cndm*(features(:,i)-undm);
    d2 = (features(:,i)-udm)'*cdm*(features(:,i)-udm);
    if (d2 < d1)
        class(i) = 1;
    end;
end;

a = 7 - sum(class(1:7));
b = sum(class(1:7));
c = 10 - sum(class(8:17));
d = sum(class(8:17));

sn = d/(c+d);
sp = a/(a+b);
pvp = d/(b+d);
nvp = a/(a+c);
```

Figure 6.4: MatLab m-file used to test DM classification based upon a particular analysis.

The classification results are displayed in Figure 6.5. A '1' indicates positive for the presence of DM and, conversely, a '0' indicates non-diabetic. As far as the feature analyses, SDSABP refers to the STD of the SABP. Also, note that the 'IDX' features, such as SDNNIDX, account for the patient action response since these analyses are applied to each 5 minute action interval of the signal. Similarly, the STFT and wavelet features also account for the action response as their time information is divided into
5 minute intervals. Lastly, the wavelet details, which reflect various frequency ranges, are separated into individual features in order to determine which details (frequency ranges) give the best classification results.

<table>
<thead>
<tr>
<th>Feature</th>
<th>Non-Diabetic</th>
<th>Diabetic</th>
</tr>
</thead>
<tbody>
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<td>N</td>
</tr>
<tr>
<td>SDNN</td>
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<td>0</td>
</tr>
<tr>
<td>SDANN</td>
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</tr>
<tr>
<td>rMSSD</td>
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<td>0</td>
</tr>
<tr>
<td>ZC</td>
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<td>0</td>
</tr>
<tr>
<td>HRNN</td>
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<td>0</td>
</tr>
<tr>
<td>PSDNN</td>
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<td>0</td>
</tr>
<tr>
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</tr>
<tr>
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<td>0</td>
</tr>
<tr>
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<td>0</td>
</tr>
<tr>
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<td>0</td>
</tr>
<tr>
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<td>0</td>
</tr>
<tr>
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<tr>
<td>WT_HF</td>
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</tr>
</tbody>
</table>

Figure 6.5: Classification results of DM screening: 0 indicates non-DM and a 1 indicates DM.

The DM classification results of Figure 6.5 are then used to determine the sensitivity, specificity, positive predictive value and negative predictive value in order to assess classifier performance. The analysis that gives the highest probabilities is the best for screening DM.
The classification results are displayed in Figure 6.6. Note that undefined results are displayed with a 'NaN' to signify the result is 'Not a Number', in accordance with MatLab convention.

<table>
<thead>
<tr>
<th>Feature</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>+PV</th>
<th>-PV</th>
</tr>
</thead>
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<td>57%</td>
<td>70%</td>
<td>57%</td>
</tr>
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<td>100%</td>
<td>88%</td>
</tr>
<tr>
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<td>100%</td>
<td>100%</td>
<td>78%</td>
</tr>
<tr>
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<td>86%</td>
<td>89%</td>
<td>75%</td>
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<td>78%</td>
<td>63%</td>
</tr>
<tr>
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<td>100%</td>
<td>100%</td>
<td>78%</td>
</tr>
<tr>
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<td>100%</td>
<td>100%</td>
<td>78%</td>
</tr>
<tr>
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<td>100%</td>
<td>100%</td>
<td>78%</td>
</tr>
<tr>
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<td>50%</td>
<td>29%</td>
</tr>
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<td>89%</td>
<td>75%</td>
</tr>
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<td>63%</td>
<td>100%</td>
</tr>
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<td>71%</td>
<td>75%</td>
<td>56%</td>
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<td>58%</td>
<td>40%</td>
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<td>14%</td>
<td>60%</td>
<td>50%</td>
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</tr>
<tr>
<td>HFPSABP/HFHRV</td>
<td>80%</td>
<td>14%</td>
<td>57%</td>
<td>33%</td>
</tr>
<tr>
<td>dP/dtmaIDX</td>
<td>100%</td>
<td>71%</td>
<td>83%</td>
<td>100%</td>
</tr>
<tr>
<td>QAIDX</td>
<td>90%</td>
<td>86%</td>
<td>90%</td>
<td>86%</td>
</tr>
<tr>
<td>STFTpsd</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>STFT LFHRV</td>
<td>90%</td>
<td>100%</td>
<td>100%</td>
<td>88%</td>
</tr>
<tr>
<td>STFT HFHRV</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>STFT LFHRV/HFHRV</td>
<td>100%</td>
<td>86%</td>
<td>91%</td>
<td>100%</td>
</tr>
<tr>
<td>WT1HRV D2</td>
<td>80%</td>
<td>100%</td>
<td>100%</td>
<td>78%</td>
</tr>
<tr>
<td>WT1HRV D3</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>WT1HRV D4</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>WT1HRV D5</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>WT1HRV D6</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>WT1HRV D7</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>WT1HRV LF/HF</td>
<td>0%</td>
<td>100%</td>
<td>NaN</td>
<td>41%</td>
</tr>
</tbody>
</table>

Figure 6.6: DM screening results for each classifier.

In reviewing the DM screening results, it is noted that the SDNNIDX, STFTpsd, STFT LFHRV, and all the WaveletHRV detail features (except level 2) gave the best classification results. Theoretically, the PSD of a sample is equivalent to its variance.
Thus, it is expected that both the STFT\textsubscript{PSD} and SDNNIDX give the same results. Also, since the STFT\textsubscript{PSD} gave similar results to the STFT HF\textsubscript{HRV}, it is noted that the HF range (0.15-0.5 Hz frequency band of the HRV signal) gives significant information to distinguish between DM and non-DM patients. Lastly, the wavelet based features with decomposition levels 3 to 7 performed equally well in distinguishing between DM and non-DM patients.

It is noted that classifier results based upon the ABP signal performed poorly in screening for DM. From the introduction, it is known that changes in the HR correlate with changes in the ABP, and therefore, also indicate the presence of DAN. However, based upon these results, the ABP does not screen well for DAN, and thus, DM.

Similarly, although the QAIDX feature gave better results than the QA interval, neither produced screening probabilities greater than 90%. This indicates that though QAIDX is affected by the presence of DM, it is not a good indicator of the disease.

As a summary result, analysis features Figure 6.6 that consider the patient actions outperform the analyses that do not consider the patient action. In other words, features, which consider the time-varying nature of the HRV signal in response to the patient's actions, better screen for DM than those features that analyse the 30-minute HRV signal as a whole. Figure 6.7 displays the average classifier results for features based upon the HRV signal that are independent of the patient actions, such as the SDNN, and those that are dependent upon the patient action, such as the SDNNIDX. The ABP based features were excluded in order for a better comparison.
### 6.3. Clinical Screening of CHD

Similar to DM screening, the HRV and ABP feature analyses of Chapter 4 and 5 are used as a basis for classification of CHD and non-CHD patients. Specifically, a minimum distance classifier is again built using supervised learning of the known patient conditions, and then applied to each patient. The classification results are compared by determining the sensitivity, specificity, positive predictive value, and negative predictive values as shown in the MatLab m-file of Figure 6.8. Note that the algorithm is very similar to that of Figure 5.7, except that the patient classes are divided into CHD and non-CHD patients for the supervised learning.

```matlab
function [sn, sp, pvp, nvp, class] = TestCHDAnalyses(features);
    % Test Results
    % sn = sensitivity, sp = specificity
    % pvp = positive predictive value, nvp = negative predictive value
    % DETERMINE THRESHOLD
    ndm = features(:,[1:5 8:12]); dm = features(:,[6:7 13:17]);
    undm = mean(ndm.'); udm = mean(dm.');
    cndm = inv(cov(ndm')); cdm = inv(cov(dm'));
    % CLASSIFY
    class = zeros(1,17);
    for i=1:17;
        d1 = (features(:,i)-undm)'*cndm*(features(:,i)-undm);
        d2 = (features(:,i)-udm)'*cdm*(features(:,i)-udm);
        if (d2 < d1)
            class(i) = 1;
        end;
    end;
    a = 10 - sum(class([1:5 8:12])); b = sum(class([1:5 8:12]));
    c = 7 - sum(class([6:7 13:17])); d = sum(class([6:7 13:17]));
    sn = d/(c+d); sp = a/(a+b); pvp = d/(b+d); nvp = a/(a+c);
end
```

The classification results are displayed in Figure 6.9 whereby a '1' indicates the presence of CHD in the patient and a '0' indicates no CHD, and thus, a N patient. As with the
previous DM screening, these classification results are used to determine the sensitivity, specificity, positive predictive value and negative predictive probabilities which are displayed in Figure 6.10.

<table>
<thead>
<tr>
<th>Feature</th>
<th>Non-CHD</th>
<th>CHD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>1</td>
</tr>
<tr>
<td>SDNN</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>SDANN</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>HRSD</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>ZC</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>IRQNN</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>PSDHRV</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>LFHRV</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>HFHRV</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>LFHRV/HFHRV</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>dPdtdmax</td>
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<td>0</td>
</tr>
<tr>
<td>SDSABP</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>QA</td>
<td>0</td>
<td>0</td>
</tr>
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<td>SDNNIDX</td>
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<td>SDSABPDX</td>
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<tr>
<td>PSDSABP</td>
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<td>0</td>
</tr>
<tr>
<td>LFHRV</td>
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</tr>
<tr>
<td>HFHRV</td>
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<td>0</td>
</tr>
<tr>
<td>LFHRV/HFHRV</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>dPdtdmaxDX</td>
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<tr>
<td>QAIDX</td>
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<td>1</td>
</tr>
<tr>
<td>STFTFHRV</td>
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</tr>
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<td>STFTLFHRV</td>
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<td>1</td>
</tr>
<tr>
<td>STFTHFHRV</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>STFTLFHRV/HFHRV</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>WTTRV D2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>WTTRV D3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>WTTRV D4</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>WTTRV D5</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>WTTRV D6</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>WTTRV D7</td>
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<td>1</td>
</tr>
<tr>
<td>WTTRV LFHF</td>
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</tr>
</tbody>
</table>

Figure 6.9: Classification results of CHD screening: 0 indicates non-CHD and a 1 indicates CHD.
<table>
<thead>
<tr>
<th>Feature</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>+PV</th>
<th>-PV</th>
</tr>
</thead>
<tbody>
<tr>
<td>SDNN</td>
<td>86%</td>
<td>50%</td>
<td>55%</td>
<td>83%</td>
</tr>
<tr>
<td>SDANN</td>
<td>86%</td>
<td>40%</td>
<td>50%</td>
<td>80%</td>
</tr>
<tr>
<td>rMSSD</td>
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<td>0%</td>
<td>38%</td>
<td>0%</td>
</tr>
<tr>
<td>ZC</td>
<td>57%</td>
<td>50%</td>
<td>44%</td>
<td>63%</td>
</tr>
<tr>
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<td>40%</td>
<td>50%</td>
<td>80%</td>
</tr>
<tr>
<td>PSD_HRV</td>
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<td>90%</td>
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<td>64%</td>
</tr>
<tr>
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<td>100%</td>
<td>NaN</td>
<td>59%</td>
</tr>
<tr>
<td>HF_HRV</td>
<td>57%</td>
<td>20%</td>
<td>33%</td>
<td>40%</td>
</tr>
<tr>
<td>LF_HRV/HF_HRV</td>
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<td>30%</td>
<td>36%</td>
<td>50%</td>
</tr>
<tr>
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<td>60%</td>
<td>43%</td>
<td>60%</td>
</tr>
<tr>
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<td>60%</td>
<td>56%</td>
<td>75%</td>
</tr>
<tr>
<td>QA</td>
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<td>60%</td>
<td>60%</td>
<td>86%</td>
</tr>
<tr>
<td>SDNNDIDX</td>
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<td>0%</td>
<td>41%</td>
<td>NaN</td>
</tr>
<tr>
<td>SDSABPIDX</td>
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<td>20%</td>
<td>47%</td>
<td>100%</td>
</tr>
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<td>100%</td>
<td>100%</td>
<td>83%</td>
</tr>
<tr>
<td>LFABP</td>
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<td>100%</td>
<td>100%</td>
<td>63%</td>
</tr>
<tr>
<td>HFABP</td>
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<td>67%</td>
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<td>NaN</td>
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</tr>
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<td>LF_ABPF/LF_HRV</td>
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<td>20%</td>
<td>47%</td>
<td>100%</td>
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<tr>
<td>HF_ABPF/HF_HRV</td>
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<td>20%</td>
<td>47%</td>
<td>100%</td>
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<td>100%</td>
<td>83%</td>
</tr>
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<td>0%</td>
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<td>100%</td>
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</tr>
<tr>
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<td>100%</td>
<td>0%</td>
<td>41%</td>
<td>NaN</td>
</tr>
<tr>
<td>WT_HRV D2</td>
<td>100%</td>
<td>0%</td>
<td>41%</td>
<td>NaN</td>
</tr>
<tr>
<td>WT_HRV D3</td>
<td>71%</td>
<td>100%</td>
<td>100%</td>
<td>83%</td>
</tr>
<tr>
<td>WT_HRV D4</td>
<td>86%</td>
<td>0%</td>
<td>38%</td>
<td>0%</td>
</tr>
<tr>
<td>WT_HRV D5</td>
<td>71%</td>
<td>100%</td>
<td>100%</td>
<td>83%</td>
</tr>
<tr>
<td>WT_HRV D6</td>
<td>86%</td>
<td>0%</td>
<td>38%</td>
<td>0%</td>
</tr>
<tr>
<td>WT_HRV D7</td>
<td>71%</td>
<td>0%</td>
<td>33%</td>
<td>0%</td>
</tr>
<tr>
<td>WT_HRV LF/HF</td>
<td>0%</td>
<td>100%</td>
<td>NaN</td>
<td>59%</td>
</tr>
</tbody>
</table>

Figure 6.10: CHD screening results for each classifier.

In reviewing the CHD screening results, it is noted that PSD_{SABP}, dP/dt_{MAXIDX}, STFT HF_HRV, and Wavelet_HRV decomposition detail level 3 and 5 features give the best classification results. The PSD_{SABP} estimates the total SABP power and gives an indication of the sum-total change in the SABP over the entire patient screening, regardless of the patient actions. This is an unexpected result that may be singular to the small number of patients in this study, and requires further investigation.
The dP/dt_{MAXIDX} feature is known to index cardiac contractility, which in turn, gives a measure of the cardiac condition and strength. Reduced contractility indicates coronary difficulty and warrants further testing of the cardiac system, such as angiography. Furthermore, this feature is indexed to the patient actions, which provides additional information about the response of the patient cardiac system.

The QA and QAIDX features have been shown to also give a measure of the cardiac contractility, as was previously discussed. However, in this study, the QA and QAIDX features were found to be poor indicators for screening patients for the presence of CHD.

Lastly, in accordance with the discussions of Chapter 1, the frequency spectrum of the HRV signal is affected by the presence of CHD. Specifically, the HF band, whether estimated by the STFT or wavelet, displays changes between non-CHD and CHD patients, and thus, is a good indicator of the presence of CHD in a patient. It is also noted that, similar to the DM screening results, the HRV features which are indexed to the patient action better screen for CHD than those features which are based on the entire 30-minute HRV signal.

### 6.4. Neural Network Screening of DM and CHD

Per the discussions in Chapter 1, NN based classification has been shown to perform better than distance based classification. In this section of the study, three different NN classifiers are designed and compared. The first design is based on the SDNNIDX feature of the HRV signal and dP/dt_{MAXIDX} feature of the ABP signal. The second is based upon the STFT PSD and HF signals. The last is based upon the WT, detail levels
3, 4, and 5. These specific features are chosen as each performed the best in screening for either DM or CHD.

For each of the NN classifiers, the same NN architecture is used in order to compare the influence of the features upon the NN classifiers. The specific NN architecture consists of three layers: an input layer, a hidden layer of 20 neurons, and an output layer. The output layer has two binary outputs: 0 / 1 to indicate the presence of DM, and 0 / 1 to indicate the presence of CHD.

In order to test the NN, a leave-one-out analysis is performed. In particular, the NN is trained using all the known patients, except one. The trained NN is then applied to the one remaining patient and the classification result is determined. This procedure is then repeated for each of the 17 patients and the sum total classification results are used to determine the sensitivity, specificity, positive predictive value, and negative predictive value. Using this procedure, it was found that all three NN classifiers scored 100% for the sensitivity, specificity, positive predictive value, and negative predictive value for both DM and CHD screening. Thus, this test shows that the NN classifier is quite strong and robust, but did not give any comparison between the three NN classifiers based upon different features.

The NN classifiers were tested again using, leave-one-class-out analysis. For this test, the NN is trained using all the known patients, except one from each condition class: N, DM, CHD, and CHDD. The trained NN is then applied to the four remaining patients and the classification results are determined. This procedure is then repeated several times for different members of each condition class and the sum total classification results are used to determine the sensitivity, specificity, positive predictive value, and negative predictive value. Using this procedure, it was again found that screening for
DM scored 100% for the sensitivity, specificity, positive predictive value, and negative predictive. However, all three NN classifiers erred in screening of CHD, as displayed in the table of Figure 6.11.

<table>
<thead>
<tr>
<th>Features used for NN Classifier</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>+PV</th>
<th>-PV</th>
</tr>
</thead>
<tbody>
<tr>
<td>SDNNIDX &amp; dP/dtmaxIDX</td>
<td>81%</td>
<td>97%</td>
<td>95%</td>
<td>88%</td>
</tr>
<tr>
<td>STFTpsD and HF</td>
<td>97%</td>
<td>97%</td>
<td>96%</td>
<td>91%</td>
</tr>
<tr>
<td>WT D3, D4 and D5</td>
<td>97%</td>
<td>97%</td>
<td>96%</td>
<td>91%</td>
</tr>
</tbody>
</table>

Figure 6.11: Comparison between NN classification results in screening for CHD.

In reviewing the NN classifier results of Figure 6.11, it is noted that the NN classifier based upon the STFT and WT time-frequency analyses performed better than the classifier based upon the SDNNIDX and dP/dtmaxIDX features. Thus, the time-frequency based features, which are indexed to the patient action, provide a better basis for classification.

6.5. Summary

Without doubt, a clinical screening system based on 17 patients is not statistically significant and warrants further testing on additional patients with known DM and CHD conditions. Even so, the initial results of this study confirm the necessity of classification features based upon time-frequency analysis in order to effectively screen for both DM and CHD. These types of analyses decompose the physiological signal over a range of frequencies while preserving the time information. That is important in order to measure how the spectrum of a signal changes over time, usually in regards to an evoked response.

As far as screening for DM, the requirement of the patient to perform various actions is important in effecting a response in the ANS, which controls the HR. This response varied between DM and non-DM patients, due to DAN. According to the classification
results, the best features are those that measure the variance in the HR per patient action, such as the SDNNIDX, STFT, and WT. As for the classification of CHD, the best features are those that consider the spectrum of the HRV signal or the maximum change in ABP, which gives an indication of cardiac contractility. Additionally, as with the DM features, those features that are dependent upon the patient actions, such as the dP/dt\text{max}IDX, STFT, and WT, give better CHD classification results.

Lastly, based upon the sensitivity, specificity, positive predictive value, and negative predictive value, the NN based classifiers performs better than the Euclidean, distance based classifiers, using the analysis features. The sensitivity is the probability that a diseased patient is correctly classified as having the disease, and the specificity is the probability that a disease-free patient is correctly classified as not having the disease. The positive predictive value is the probability that a patient actually has the disease when the clinic screening indicates the disease is present in a patient. The negative predictive value is the probability that a patient actually does not have the disease when the clinic screening indicates the disease is not present in a patient. For DM screening, each of these probabilities scored 100% for classifiers based upon the SDNNIDX, STFT, or WT features. For CHD screening, the probabilities scored less than 100%, but well over 90%, indicating the ability of the STFT and WT of the HRV signal to screen for CHD. However, as previously mentioned, these results are far from providing sufficient statistics and additional patients with known conditions are required to better assess the classification performance.
Chapter 7 - Conclusions

7.1. Summary

A successful clinical screening procedure depends on many factors. Foremost, the procedure must be cost effective, reproducible, and have easily interpretable results. Additionally, the screening must incorporate a methodology that requires simple training of the clinical staff and minimal patient cooperation. Lastly, the procedure must be safe and entail no unnecessary risk to the patient.

The researched clinical screening system employed a low-cost, PC and turnkey DAQ system for collecting ECG, respiration, and ABP from the patient. The measurement of non-invasive physiological signals minimises the patient risk of infection, requires no analgesics, and reduces measurement artefact due to patient stress. The clinical methodology required the patient to lie quietly (supine) for 5 minutes while the physiological data is collected. Then the patient is request to stand while an additional 5 minutes of data is collected. Similarly, the patient is requested to sit/squat and breathe at 3 different rates while the physiological data is again collected, for a sum total of 30 minutes of physiological DAQ. These actions are required in order to evoke a response from the patient's HR control system which is managed by the ANS. Although this procedure is somewhat time consuming, this research shows that these patient actions give enhanced screening of CHD and the presence of DM.

The patient HR is determined from the ECG. Specifically, Lead II Einthoven bipolar positions are used to maximise the R-wave of the QRS complex in the ECG and require only three electrode connections to the patient. The R-waves are detected using a secant-maximum slope, peak detector and the patient HR is computed as the time
interval between each R-wave. Fluctuations in the beat-to-beat patient HR define the HRV. Since the HR is controlled by the ANS, a measure of the HRV provides information about the sympathetic and parasympathetic cardiovascular control mechanisms and indexes possible damage due to CHD or DAN. Signal processing algorithms were investigated and applied to the patient HRV signal in order to determine which algorithms best distinguish between diseased and normal patients. These analyses were time based, such as the standard deviation, frequency based, such as the PSD, and time-frequency based, such as the STFT and WT. Each of these analyses were applied to both the 30 minute HRV signal and indexed to 5 minute intervals corresponding to the patient actions. Furthermore, additional analyses were investigated and applied to the patient respiration and ABP signals in order to research if additional physiological information provides for enhanced patient screening of disease. Lastly, two data fusion analyses were researched. The inter-breath algorithm analysed the change in the HR between breaths. When applied to a normal patient, the inter-breath algorithm proved that, in general, the patient HR lowers between breaths; however, it was also determined that the measurement precision was unacceptable high in order to screen the patient condition. The other data fusion analysis was the QA interval which is a measure of the transit time between the start of the bioelectrical QRS complex and initial rise in ABP. When used as a basis for classification of the patient condition, the QA interval was also determined to be a poor feature for screening the presence of DM and CHD in a patient.

The medical statistics of sensitivity, specificity, positive predictive value and negative predictive value were used to compare classifiers based upon the analyses features. The initial screening employed a nearest-neighbour classifier using supervised learning and through this research, it was determined that the PSD and HF estimated by the STFT or WT gave the best basis for screening the presence of DM and CHD. The STFT and WT
based features gave the best classification as these analyses decomposed the patient HRV in various frequency ranges of interest while preserving the time events of the patient actions. In other words, these time-frequency analyses allowed the classifier to correlate spectrum changes in the HRV signal against actions performed by the patient, which gave enhanced screening. Although the WT gives multiple-higher resolutions for the time and frequency domains, the classification results compared to the uniform resolutions of the STFT. This likely due to the fact that each analysis used 5 minute averages; even though the WT is able to give a much higher time resolution.

Based upon these initial results of this new methodology, further investigation is warranted in order to statistically prove the benefits of this clinical screening for DM and CHD over traditional blood-fasting and exercise ECG tests. These results are encouraging, especially for the screening of DM, which may be used to index the progression of DAN. However, the sample set of patients with known conditions was small due to the complex task of traditional laboratory testing for DM and CHD. The diagnosis of CHD was found to be not as precise as that for the DM, but does provide a new clinical tool for quick screening, which is far cheaper than angiography and less complicated than the exercise ECG. In view of recent studies, this methodology may provide enhanced detection of CHD over that of the exercise ECG test.

7.2. Original Contributions

In researching the development the clinical DAQ system, the author extensively investigated physiological peak detection and outlier removal. A robust, secant differential approximation with refractory algorithm was applied to the ECG signal in order to remove the effects of baseline wander, reduce higher frequency noise, avoid T-wave detection and enhance the presence of the R-wave. This allowed for precise
measurement of the beat-to-beat HRV, and thus, the HRV signal. Even so, it was found
that the HRV signal is greatly affected by ectopic beats, such as PVC, and skipped beats
and prohibits its use in screening for disease. Outlier removal was statistically
investigated and determined to not be applicable due to the varying nature of the HRV
signal. Instead, a priori physiological information was used in order to determine outlier
limits for individual samples of the HRV signal.

More importantly, this research proved that a 30-minute HRV signal is able to screen
for the presence of DM and CHD. Per the discussions in Chapter 1, the HRV signal is
traditionally measured over a 24 hour period, prohibiting its use in a clinical setting.
This research shows that, when coupled with specific patient actions, a 30 minute
sample with 6 different patient actions is sufficient to distinguish between N, DM,
CHD, and CHDD patients.

Lastly, this research highlights the importance of indexing the patient actions when
classifying their condition. That is to say, analysis features that consider the time of the
actions performed significantly better than those features that analysed the HRV signal
as a 30 minute sample. Furthermore, although the SDNNIDX and dp/dtmaxIDX did well
in screening for DM and CHD, respectively, the STFT and WT performed equally well
in screening for both DM and CHD. Therefore, this research indicates that the clinical
procedure may be simplified by acquiring only patient HRV and not the patient
respiration and ABP.

7.3. Further Investigation

Foremost, additional known patient data is required for further investigation. As this is a
funded, United Arab Emirates University study, clinical technicians are continuing to
acquire known patient data with a final goal of 50 N, 50 DM, 50 CHD, and 50 CHDD patients. Once the full number of patients is available for testing, the analyses features introduced in Chapters 3, 4, and 5 will be computed and again used as bases for classifiers that are trained using supervised learning, as in Chapter 6. Similarly, the screening probabilities will again be computed and compared in order to determine the best features for classification and screening DM and CHD.

Additionally, it is not readily apparent that controlled breathing by patients evokes a response significantly different than having the patient stand and sit/squat after supine measurement. Removal of the controlled breathing actions greatly simplifies the screening procedure by reducing the patient acquisition time in half, requiring less computer storage and computations, and requiring less dependence upon patient cooperation.

Lastly, it known that the HRV physiology is affected by gender and age. Collection of female data sets and correlation of patient age will create a more robust and generalised clinical system for all patients. However, the task of collecting this amount and variety of data from patient who have laboratory confirmed conditions is surmountable. Additionally, the progressive effect of Type II DM upon the cardiac system has never been indexed. Therefore, an animal study is proposed that continually monitors the animal ECG and activity over at least one year's time as the Type II DM progresses. Specifically, implantable telemetry is proposed to ensure continuous ECG recording. From this information, the HRV and ECG PQRST complex intervals are computed and indexed against the progression of Type 2 DM. The data obtained from this study may provide early markers for DM and DM induced CHD. That will have important clinical diagnostic implications in screening CHD in DM patients. Clarification of the
mechanisms that underlie cardiac dysfunction will pave the way for the development of improved clinical screening and treatments. [94]
Appendix A: Activity Index Questionnaire

This four level (0 to 3) index is used to give a brief indication of the patient's activity based on regular exercise and walking. The following flow chart is used to determine the activity index.

Do you follow a weekly exercise routine?

- Yes → Index = 3
- No → Do you take walks during the week?
  - No → Index = 0
  - Yes → How many times in a week do you take walks?
    - ≥ 3 → Index = 2
    - 1 or 2 → Index = 1
Appendix B: Anxiety Index Questionnaire

This index is based on the Hospital Anxiety and Depression (HAD) scale developed by Zigmond and Snaith. [95] The clinic technician reads to the patient the questionnaire introduction and then proceeds to ask the patient which response best describes their current feelings and emotions.

At the end of the questionnaire, the A numbers and D numbers are summed together as a patient anxiety index and depression index.

Considering the national language of the United Arab Emirates, the questionnaire has been translated into Arabic, as per the permission of the publisher.

Questionnaire Introduction

Doctors are aware that emotions play an important part in most illnesses. If your doctor knows about these feelings, he will be able to help you more.

This questionnaire is designed to help your doctor to know how you feel. Listen to each statement and indicate which response best describes how you are feeling. Don't take long to think over your replies; your immediate reaction to each item will probably be more accurate than a long thought out response.

<table>
<thead>
<tr>
<th>Question</th>
<th>Patient Response</th>
<th>Questionnaire Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. I feel tense or 'wound up'.</td>
<td>Most of the time A lot of the time From time to time, occasionally Not at all</td>
<td>A3 A2 A1 A0</td>
</tr>
</tbody>
</table>

184
| 2. I still enjoy the things I used to enjoy. | Definitely as much | D0
| Note quite so much | D1
| Only a little | D2
| Hardly at all | D3
| 3. I get a sort of frightened feeling as if something awful is about to happen. | Very definitely and quite badly | A3
| Yes, but not too badly | A2
| A little, but it doesn’t worry me | A1
| Not at all | A0
| 4. I can laugh and see the funny side of things. | As much as I always could | D0
| Not quite so much now | D1
| Definitely not so much now | D2
| Not at all | D3
| 5. Worrying thoughts go through my mind. | A great deal of the time | A3
| A lot of the time | A2
| From time to time, but not too often | A1
| Only occasionally | A0
| 6. I feel cheerful. | Not at all | D3
| Not often | D2
| Sometimes | D1
| Most of the time | D0
| 7. I can sit at ease and feel relaxed. | Definitely | A0
| Usually | A1
| Not often | A2
| Not at all | A3
| 8. I feel as if I am slowed down. | Nearly all the time | D3
| Very often | D2
| Sometimes | D1
| Not at all | D0
| 9. I get a sort of frightened feeling like ‘butterflies’ in the stomach. | Not at all | A0
| Occasionally | A1
| Quite often | A2
| Very often | A3

185
10. I have lost interest in my appearance.

<table>
<thead>
<tr>
<th>Definitely D3</th>
<th>Definitely not D0</th>
</tr>
</thead>
<tbody>
<tr>
<td>I don't take so much care as I should D2</td>
<td></td>
</tr>
<tr>
<td>I may not take quite as much care D1</td>
<td></td>
</tr>
<tr>
<td>I take just as much care as ever D0</td>
<td></td>
</tr>
</tbody>
</table>

11. I feel restless as if I have to be on the move.

<table>
<thead>
<tr>
<th>Very much indeed A3</th>
<th>Not at all A0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quite a lot A2</td>
<td></td>
</tr>
<tr>
<td>Not very much A1</td>
<td></td>
</tr>
</tbody>
</table>

12. I look forward with enjoyment to things.

<table>
<thead>
<tr>
<th>As much as ever I did D0</th>
<th>Hardly at all D3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rather less than I used to do D1</td>
<td></td>
</tr>
<tr>
<td>Definitely less than I used to D2</td>
<td></td>
</tr>
</tbody>
</table>

13. I get sudden feelings of panic.

<table>
<thead>
<tr>
<th>Very often indeed A3</th>
<th>Not at all A0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quite often A2</td>
<td></td>
</tr>
<tr>
<td>Not very often A1</td>
<td></td>
</tr>
</tbody>
</table>

14. I can enjoy a good book or radio or TV programme.

<table>
<thead>
<tr>
<th>Often D0</th>
<th>Very seldom D3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sometimes D1</td>
<td></td>
</tr>
<tr>
<td>Not often D2</td>
<td></td>
</tr>
</tbody>
</table>

Translation: Dr. Omar Al Farouq from the Department of Medicine, United Arab Emirates University.

<table>
<thead>
<tr>
<th>Result</th>
<th>Arabic Question</th>
</tr>
</thead>
<tbody>
<tr>
<td>A3</td>
<td>أشعر بحالة توتر وضيق.</td>
</tr>
<tr>
<td>A2</td>
<td>أكثر من الوقت</td>
</tr>
<tr>
<td>A1</td>
<td>لا يحدث ذلك إطلاقًا</td>
</tr>
<tr>
<td>A0</td>
<td></td>
</tr>
</tbody>
</table>
2 ما زلت أستطيع بالأشياء التي كنت أستطيع بها من قبل.

3 أنتابني أحساس بالخوف وكان شيئاً سيئاً على وشك أن يحدث.

نعم ولكن ليس بصورة سئية جداً
قليلًا ولكنه لا يزعجني
لا أطفالةً

لا أستطيع أن أضحك وأن أرى الفكاهه في المواقف.

لم تكن من قبل

معظم الوقت
كثيراً من الوقت
أشياءاً
قليلًا جداً

لا بالمرة
قليلًا
أشياءاً
في معظم الوقت

بالتأكيد
عادة
ليس كثيراً
لا إطالةً

7 أستطيع أن أجلس هدوء وانتباه وأحس بالاسترخاء.

A0
A1
A2
A3
<table>
<thead>
<tr>
<th>D3</th>
<th>في كل الأوقات تقريبًا</th>
</tr>
</thead>
<tbody>
<tr>
<td>D2</td>
<td>في كثير من الأحيان</td>
</tr>
<tr>
<td>D1</td>
<td>في بعض الأحيان</td>
</tr>
<tr>
<td>D0</td>
<td>لا إطلاقًا</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>A0</th>
<th>لا إطلاقًا</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1</td>
<td>أحيانًا</td>
</tr>
<tr>
<td>A2</td>
<td>كثيرًا</td>
</tr>
<tr>
<td>A3</td>
<td>كثيرًا جدًا</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>D3</th>
<th>بالتأكيد</th>
</tr>
</thead>
<tbody>
<tr>
<td>D2</td>
<td>أهتم مظهري أقل مما ينبغي</td>
</tr>
<tr>
<td>D1</td>
<td>لا أهتم مظهري كما كنت سابقاً</td>
</tr>
<tr>
<td>D0</td>
<td>ما زلت أهتم مظهري كما كنت</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>A3</th>
<th>بدرجة كبيرة حدًا بالتأكيد</th>
</tr>
</thead>
<tbody>
<tr>
<td>A2</td>
<td>بدرجة كبيرة</td>
</tr>
<tr>
<td>A1</td>
<td>بدرجة قليلة</td>
</tr>
<tr>
<td>A0</td>
<td>لا إطلاقًا</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>D0</th>
<th>مثلما كنت دائمًا</th>
</tr>
</thead>
<tbody>
<tr>
<td>D1</td>
<td>أقل مما كنت سابقاً</td>
</tr>
<tr>
<td>D2</td>
<td>بالتأكيد أقل كثيرًا</td>
</tr>
<tr>
<td>D3</td>
<td>لا أطلع لذلك على الإطلاق</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>A3</th>
<th>كثيرًا جدًا</th>
</tr>
</thead>
<tbody>
<tr>
<td>A2</td>
<td>كثيرًا</td>
</tr>
<tr>
<td>A1</td>
<td>أحيانًا قليلة</td>
</tr>
<tr>
<td>A0</td>
<td>لا إطلاقًا</td>
</tr>
</tbody>
</table>

13 تشتبه نوبات مفاجئة من الخوف والرعب والهلع.

12 أطلع إلى الاهتمام بالأشياء.

11 ينتابي شعور بالنضج والملل وعدم المقدرة على الاشتراق.

9 ينتبى أحساس في المعدة كالشعور بالخوف أو وجود فراشات بداخلها.

8 أشعر وكأنى أصبحت عصيماً وعطيناً في حركتي.
<table>
<thead>
<tr>
<th>D0</th>
<th>دائمًا</th>
</tr>
</thead>
<tbody>
<tr>
<td>D1</td>
<td>أحيانًا</td>
</tr>
<tr>
<td>D2</td>
<td>قليلاً</td>
</tr>
<tr>
<td>D3</td>
<td>نادراً</td>
</tr>
</tbody>
</table>

۱۴ أستطيع أن أستطيع بقراءة كتاب جيد أو الاستماع للراديو أو مشاهدة التلفزيون.
Appendix C: List of Laboratory Tests

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description of the laboratory test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ret. #</td>
<td>Retinopathy Index (0 = nil, 1 = back-ground, 2 = proliferative)</td>
</tr>
<tr>
<td>Neuro. #</td>
<td>Neuropathy Index (0 = nil, 1 = sensory-motor, 2 = autonomic)</td>
</tr>
<tr>
<td>Neph. #</td>
<td>Nephropathy Index (0 = nil, 1 = impaired renal function, 2 = renal failure)</td>
</tr>
</tbody>
</table>

**Glycaemia**

<table>
<thead>
<tr>
<th>Test</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>FBS1</td>
<td>Fasting Blood Sugar 1 (1st hour)</td>
</tr>
<tr>
<td>FBS2</td>
<td>Fasting Blood Sugar 2 (2nd hour)</td>
</tr>
<tr>
<td>FBS3</td>
<td>Fasting Blood Sugar 3 (3rd hour)</td>
</tr>
<tr>
<td>FS</td>
<td>Fasting Serum Insulin</td>
</tr>
<tr>
<td>HBAIC</td>
<td>Haemoglobin A1c</td>
</tr>
<tr>
<td>FC-Peptide</td>
<td>Fasting C-Peptide</td>
</tr>
<tr>
<td>UP</td>
<td>Urinary Protein</td>
</tr>
<tr>
<td>UMA</td>
<td>Urinary Micro-albumin</td>
</tr>
</tbody>
</table>

**Lipid**

<table>
<thead>
<tr>
<th>Test</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>TChol</td>
<td>Total Cholesterol</td>
</tr>
<tr>
<td>TG</td>
<td>Triglyceride</td>
</tr>
<tr>
<td>HDL</td>
<td>High Density Lipoprotein</td>
</tr>
<tr>
<td>LDL</td>
<td>Low Density Lipoprotein</td>
</tr>
<tr>
<td>Apo Prot.</td>
<td>Apoproteins A1, B100, C11</td>
</tr>
<tr>
<td>VLDL</td>
<td>Very Low Density Lipoprotein</td>
</tr>
</tbody>
</table>

**Angiography**

<table>
<thead>
<tr>
<th>Test</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stenosis of SAN</td>
<td>Stenosis of SAN Artery</td>
</tr>
<tr>
<td>LVFEF</td>
<td>Left Ventricular Ejection Fraction</td>
</tr>
<tr>
<td>Location of D vessel</td>
<td>Location of Diseased Vessels</td>
</tr>
<tr>
<td>Stenosis of AVN</td>
<td>Stenosis of Atrio-Ventricular (AVN) Artery</td>
</tr>
<tr>
<td>LVEDP</td>
<td>Left Ventricular End Diastolic Pressure</td>
</tr>
</tbody>
</table>
### Appendix D: Database Structure

<table>
<thead>
<tr>
<th>2 Bytes</th>
<th>Word specifying the number of Name data bytes followed by the patient's name.</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 Bytes</td>
<td>Word specifying the number of Telephone data bytes followed by the patient's number.</td>
</tr>
<tr>
<td>2 Bytes</td>
<td>Word specifying the number of integers in the patient information record. Array of word integers containing the patient information record. Three-column array of word integers containing physiological information, respiration, blood pressure, electrocardiogram, respectively.</td>
</tr>
</tbody>
</table>

### Appendix D.1. Patient Information Record

<table>
<thead>
<tr>
<th>1. Hospital # (lower 4 digits)</th>
<th>2. Sex</th>
<th>3. Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>4. DM Type</td>
<td>5. Cigarettes per day</td>
<td>6. Years of cig. use</td>
</tr>
<tr>
<td>10. Waist circumference</td>
<td>11. BP supine systolic</td>
<td>12. BP standing systolic</td>
</tr>
<tr>
<td>13. BP supine diastolic</td>
<td>14. BP standing diastolic</td>
<td>15. BMI</td>
</tr>
<tr>
<td>22. FBS1</td>
<td>23. FBS2</td>
<td>24. FBS3</td>
</tr>
<tr>
<td>25. FS Insulin</td>
<td>26. HBAIC</td>
<td>27. FC-Peptide</td>
</tr>
<tr>
<td>28. UP</td>
<td>29. UMA</td>
<td>30. TChol</td>
</tr>
<tr>
<td>31. TG</td>
<td>32. HDL</td>
<td>33. LDL</td>
</tr>
<tr>
<td>34. Apo Prot.</td>
<td>35. VLDL</td>
<td>36. A1</td>
</tr>
<tr>
<td>37. Stenosis of SAN</td>
<td>38. LVFEF</td>
<td>39. Location of D vessel</td>
</tr>
<tr>
<td>40. Stenosis of AVN</td>
<td>41. LVEDP</td>
<td>42. Date type</td>
</tr>
<tr>
<td>43. Patient type index</td>
<td>44. Hospital # (2 digits)</td>
<td>45. Sampling frequency</td>
</tr>
<tr>
<td>46. Number of channels (3)</td>
<td>47. Channel 1 Mode</td>
<td>48. Channel 1 High</td>
</tr>
<tr>
<td>49. Channel 1 Scale</td>
<td>50. Channel 2 Mode</td>
<td>51. Channel 2 High</td>
</tr>
<tr>
<td>52. Channel 2 Scale</td>
<td>53. Channel 3 Mode</td>
<td>54. Channel 3 High</td>
</tr>
<tr>
<td>55. Channel 3 Scale</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Appendix E: Clinical Procedure

1. Complete part I of the patient form
2. Briefly train the patient on using the breath monitor
3. Connect ECG Lead II electrodes
4. Connect ABP monitor
5. Connect respiration pressure transducer
6. Ask patient to lie quietly on the table
7. Complete part II of the patient form
8. Begin sampling 5 minutes of supine data
   Ensure the data displays correctly
9. Ask the patient to stand quietly
10. Begin sampling 5 minutes of standing data
11. Ask the patient to squat/sit quietly
12. Begin sampling 5 minutes of sitting data
13. With patient sitting, request patient to breathe in and out according to the breath monitor
14. Set the breath monitor and begin sampling 5 minutes of 9 breaths per min.
15. Set the breath monitor and begin sampling 5 minutes of 12 breaths per min.
16. Set the breath monitor and begin sampling 5 minutes of 15 breaths per min.
17. Disconnect the cables and thank patient for their assistance
18. TURN OFF THE ECG PRE-AMP (Save the battery!)
# Appendix F: Patient Form

## PART I

<table>
<thead>
<tr>
<th>Type</th>
<th>Normal</th>
<th>DM</th>
<th>CHD</th>
<th>CHDD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Telephone #</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospital #</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nationality</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medication</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cigarettes per day</td>
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<tr>
<td>Years of smoking</td>
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</tr>
<tr>
<td>Height (cm)</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Weight (Kg)</td>
<td></td>
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<tr>
<td>Hip circumference (cm)</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td></td>
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</tr>
<tr>
<td>Standing systolic BP</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standing diastolic BP</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Notes</td>
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</table>

## PART II

<table>
<thead>
<tr>
<th>Supine systolic BP</th>
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<tbody>
<tr>
<td>Supine diastolic BP</td>
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### Anxiety & Depression Questionnaire

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<tbody>
<tr>
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<td>D</td>
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<td>D</td>
<td>A</td>
<td>D</td>
</tr>
</tbody>
</table>

| D Total | A Total |

### Activity Index

**Do you follow a weekly exercise routine?**

- Yes: Index = 3
- No:  
  **Do you take walks during the week?**
  - Yes: 1 or 2  
  - No:  
    **How many times in a week do you take walks?**
    - 1 or 2: Index = 1  
    - ≥ 3: Index = 2

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Author's Recent Publications


Jacobson, M., Neural network based clinical system for early detection of diabetes and coronary heart disease, College of Information Technology Seminar Series, United Arab Emirates University, October 2001.


Jacobson, M., Acquisition and classification of heart rate variability by use of time-frequency representation, MPhil to PhD Transfer Report, School of Engineering, Napier University, Edinburgh, Scotland, April 2000.


Jacobson, M., Mathematics of human direction finding: why is it so hard to tell whose beeper it is? Bottom Line, Mathematics and Computer Applications Unit Newsletter, United Arab Emirates University, Volume 2.1, October 1995.


References

[1] Saudek C, President American Diabetes Association and Professor of Medicine at John Hopkins University School of Medicine, "Diabetes," US News and World Report, 1 April 2002.


[10] Saudek C, President American Diabetes Association and Professor of Medicine at John Hopkins University School of Medicine, "Diabetes," US News and World Report, 1 April 2002.


[58] Taha, I, Faulty of Biophysics, United Arab Emirates University, 1993.


