

ON THE DYNAMICS OF HEART RATE VARIABILITY

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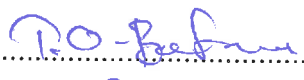
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The undersigned certifies that he has read and hereby recommends for acceptance by the College of Science a thesis titled: ON THE DYNAMICS OF HEART RATE VARIABILITY, in partial fulfilment of the requirements for the degree of Master of Science in Applied Mathematics of the Botswana International University of Science And Technology.

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Abstract

Heart rate variability refers to the variations in time interval between successive heart beats. An understanding of its dynamics can have clinical importance since it can help distinguish persons with healthy heart beats from those without. Our aim in this thesis was to characterise the dynamics of the human heart rate variability from three different groups: normal, heart failure and atrial fibrillation subjects. In particular, we wanted to establish if the dynamics of heart rate variability from these groups are stationary, nonlinear and/or chaotic.

We used recurrence analysis to explore the stationarity of heart rate variability using time series provided, breaking it into epochs within which the dynamics were stationary. We then used the technique of surrogate data testing to determine nonlinearity. The technique involves generating several artificial time series similar to the original time series but consistent with a specified hypothesis and the computation of a discriminating statistic. A discriminating statistic is computed for the original time series as well as all its surrogates and it provides guidance in accepting or rejecting the hypothesis. Finally we computed the maximal Lyapunov exponent and the correlation dimension from time series to determine the chaotic nature and dimensionality respectively. The maximal Lyapunov exponent quantifies the average rate of divergence of two trajectories that are initially close to each other. Correlation dimension on the other hand quantifies the number of degrees of freedom that govern the observed dynamics of the system.

Our results indicate that the dynamics of human heart rate variability are generally nonstationary. In some cases, we were able to establish stationary epochs thought to correspond to abrupt changes in the dynamics. We found the dynamics from the normal group to be nonlinear. Some of the dynamics from the atrial fibrillation and heart failure groups were found to be nonlinear while others could not be characterised by the technique used. Finally, the maximal Lyapunov exponents computed from our various time series seem to converge to positive numbers at both low and high dimensions. The correlation dimensions computed point to high dimensional systems.

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Chapter 1

Introduction

The heart is a vital organ. It is responsible for circulating blood throughout the body, supplying oxygen and nutrients to tissues and removing waste products such as carbon dioxide. It pumps the blood via blood vessels by continuously contracting and relaxing its muscles. These repeated heart activities result in heart beats. Studies have shown that quantities derived from hearts beats can be used in diagnosis of health conditions such as high blood pressure and diabetes [9]. One such quantity that is of enormous significance to this thesis is heart rate variability.

Heart rate variability (HRV) is the variation in time intervals between successive heart beats. It is obtained from the electrocardiogram (ECG) as the difference between successive R-peaks [7, 9]. An ECG is a record of how the electrical activity of the heart varies over time as electrical signals spread throughout the heart during each cardiac cycle [7]. Clinical relevance of HRV was first appreciated in the 1960's when it was found to be an indicator of fetal distress [7, 9]. It has since become a popular and useful noninvasive tool for assessing diseases and conditions related to the heart [7, 9]. For instance, it has been shown that HRV decreases in patients who just had a heart attack [9].

Nearly half a century of clinical research has also shown that HRV can indicate stress levels in people [9]. High and low levels of stress have been found to correspond to low and high heart rate variability respectively [9]. Despite these findings, numerous important issues concerning HRV such as the nature of its dynamics are continuing to gain widespread interest within the research community. This is evidenced by among others, the 2008 challenge on dynamical characterisation of HRV proposed by the editors of the journal of Chaos [28].

This chapter gives an overview of the heart and electrocardiogram which need to be understood in order to probe heart rate variability. Basic functions and characteristics of the heart together with electrical properties of the heart and electrocardiogram are provided. A detailed description of heart rate variability, research problem and

justification, research questions and objectives are given. Finally the organisation of the thesis is provided.

1.1 The Heart and Electrocardiogram

The heart consists of two smaller upper chambers called atria and two larger lower chambers called ventricles. The four chambers work together to pump and distribute blood throughout the body. (See Figure 1.1 for major components of the heart and direction of blood flow). The right hand side which includes the right atrium and right ventricle receives blood low in oxygen from the body and pumps it at low pressure to lungs to be oxygenated. The left hand side which consists of the left atrium and left ventricle receives oxygenated blood from the lungs and pumps it at high pressure to all other body systems. The pressure exerted by the left ventricle to keep blood circulating throughout the body is called blood pressure.

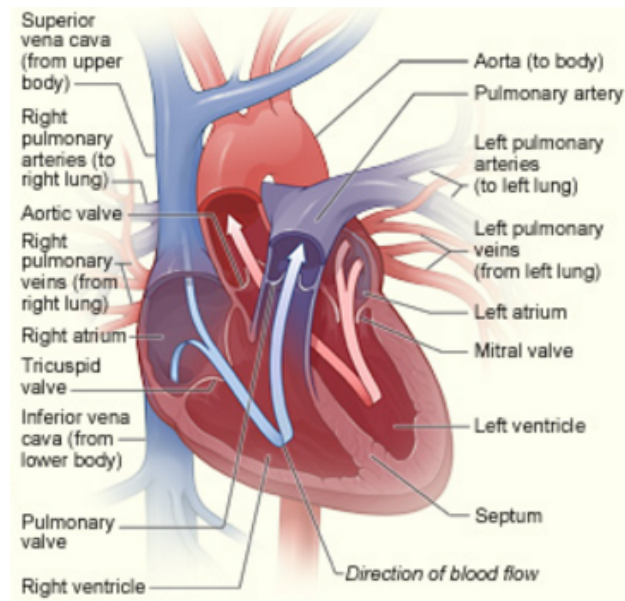


Figure 1.1: A general figure of the heart showing major parts and the direction of blood flow. The figure was adopted from [1].

The pumping action of the heart is triggered by electrical signals which are transmitted through the heart's electrical conduction system. These signals stimulate cardiac muscles to contract and relax. The heart's electrical conduction system is a network of highly specialised cardiac cells which possess the properties of *automaticity*¹, *excitability*² and *conductivity*³ [76]. It includes three important components; sinoa-

¹Automaticity is the ability of cardiac cells to spontaneously generate and discharge electrical impulses.

²Excitability is the ability of cardiac cells to respond to electrical impulses.

³Conductivity is the ability of cardiac cells to transmit electrical impulses from one cardiac cell to the other.

trial node, atrioventricular node and His-Purkinje system.

The sinoatrial node, which is a group of dominant pacemaker cells situated high up in the right atrium, is responsible for initiating each heart beat. It generates electrical signals that stimulate atrial muscles causing them to contract. These signals are then transmitted to the atrioventricular node which is a junction between the atria and ventricles. Here, transmission of the signals is delayed slightly to allow atrial muscles to complete their contractions before ventricular muscles begin theirs. From the atrioventricular node, the signals travel down His-Purkinje system which consists of the left and right bundle branches and Purkinje fibers. The His-Purkinje system is a network of conduction tissues responsible for coordinating ventricular contractions. (See Figure 1.2(b) for the heart's electrical conduction system).

The electrical activity taking place in the heart creates electrical currents that cause field potentials over the whole body [82]. By placing electrodes at specific places on the surface of the body, differences between these potentials can be detected [76] (See Figure 1.2(a) for specific places on the surface of the body where electrodes are placed). A record of how the electrical activity of the heart varies over time as electrical signals spread throughout the heart during each cardiac cycle is referred to as an electrocardiogram. There are different types of electrocardiograms such as 12-lead electrocardiogram and 3-lead electrocardiogram. The number of leads is usually used to determine the type of an electrocardiogram. A 12-lead electrocardiogram is commonly used in clinical reasearch. It uses 10 electrodes to record the heart's electrical activity. (See Figure 1.2(a) for some of the standard electrode locations for 12-lead electrocardiogram recordings).

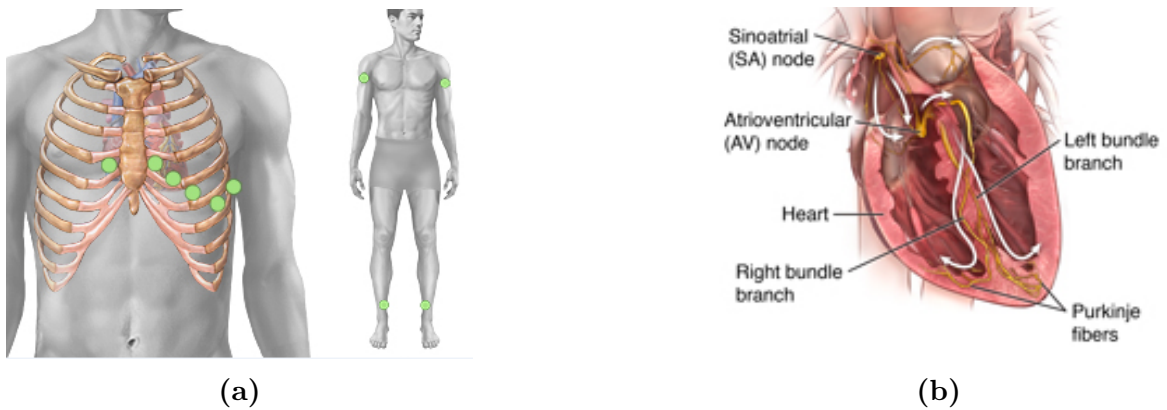


Figure 1.2: A figure showing (a) green dots indicating where electrodes are placed to detect the heart's electrical activity. The figure courtesy of [2]. (b) the heart's electrical conduction system. The figure adopted from [3].

A typical electrocardiogram comprises an initial P-wave, the main QRS complex (the largest amplitude portion of the electrocardiogram) and a trailing T-wave [76, 82] (see

Figure 1.3(a)). The P-wave is produced by the propagation of electrical signals during atrial *depolarisation*⁴ [76, 82]. The QRS complex on the other hand is a result of ventricular depolarisation while the T-wave is produced by the ventricular *repolarisation*⁵ [76, 82]. The global maxima of QRS complexes are called R-peaks and the distance between two consecutive R-peaks defines the time between two successive heart beats. A series of PQRST complexes constitute a heart rhythm (see Figure 1.3). There are various types of heart rhythms and most of them are well documented in medical literature [76]. They are classified as either normal or abnormal.

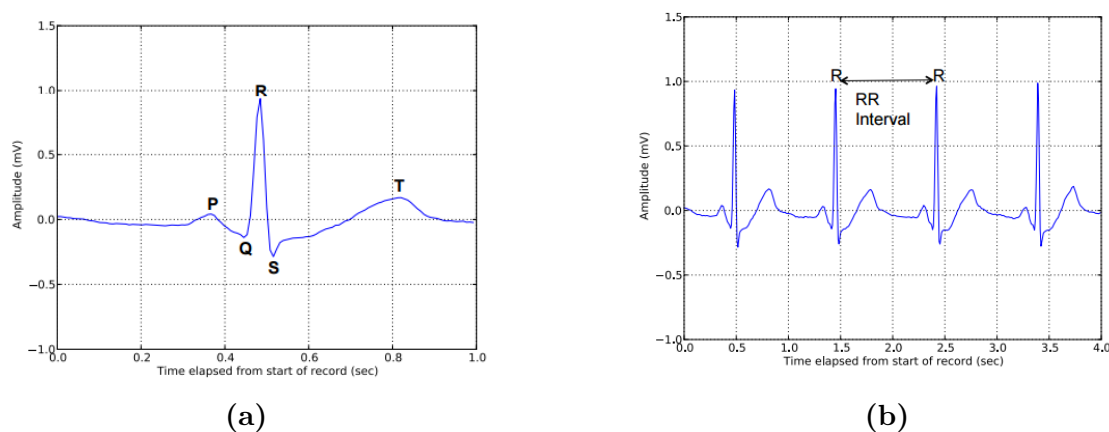


Figure 1.3: A figure showing (a) a single PQRST complex of the electrocardiogram (b) a series of PQRST complexes/heart rhythm with an RR-interval between two R-peaks. Figures courtesy of [27]

A heart rhythm is normal if it originates from the sinoatrial node and is characterised by a *heart rate*⁶ ranging from 60 to 100 beats per minute [4]. It is otherwise abnormal. A normal heart rhythm is also called a normal sinus rhythm while an abnormal one is called an arrhythmia or sinus arrhythmia if it originates from the sinoatrial node. Abnormal heart rhythms are caused by conditions such as congestive heart failure. Congestive heart failure happens when the heart cannot pump enough blood to meet the body's needs.

One of the common abnormal heart rhythms is atrial fibrillation [5]. It is characterised by the absence of the P-wave on the electrocardiogram [76]. Atrial fibrillation occurs as a result of abnormal electrical impulses in the atria [5, 4] (see Figure 1.4). Instead of a single impulse being transmitted through the heart, several impulses start in the atria and fight to get through the atrioventricular node [5]. As the electrical pathway

⁴Movement of ions across a cardiac cell membrane causing the inside of the cell to become positive is called depolarisation.

⁵Repolarisation refers to the movement of ions across a cardiac cell membrane making the inside of the cell to be negative.

⁶A heart rate is the average number of heart beats per minute. A normal heart rate ranges between 60 and 100 beats per minute otherwise it is abnormal.

changes, atleast an extra electrical circuit that transmits impulses at a faster than usual rate develops [4]. Due to the extra impulses, the atria start vibrating in a fast and disorganised way resulting in atrial fibrillation [4].

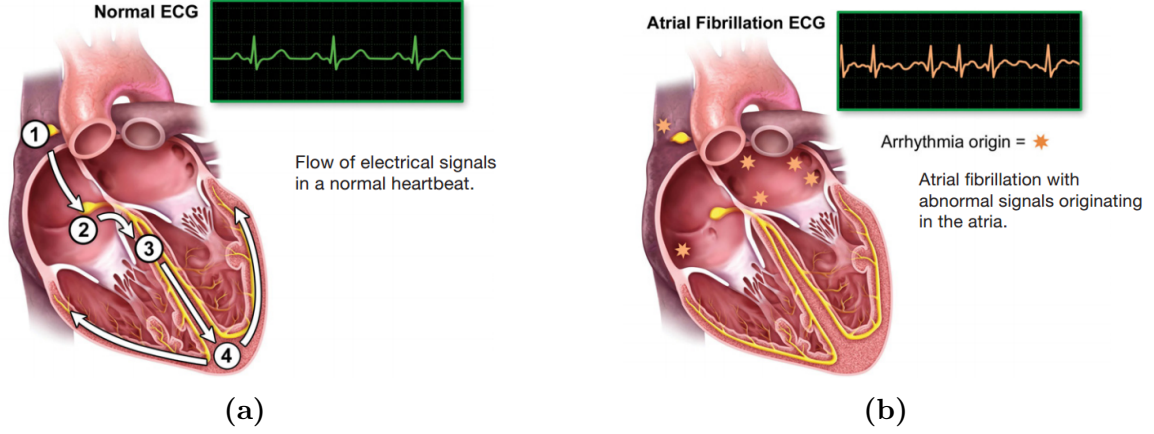


Figure 1.4: A figure showing flow of electrical signal in (a) a normal heart (b) a heart with atrial fibrillation. Figures courtesy of [4]

1.2 Heart Rate Variability

It was mentioned earlier that HRV is obtained from the electrocardiogram (ECG) as the difference between successive R-peaks [7, 9]. The difference between two consecutive R-peaks is referred to as RR-interval (see Figure 1.3(b)), interbeat interval or interval function [7]. The difference is called normal to normal interval (NN-interval) if the R-peaks originate in sinoatrial node [27]. The i^{th} RR-interval (x_i) is given by the equation

$$x_i = \alpha(t_i - t_{i-1}), i \in \mathbb{Z} \geq 1 \quad (1.1)$$

where t_i 's are R-peak times and α is a conversion parameter that varies depending on the units in which the RR-intervals are expressed [6]. A series of RR-intervals consists of unevenly spaced pairs of measurements (t_i, x_i) . These measurements are unevenly spaced because the heart rate varies from heart beat to heart beat. The fluctuations can be spontaneous or are triggered by either physical or mental stimulation or pharmacological interventions [9, 54].

As a measure of the fluctuations in the heart rate, HRV is a useful quantity for understanding the status of autonomic nervous system [7, 9]. A detailed account of its clinical relevance to the understanding of the status of the autonomic nervous system is provided in [7, 9]. The autonomic nervous system is part of the nervous system which deals with internal organs like stomach, glands, intestines and the heart. It regulates systems that are unconsciously carried out to keep our bodies alive and well

such as blood pressure, body temperature, breathing, digestion and regulation of the heart beat. The functionality of the autonomic nervous system is divided into two components, sympathetic and parasympathetic nervous systems. The sympathetic nervous system is concerned with readying the body to deal with threat or danger. It is triggered in physically or mentally stressful situations. It increases the heart rate and blood pressure, among others. The parasympathetic nervous system works to conserve energy by lowering the heart rate and blood pressure. It controls the calming responses such as relaxation and sleep.

A number of methods, linear and nonlinear, have been used in the literature to analyse heart rate variability. Linear techniques, which comprise time and frequency domain measures, are the most widely used. Time domain measures are based on simple statistical quantities (mean and variance) derived from NN-intervals as well as the difference between them. They include the standard deviation of NN-intervals and the root mean square of the difference adjacent N-intervals. Frequency domain measures comprise power spectral density of NN-intervals and breakdown of the powers spectral density into different frequency bands. Commonly used frequency and time domain measures are detailed in [7]. Linear measures such as standard deviation of NN-intervals have been used successfully in the literature to distinguish healthy individuals from those with congestive heart failure and atrial fibrillation [7, 9].

Nonlinear measures used to analyse heart rate variability include Poincare plots and second order difference plots [27]. In a Poincare plot, successive RR-intervals are plotted against each other while a second order difference plot plots the difference between successive RR-intervals against the difference of immediately following RR-intervals [7, 27]. These plots have been used to distinguish healthy individuals from congestive heart failure ones [7, 27]. A detailed account of nonlinear measures applied to heart rate variability is provided by Wessel *et al* [85]. In their work, Wessel *et al* [85] showed that nonlinear measures substantially improve the diagnostic value of heart rate variability beyond that achieved by using solely linear measures.

1.3 Research Problem And Its Justification

Heart rate variability has gained a lot of popularity as a noninvasive tool for assessing diseases and conditions related to the heart [9]. Its clinical relevance was first appreciated in 1965 when it was found to be an indicator of fetal distress [7]. Research on heart rate variability has since provided valuable information regarding, amongst others, neurocardiac functioning in autonomic nervous system diseases such as hypertension, congestive heart failure and coronary heart diseases [9, 54]. However, as pointed out earlier, numerous important issues concerning heart rate variability such

as the nature of its dynamics are yet to be fully understood within the reasearch community. As a result, widespread interest in the study of heart rate variability has continued to increase.

One of the long standing controversies surrounding HRV is the question of whether its dynamics are chaotic or not [28]. Chaotic dynamics are those that are nonlinear, deterministic but sensitive to initial conditions [72]. They can be predicted accurately in the short term but the possibility of accurate prediction in the long term is eliminated [25, 39, 72]. The idea that the nature of the dynamics of HRV may be chaotic can be traced back to the 1980's. It was around this period that it was first proposed that the dynamics of both the normal and abnormal HRV may be chaotic [29]. Since then, there has been a major debate within the research community concerning whether the nature of HRV dynamics might be chaotic or not [28].

Various studies have been carried out in the literature using nonlinear deterministic measures such as the correlation dimension and Lyapunov exponents to establish the deterministic and chaotic nature of HRV respectively. Studies such as those by Lefebvre *et al* [48] and Gomez *et al* [30] have claimed the presence of determinism and/or chaos in the dynamics of HRV while those by Kanters *et al* [38], Costa *et al* [15] and Baille *et al* [10] found no evidence of chaos. The works that report finding no evidence of chaos in HRV are careful and only rule out low dimensional chaos.

A new section to occasionally address timely and controversial topics related to nonlinear science was instituted by the editors of the journal of Chaos in June 2008 [28]. One of the topics discussed in the special issue of the journal concerned long standing questions regarding the characterisation of the human heart rate variability. The question of whether the dynamics of HRV are chaotic or not was among those discussed. Some of the papers in the special issue appeared to avoid this question and recast it in forms they considered to be most appropriate [28, 86], while others found the tools used to address the question incapable of yielding conclusive answers [23, 28]. In fact, among some reasons of the former groups approach were challenges highlighted by the latter. Consequently, the question of whether the dynamics of HRV are chaotic or not still remains open despite ongoing efforts.

1.4 Research Objectives And Research Questions

Using data sets provided by *PhysioNet*⁷ and deterministic nonlinear time series analysis tools [20, 21, 52, 71], this thesis aims to revisit the controversial questions related

⁷PhysioNet is a web-based resource established in 1999 under the financial support of the National Center for Research Resources of the National Institutes of Health, a part of the United States Department of Health and Human Services. Its purpose is to support and stimulate current research and novel investigations in the study of complex biomedical and physiological signals.

to the dynamical classification of the human heart rate variability. The questions that we concentrate on are:

- Are the dynamics stationary⁸?
- Are they linear or nonlinear?
- If they are nonlinear are they chaotic?

Our objectives are:

- To use the time series provided to study the dynamics of heart rate variability.
- To determine whether it is possible to break down the time series into epochs within which the dynamics are stationary.
- To address the last two questions within epochs where the time series are stationary.

1.5 Organisation of the Thesis

In the next chapter we introduce a number of techniques commonly used in analysis of heart rate variability. Justification of why nonlinear techniques are better suited to our study is given. The chapter also reviews some of the literature that have attempted to tackle the question of whether the human heart rate variability is stationary, nonlinear and/or chaotic. Chapter 3 considers in detail specific nonlinear analysis techniques and measures which are used for determining the nature of heart rate variability in Chapter 4. Chapter 4 provides a detailed analysis of the time series provided by PhysioNet. It is in this chapter that we discuss the results obtained. Finally, Chapter 5 gives a conclusion and comments on further work.

⁸Stationarity is defined in Chapter 2.

Chapter 2

Characterising the Dynamics of Heart Rate Variability

The human heart rate variability is known to exhibit highly complex behaviour. Various studies have characterised its dynamics as nonlinear and/or deterministic [11, 30, 48, 60, 86], fractal [25, 36, 60] and stochastic [13, 60, 67] amongst others. It is however not obvious what the true nature of the dynamics of HRV are, but in extreme cases they can be considered to be deterministic or stochastic in nature [60]. Furthermore, since determinism is a necessary but not sufficient condition for chaos, deterministic dynamics may be chaotic.

This chapter briefly introduces dynamical systems¹ and the concept of phase space² reconstruction. It then discusses some of the ways in which the dynamics of HRV can be characterised together with some previous works that have attempted to classify these dynamics. The focus is on the works that address the research questions stated in the previous chapter which are as follows: Are the dynamics of the human heart rate variability stationary or nonstationary? Are they linear or nonlinear? If they are nonlinear, are they chaotic?

2.1 Dynamical systems

The theory of nonlinear, deterministic dynamical systems studies among others, evolutions of dynamical systems, with the aim of predicting as accurately as possible the behaviour of the systems [25, 39, 72]. According to [72], the notion of a dynamical system is a mathematical formalisation of the general scientific concept of a deterministic process. A purely deterministic process can be modelled as completely specified func-

¹Since this work considers dynamical systems from a deterministic point of view, dynamical systems mean deterministic dynamical systems in the present work.

²Phase space and state space are used interchangeably in the present work as commonly done in the related literature.

tions of time. There is no uncertainty about the values of the process at any time and its values are predictable for any arbitrary time and space. Thus, the notion of a dynamical systems comprise a set of possible states together with a rule that determines the current states from the previous states [18, 47]. Formally, the set $X = \mathbb{R}^m, m \in \mathbb{Z}^+$ of all possible states of a dynamical system is called a state space or phase space while the change of the state in time $t \in T$, where T can be one of the sets $\mathbb{Z}$ or $\mathbb{R}$, is called an evolution [47]. The evolution of an initial state $\mathbf{x}_0 \in X$ to a state $\mathbf{x}_t \in X$ at time $t \in T$ is given by

$$\boldsymbol{\psi}^t : X \rightarrow X, \mathbf{x}_t = \boldsymbol{\psi}^t(\mathbf{x}_0), \quad (2.1)$$

where $\boldsymbol{\psi}^t$ is an evolution operator [47]. A dynamical system is then defined mathematically as a triple $\{T, X, \boldsymbol{\psi}^t\}$ [47], where T can be one of the sets $\mathbb{Z}$ or $\mathbb{R}$, X is the phase space and $\boldsymbol{\psi}^t : X \rightarrow X$ is a family of evolution operators satisfying the properties

$$\boldsymbol{\psi}^0(\mathbf{x}) = \mathbf{x}, \forall \mathbf{x} \in X, \quad (2.2)$$

$$\boldsymbol{\psi}^{t+s}(\mathbf{x}) = \boldsymbol{\psi}^s(\boldsymbol{\psi}^t(\mathbf{x})), \forall \mathbf{x} \in X, t, s \in T. \quad (2.3)$$

The most common way of defining a dynamical systems is by ordinary differential equations

$$\mathbf{x}'(t) = \mathbf{F}(\mathbf{x}(t)), t \in \mathbb{R}, \quad (2.4)$$

or difference equations

$$\mathbf{x}_{n+1} = \mathbf{F}(\mathbf{x}_n), n \in \mathbb{Z}, \quad (2.5)$$

where $\mathbf{x}, \mathbf{F} \in \mathbb{R}^m, m \in \mathbb{Z} \geq 1$, $\mathbf{F}$ is sufficiently differentiable and t denotes time [18, 39, 47]. Considering the ordinary differential equation given by Equation (2.4), $\{T, X, \boldsymbol{\psi}^t\}$ becomes a continuous time dynamical system if one sets $T = \mathbb{R}$, $X = \mathbb{R}^m$ and let $\boldsymbol{\psi}^t(\mathbf{x}) = \boldsymbol{\varphi}(\mathbf{x}(t))$ be the solution operator or flow that takes initial conditions $\mathbf{x}_0$ up to their solution at time t , that is

$$\frac{\partial}{\partial t} \boldsymbol{\varphi}(\mathbf{x}(t)) = \mathbf{F}(\boldsymbol{\varphi}(\mathbf{x}(t))), \boldsymbol{\varphi}(\mathbf{x}(0)) = \mathbf{x}_0. \quad (2.6)$$

Similarly, if one considers the difference equation given by Equation (2.5), $\{T, X, \boldsymbol{\psi}^t\}$ becomes a discrete time dynamical system if $T = \mathbb{Z}$, $X = \mathbb{R}^m$ and the operator $\boldsymbol{\psi}$ is just $\mathbf{F}$. Evolving through discrete time $n > 0$ involves taking the n^{th} iterate of $\boldsymbol{\psi}$, that is

$$\boldsymbol{\psi}^n(\mathbf{x}_0) = \mathbf{x}_n = \mathbf{F}(\mathbf{x}_{n-1}) = \mathbf{F}(\mathbf{F}(\mathbf{x}_{n-2})) = \dots = \mathbf{F} \circ \mathbf{F} \circ \dots \circ \mathbf{F}(\mathbf{x}_0). \quad (2.7)$$

Most of the ideas, measures and techniques discussed throughout this work are based on a geometrical point of view of dynamical systems. It is therefore important that

we provide a brief overview of some of the geometrical objects inherent in dynamical systems. The basic geometrical objects associated with a dynamical system $\{T, X, \psi^t\}$ are its orbits in the phase space and the phase portrait made up of these orbits [18, 47]. The set $\mathcal{O}(\mathbf{x}_0) = \{\mathbf{x} \in X : \mathbf{x} = \psi^t(\mathbf{x}_0), \forall t \in T\}$ is called an orbit or trajectory with initial condition $\mathbf{x}_0$ [47]. For a continuous time dynamical system, its orbits are curves in the phase space X parametrised by the time t and oriented by its direction of increase [18, 47]. The orbits of a discrete time dynamical system are the sequences of points in the phase space X enumerated by increasing integers [18, 47]. The phase portrait of the dynamical system $\{T, X, \psi^t\}$ is the partitioning of the phase space X into orbits [18, 47].

The phase portrait contains a lot of information on the behaviour of a dynamical system. One can deduce from a phase portrait among others the asymptotic states as $t \rightarrow \infty$. This geometric interpretation is however not useful when the phase space has more than 3 dimensions since humans can only visualise objects up to 3 dimensions. To further characterise the elements of a phase portrait, in particular possible long term observable dynamics, it is important to briefly discuss what an invariant set of a dynamical system is. An invariant set of a dynamical system $\{T, X, \psi^t\}$ is a subset $U \subset X$ such that $\mathbf{x} \in U$ implies $\psi^t(\mathbf{x}) \in U, \forall t \in T$ [18, 47]. A closed and bounded invariant set $U \subset X$ is called an attractor if there is some neighbourhood $V \in U$ such that $\psi^t(\mathbf{x}) \in V, \forall t \geq 0$ and $\psi^t(\mathbf{x}) \rightarrow U$ as $t \rightarrow \infty, \forall \mathbf{x} \in V$ [18, 47]. The basin of attraction or domain of attraction of an attractor U is the maximal set $\mathcal{U}$ for which $\mathbf{x} \in \mathcal{U}$ implies $\psi^t(\mathbf{x}) \rightarrow U$ as $t \rightarrow \infty$ [47, 83].

The theory of nonlinear deterministic dynamical systems is based on the assumption that the states $\mathbf{x}(t)$ of the underlying dynamical system $\{T, X, \psi^t\}$ are known *a priori*. This assumption however does not always hold in practice because the states of the underlying system are often unknown [39]. Another reason why the assumption does not usually hold is that, the states of the system often cannot be observed directly but only through a measurement function, typically involving a projection onto fewer variables than phase space dimensions [19, 39, 72]. So, in practice, one then has to analyse a time series $x_i = h(\mathbf{x}(t)), i \in \mathbb{Z} \geq 1$ obtained by applying a measurement function $h : \mathbb{R}^m \rightarrow \mathbb{R}^{m'}$ to the states $\mathbf{x}(t)$, where $m > m'$. In the case of this work, the heart beat measurements used are scalar numbers so $m' = 1$. Phase space reconstruction techniques can then be used to obtain an estimate of the underlying dynamical system. The concept of phase space reconstruction is discussed in the next section.

2.2 Phase space reconstruction

The concept of phase space reconstruction was first introduced in dynamical systems theory by Pickard *et al* in 1980, formalised as theorems by Takens in 1981 and Sauer *et al* in 1991 [39]. The idea behind this concept is to take a time series generated by an unknown dynamical system, transform it into a set of state vectors and obtain an estimate of the underlying dynamical system. The most widely used phase space reconstruction technique is the method of delay embeddings [75, 79]. Given a series $\{x_i\}$, the method allows one to form a vector that defines a point in a new space using a sequence of past values of the series [32]. Specifically, one constructs m -dimensional vectors $\mathbf{x}_i$ from m time delayed samples of $\{x_i\}$ such that

$$\mathbf{x}_i = (x_i, x_{i+\tau}, x_{i+2\tau}, \dots, x_{i+(m-1)\tau}), \quad (2.8)$$

where τ and m are called the time delay and embedding dimension respectively [24, 39]. In theory, the reconstruction process does not only preserve the attractor of the original system, it also provides a representation of the system's dynamics [24, 39]. Furthermore, embedding theorems by Takens [75] and Sauer *et al* [79] guarantee that if indeed the elements of $\{x_i\}$ are scalar measurements of a dynamical system, then under certain genericity conditions, the method of delay embeddings provides a one-to-one image of the original attractor provided m is sufficiently large [79]. These theorems are only applicable when the series $\{x_i\}$ is uniformly sampled [24, 39]. If $\{x_i\}$ is not uniformly sampled, constructing the delay vectors $\mathbf{x}_i$ is impossible without interpolation which can introduce spurious dynamics into the results [39]. However, if $\{x_i\}$ is a sequence of discrete events (for example heart beats) occurring at time $\{t_i\}$, the interspike interval embedding (IIE) technique can be employed to construct the attractor of $\{x_i\}$ [70].

The IIE method is a direct analogy of the technique of delay embeddings. Specifically, given a series $\{x_i\}$ of interspike intervals generated by an unknown dynamical system, the technique says one can simply employ the method of delay embeddings to construct m -dimensional vectors $\mathbf{x}_i$ from m delayed samples of $\{x_i\}$ such that [70]

$$\mathbf{x}_i = (x_i, x_{i+1}, x_{i+2}, \dots, x_{i+(m-1)}). \quad (2.9)$$

Notice from Equation (2.9) that the time delay τ is taken as 1 when constructing the m -dimensional vectors $\mathbf{x}_i$. According to [39, 70], $\tau = 1$ is enough since there is no explicit time delay involved in the series $\{x_i\}$ of interspike intervals. In fact, one has to understand that even though the series $\{x_i\}$ of interspike intervals is often treated as an ordinary time series, the index i is the event number and not the true time

[39]. In 1994, Sauer [70] provided the IIE theorem which is analogous to the classical embedding theorem by Takens [75] and Sauer *et al* [79]. The theorem gives us the possibility of reconstructing m -dimensional vectors $\mathbf{x}_i$ from m time delayed samples of the series $\{x_i\}$ of interspike intervals.

The embedding parameters, that is, τ and m from Equation (2.8) are critical in the reconstruction of an attractor from series. Since the IIE technique is adopted in the present work, these parameters are discussed in relation to it. It is justified why the interspike interval embedding technique is applicable to the present work in Section 4. The point to note from Equation (2.9) is that, $\tau = 1$ is enough in the context of the IIE technique. Therefore, the remainder of this subsection concerns only the embedding dimension m . The theoretical requirements on m are quite straightforward [24, 39]. However, in practice one often does not know the dimension of the system under study neither does one have an infinite series nor an infinite precision. Therefore in practice m has to be estimated in order to be able to reconstruct the attractor from a finite series with finite precision. There exists a number of techniques in the literature that are often employed to estimate m [24, 39]. In the present work, the commonly used method of false nearest neighbours (FNN) is employed to determine m .

The FNN technique was proposed by Kennel *et al* [42] to establish the minimal sufficient embedding dimension m , required to reconstruct the attractor from a time series or interspike intervals. The technique was later improved by Hegger and Kantz [39]. The method is based on the assumption that for a sufficient m , two points that are near each other should remain close as m is increased. When an insufficient m is used, points that are actually far apart in reality could seem to be neighbours as a consequence of being projected into a space of smaller m [39, 42]. This means if m_0 is the minimal embedding dimension of the series $\{x_i\}$, then in an m_0 -dimensional reconstructed phase space, the reconstructed attractor from $\{x_i\}$ is a one-to-one image of the attractor in the original phase space [39, 42]. Consequently, the dynamics of the original system are preserved [39, 42]. In the case that an embedding dimension $m < m_0$ is used, the attractor and dynamics of the original system might not be preserved.

2.3 Stationarity and nonstationarity in HRV dynamics

Heart rate variability is generally a nonstationary signal [25]. Since HRV is often analysed using techniques from time series analysis, its nonstationary behaviour poses a huge challenge in time series analysis [25, 39]. This is because most of the techniques

often used in HRV analysis are based on the assumption of stationarity [39]. In mathematical statistics, a series $x_1, x_2, \dots$ is called strongly stationary if for all j , the joint probability distribution of $x_i, x_{i+1}, \dots, x_{i+j-1}$ is not dependent on the time index i [39]. If the mean, variance and covariance of the series are constant, the series is said to be weakly stationary [19, 17]. In the context of dynamical systems, stationarity means the system observed through the series $\{x_i\}$ generates an invariant measure which is wholly sampled by the observations [19, 39]. This means the characteristic time scales of the series $\{x_i\}$ are much shorter than the length of $\{x_i\}$ [37, 39, 41, 55]. If slow variations exist on a time scale comparable to the length of the series $\{x_i\}$, it is a possibility that $\{x_i\}$ is nonstationary [39, 41, 55]. Nonstationarity may be attributed to among others, changes in a system's parameters during the period when measurements are made [40]. Furthermore, in a nonlinear dynamical setting, dynamical nonstationarity is mostly demonstrated by the relation between proximity in phase space and time [19, 39].

Numerous approaches exist in the literature which suggest ways of dealing with nonstationarity HRV signals prior to characterising them with methods based on the assumption of stationarity. A comprehensive review of some of these approaches can be found in [19, 24, 25, 39]. In the current work, two approaches commonly employed in HRV analysis to address nonstationarity are discussed. The first approach attempts to remove nonstationarity through a transform called differencing. A series is differenced by simply computing the difference between consecutive observations. The series obtained after differencing often has constant mean and variance [51]. This series can therefore be analysed using techniques based on the assumption of stationarity because it is at least stationary in terms of its mean and variance. A nonstationary series sometimes needs differencing more than once before its mean and variance are stabilised. A series which becomes stationary after being differenced d times is said to be integrated of order d and is denoted by $I(d)$. Mathematically, a series $\{x_i\}$ is $I(d)$ if

$$y_i = (1 - L)^d x_i, d \in \mathbb{Z} \quad (2.10)$$

is stationary, where $\{y_i\}$ is the differenced series and L is the lag operator. The lag operator L is defined by $Lx_i = x_{i-1}$. L can be raised to arbitrary integer powers so that $L^k x_i = x_{i-k}, k \in \mathbb{Z}$. If the order of integration d from Equation (2.10) is allowed to take any noninteger value, then $\{y_i\}$ becomes a fractionally differenced series. Furthermore, the term $(1 - L)^d$ from Equation (2.10) is called a difference operator. It is called a fractional difference operator when d is a noninteger value.

Differencing a nonstationary series to make it stationary implies the series is an integrated process [10]. Similarly, the implication of fractionally differencing a nonstationary series to make it stationary is that the series is assumed to be a fractionally

integrated process [49]. Integrated and fractionally integrated processes have integer and noninteger orders of integration respectively [10]. Common examples of stationary and nonstationary processes include the white noise and random walk processes respectively. A white noise process is a process with mean zero and no correlation between its values at various times. A random walk process is a process where the current value of a variable is made up of the immediate past value plus an error term which is a realisation of a white noise process. Differencing a random walk process once thus gives a white noise process which is stationary. Differencing is well documented in time series analysis textbooks such as [16, 64] while the classical paper by Hosking [35] provides a comprehensive discussion of fractional differencing.

Some previous studies that employed differencing in an attempt to transform nonstationary heart beat series into stationary ones were done by Baille *et al* [10], Freitas *et al* [23] and Lefebvre *et al* [48]. The works by Baille *et al* [10] and Freitas *et al* [23] appeared in the special issue of the journal of Chaos. In their works, Freitas *et al* [23] and Lefebvre *et al* [48] used an order of integration $d = 1$ to obtain the differenced series given by

$$\Delta x_i = x_i - x_{i-1}, \quad (2.11)$$

where $\{x_i\}$ represents a heart beat series. The authors in [23, 48] argued that by working with the differenced series, possible long term drifts associated with the heart beat series would be avoided. As mentioned earlier though, using an order of integration $d = 1$ to obtain the differenced series from the original heart beat series implies the original series is assumed to be an $I(1)$ process. However, the assumption of an $I(1)$ process may not hold since it can lead to overdifferencing of the heart beat series as evidenced by Baillie *et al* [10]. Overdifferencing can happen when a series is $I(1)$ but it is differenced more than once. The problem with overdifferencing is that an overdifferenced series is often stripped of its statistical properties such as the variance which are important during modelling [64].

In their study, Baillie *et al* [10] fractionally differenced the heart beat series in an attempt to mitigate the problem of overdifferencing. Using the fractionally differenced series, they computed the maximal Lyapunov exponent and correlation dimension to test for the existence of a low dimensional attractor in the normal heart beat series. However, they reported no significant difference between the maximal Lyapunov and correlation dimension estimates obtained when heart beat series were first differenced or fractionally differenced. It is important here to note that both differencing and fractional differencing are limited to weak stationarity. Weak stationarity only requires the mean, variance and covariance to be constant functions of time. As highlighted by Holger and Schreiber [39], if nonlinearities are involved, weak stationarity is not

enough since it employs only linear quantities.

In order to take into consideration the possibility of nonlinearities being involved in nonstationary HRV signals, we discuss a second approach commonly employed in HRV analysis to deal with the issue of nonstationarity. The approach involves searching for stationary epochs³ within heart beat series to exclude trends that may simulate nonlinear properties of the series. This is often done through the application of methods which test the series for stationarity. Some of these techniques include space time separation plots [66], probability distributions [37], recurrence plots [56], recurrence time statistics [68] and space time index plots [89, 90]. Recurrence and space time separation plots probe dynamical nonstationarity by evaluating temporal and phase space distances of state vectors in state space [66, 68]. Space time index plots introduced by Yu *et al* [89, 90] investigate dynamical nonstationarity in time series by inspecting the time distribution of state vectors at various space scales in phase space [89]. Recurrence time statistics were proposed by Rieke *et al* [68]. They probe dynamical nonstationarity by analysing temporal distances of neighbouring vectors in a phase space [68].

The technique of employing probability distributions to determine the stationarity of a series was introduced by Isliker and Kurths [37]. In order to establish stationarity of a series, the time independence of its probability distribution is tested using a χ^2 -statistic. A method similar to that Isliker and Kurths [37] was later proposed by Witt *et al* [87]. The method determines the stationarity of a series by testing the time independence of its probability distribution and power spectra [87]. Witt *et al* [87] were able to identify stationary epochs in heart beats series using their method. Braun *et al* [11] also used Isliker and Kurths's technique in their work to detect stationary epochs within heart beats series. They were able to select stationary epochs which they further analysed and determined to be nonlinear. One of the limitations of the techniques introduced in this paragraph is that they only test the one dimensional marginal distributions of the series. As noted by Kennel [41], testing only the one dimensional probability distributions of the series ignores dynamical information which may be contained in higher dimensions. Since the methods introduced in the preceding paragraph consider dynamical information in higher dimensions, we chose to employ one of these methods in our work to identify stationary epochs in heart beats series. In particular, we chose the technique of recurrence plots. A detailed description of this method is provided in Chapter 3.

³In the present work, stationary epochs or stationary segments refer to epochs/segments within which the dynamics of HRV are understood to be stationary.

2.4 Linearity and nonlinearity in HRV dynamics

The dynamics of HRV are known theoretically to contain some nonlinearities [40]. However, this theoretical knowledge is not sufficient when it comes to determining which time series analysis techniques could best characterise the dynamics of HRV. For instance, when one wants to apply nonlinear techniques to some data in order to describe the dynamics of HRV, evidence of nonlinearity in the data used is required [39, 40]. If no signatures of nonlinearity can be identified in the data, one might be better off using well established linear techniques such as spectral analysis. In the context of dynamical systems, nonlinearity implies the superposition principle does not hold [19, 72]. The superposition principle states that for a linear homogenous ordinary differential equation, if $\psi^1(\mathbf{x})$ and $\psi^2(\mathbf{x})$ are solutions then so is $\psi^1(\mathbf{x}) + \psi^2(\mathbf{x})$. The superposition principle is in fact a fundamental property of all linear systems. In time series analysis, a series $\{x_i\}$ is said to be linear if it satisfies the equation

$$x_i = \sum_{j=-\infty}^{\infty} \alpha_j y_i, i, j \in \mathbb{Z}, \quad (2.12)$$

where the coefficients α_j are at least square summable and the series $\{y_i\}$ is independent, identitically distributed with mean $\mu = 0$ and variance $\sigma^2 > 0$ [17]. Otherwise the series is nonlinear. A linear time series is generally easier to work with compared to a nonlinear one. This is due in part to the fact that the theory on linear time series analysis is well developed and mature.

In determining whether a particular series is linear or nonlinear, tests for both linearity and nonlinearity are often employed and the literature contains a lot of these tests. Classical tests include those by Brock *et al* [12], Hinich [33], McLeod and Li [61] and Tsay [80]. Given a series $\{x_i\}$, the test by Brock *et al* [12] establishes whether the series was generated from a white noise process [12]. McLeod and Li's test [61] checks for autoregressive conditional heteroskedasticity effects [10]. In particular, it tests whether the first k autocorrelations of the squares of $\{x_i\}$ are 0. Hinich's bicovariance test [33] assumes that the series $\{x_i\}$ was generated from a third order stationary process. It uses the sample bicovariance of $\{x_i\}$ to test for serial independence [50]. The test by Tsay [80] looks for quadratic serial dependence in the series $\{x_i\}$ [63]. These tests were applied by Baillie *et al* [10] to determine whether dynamics of the normal HRV are nonlinear. To test for nonlinearities, they used heart beat series from a normal subject. All the four tests rejected the null hypothesis that the heart beat series was generated by a linear process. The tests employed in Baillie *et al* [10]'s work are often implemented using analytically derived null distributions. A null distribution is an asymptotic distribution of a test statistic under a given null hypothesis. However,

it has been highlighted by Kugiumtzis [44] that the analytic null distribution may not always be accurate. It therefore means the performance of these tests can be altered by the inaccuracy in the distribution [44, 77].

Surrogate data analysis [71] is also a common method in testing for nonlinearity. The technique is a statistical proof by contradiction. Particularly, if the method is used to establish whether $\{x_i\}$ possesses a property, say Q , the null hypothesis selected should assume a property P opposite to Q . The technique involves generating several artificial series similar to the original series $\{x_i\}$ but consistent with a specified null hypothesis and the computation of a discriminating statistic. A discriminating statistic is computed for the original series as well as each of the surrogates. Rejection of the null hypothesis is established by using either a parametric or nonparametric approach. In his thesis, Hoekstra [34] used the method of surrogate data analysis to establish the presence of nonlinearities in normal and abnormal HRV. To test for nonlinearities, surrogate series were constructed from heart beat series from healthy and atrial fibrillation subjects. Using the correlation sum as a discriminating statistic, Hoekstra [34] determined the normal HRV to be nonlinear. Some of the dynamics from atrial fibrillation subjects were determined to be nonlinear while the discriminating statistic used failed to characterise others.

The works of Braun *et al* [11] and Costa *et al* [15] also used surrogate data analysis to determine the presence of nonlinearities in the dynamics of HRV. In their work, Braun *et al* [11] compared the correlation sums from stationary segments of normal heart beat series and their corresponding surrogate series. Their test rejected the null hypothesis that the original series were a realisation of linear processes. The measure of significance used by Braun *et al* [11] assumed the test statistic to be normally distributed. This is however does not always hold and can lead to spurious results since the distribution of the test statistic is often unknown [77]. Braun *et al* [11] also showed that the stationary segments from normal heart beat series are not time reversible. Time irreversibility is a strong indicator of nonlinearities [71].

In order to establish the presence of nonlinear correlations in the dynamics of the normal and abnormal HRV, Costa *et al* [15] first built the surrogates series from heart beat series from healthy and cardiac transplant subjects. They then compared the correlation sums of the original series and their corresponding surrogates series. Their results indicated the presence of nonlinear correlations in HRV of healthy subjects but not in HRV of cardiac transplant subjects. In surrogate data analysis, distribution of the test statistic under a given null hypothesis is estimated by direct Monte Carlo simulation [39, 77]. This approach avoids the disadvantages of deriving the null distribution analytically. It also leads to increased flexibility in the choice of null hypotheses and test statistics. In particular, Theiler *et al* [77] demonstrated that the null

hypotheses and test statistics can be chosen independently. Due to these advantages, the surrogate data analysis method is adopted in this work. A detailed description of this method is provided in Chapter 3.

2.5 Chaos in HRV dynamics

Various studies have reported evidence of nonlinearities in the dynamics of HRV [30, 36, 39, 60, 86]. The question then is; Are the nonlinear dynamics chaotic? Chaotic dynamics are those that are nonlinear, deterministic but sensitive to initial conditions [81]. In particular, chaotic dynamics can be predicted accurately in the short term but the possibility of accurate prediction in the long term is eliminated [72, 81]. Mathematically, a closed and bounded invariant set $U \subset X$ is called chaotic [18, 47, 83] if it satisfies the following conditions:

- It has sensitive dependence on initial conditions, that is, there exist an $\epsilon > 0$ such that, for any $\mathbf{x} \in U$ and any neighbourhood $\mathcal{V} \subset U$ of $\mathbf{x}$, there exists $\mathbf{y} \in \mathcal{V}$ and $t > 0$ such that $|\psi^t(\mathbf{x}) - \psi^t(\mathbf{y})| > \epsilon$.
- There exist a dense trajectory that eventually visits arbitrarily close to every point of the attractor, that is, there exists an $\mathbf{x} \in U_0 \subset X$ such that, for each $\mathbf{y} \in U_0 \subset X$ and each $\epsilon > 0$, there exists a time t such that $|\psi^t(\mathbf{x}) - \mathbf{y}| < \epsilon$.

A variety of tools exist in literature which can be used to establish whether the dynamics of HRV are chaotic or not. Some of these tools include correlation dimension [39], Lyapunov exponents [81] and the variants of Lyapunov exponents such as finite growth rates [84] and scale dependent Lyapunov exponent [25].

Studies which previously attempted to establish whether the dynamics of HRV are chaotic or not include those by Baille *et al* [10], Costa *et al* [15], Freitas *et al* [23], Gomez *et al* [30], Hu *et al* [36], Lefebvre *et al* [48] and Wessel *et al* [86]. Baille *et al* [10] computed the maximal Lyapunov exponent (λ_1) and correlation dimension (D_2) estimates of differenced heart beat series from a healthy subject in order to establish whether the dynamics of the normal HRV are governed by a low dimensional attractor. They considered a low dimensional attractor to satisfy the condition $D_2 \leq 5$. Otherwise they characterised the underlying dynamical process to be stochastic. They further adopted the conditions $\lambda_1 < 0$ and $D_2 \leq 5$ as operational definition of low dimensional chaos. They concluded from their results that the dynamics of the normal HRV are stochastic and not chaotic.

In their attempt to determine the presence of determinism in the dynamics of HRV, where determinism is necessary for chaos, Costa *et al* [15] tried to estimate D_2 from heart beat series obtained from healthy and cardiac transplant subjects. They however

reported that no D_2 was found for the heart beat series from both the healthy and cardiac transplant subjects. They then came to a conclusion that the dynamics of HRV are not chaotic. Hu *et al* [36] used the scale dependent Lyapunov exponent (SDLE), where a constant SDLE implies chaos [36] in an attempt to determine whether the dynamics of HRV are chaotic or not. Using heart beat series from healthy, congestive heart failure and atrial fibrillation subjects, they tried to estimate SDLEs from these heart beat series. They however reported finding no constant SDLEs on significant scale ranges from any of the heart beat series they considered. They concluded from their results that the dynamics of HRV are not chaotic.

In order to establish chaos in the dynamics of HRV, Wessel *et al* [86] computed the finite time growth rate as an analog of Lyapunov exponents in finite time from the heart beat series. They then obtained averaged finite growth rate values greater than zero, where averaged finite growth rate values greater than zero are necessary for chaos [85]. They however concluded that their results were only consistent but not specific to chaos. They argued that establishing chaos in HRV can only be done by taking into consideration all the mechanisms influencing HRV. In their study, Freitas *et al* [23] argued that since a clear evidence of determinism should exist prior to declaring a behaviour chaotic, obtaining nonlinear autoregressive models from the heart beat series was a worthy approach. They however reported not being able to obtain satisfactory models. Consequently, they found it difficult to provide a conclusive answer to the question of whether HRV is chaotic or not.

Lefebvre *et al* [48] used three approaches in their attempt to establish whether the dynamics of the normal HRV are chaotic or not. They started by estimating D_2 of differenced heart beat series from a group healthy and heart failure individuals to determine the presence of a low dimensional attractor. They considered a low dimensional attractor to satisfy the condition $D_2 < 4$. They then employed a prediction technique that was proposed by Sugihara and May [74] and an autoregressive linear predictor to determine the presence of nonlinear deterministic behaviour in the differenced heart beat series. They found no $D_2 < 4$, however they reported the presence of nonlinear deterministic behaviour in the differenced heart beat series. They then came to a conclusion that there is an element of deterministic chaos in the dynamics of HRV.

Other researchers such as Gomez *et al* [30] attempted to establish the presence of determinism in the dynamics of HRV by employing an approach based on nonlinear autoregressive moving average modelling and free run prediction together with surrogate data analysis. Their study considered heart beats series obtained from Wistar rats before and after the administration of autonomic blockade drugs. In their results, they found the dynamics of HRV to be highly deterministic before the administration of

autonomic blockade drugs compared to after the drugs have been administered. They concluded from these results that the dynamics of the normal HRV are deterministic. They further suggested that based on their results, tools from nonlinear dynamics and deterministic chaos may be applied to further characterise the dynamics of HRV. Finally, the works reviewed so far show that in general the question of whether the dynamics of HRV are chaotic or not is still open. The current work therefore revisits this question. We adopt an approach similar to the work of Baille *et al* [10]. In particular, we estimate λ_1 and D_2 from nonlinear stationary segments of heart beats series to establish the deterministic and chaotic nature of HRV respectively. However, we avoid using differenced series as in the case of Baille *et al* [10] and Lefebvre *et al* [48] because, as highlighted earlier, differencing is a linear transformation and there is a concern that it can alter the nonlinear dynamics of a series if they exist [73]. It is also worth noting that linear transformations cannot destroy chaos but actions like prewhitening can make it more difficult to see. The correlation dimension and maximal Lyapunov exponent are detailed in Chapter 3.

Chapter 3

Nonlinear Time Series Analysis Techniques and Measures

This chapter details nonlinear techniques and measures used in the present work. The study only considers HRV from a deterministic point of view. Therefore, the tools employed in the current work are mostly from nonlinear dynamics and chaos. The natural basis to formulate these tools is a multidimensional phase space reconstruction discussed in the Chapter 2 rather than the time or frequency domain [39].

The tools discussed here are recurrence plots, surrogate data analysis, correlation dimension and maximal Lyapunov exponent. As argued in the preceding chapter, these tools enable one to characterise dynamical systems in which nonlinearities give rise to complex temporal evolutions which is why they are applied in this work. Another motivating factor in using these tools is that their application in previous studies as highlighted earlier have provided some useful insights on the nature of the dynamics of HRV.

3.1 Recurrence plots

The method of recurrence plots was introduced by Eckmann *et al* [21]. It is a two dimensional graphical tool that can be used to establish whether the dynamics of a given dynamical system are stationary or not. The technique exploits the fundamental property of dynamical systems called recurrence to characterise the dynamics of a dynamical system. Recurrences take place in a system's phase space, so in order to construct a recurrence plot of a given series $\{x_i\}$, one starts by converting the observations x_i 's into state vectors through phase space reconstruction. The state vectors $\mathbf{x}_i$ are then used to compute the recurrence matrix given by

$$R(i, j) = \Theta(\epsilon - \|\mathbf{x}_i - \mathbf{x}_j\|), \quad (3.1)$$

where $\Theta(\cdot)$ is a Heaviside function, ϵ is a recurrence threshold and $||\cdot||$ is an arbitrary norm. For states with an ϵ -neighbourhood, $\mathbf{x}_i \approx \mathbf{x}_j \Leftrightarrow \mathbf{R}(i, j) \equiv 1$. [21, 59]. Plotting the recurrence matrix and using a variety of colours for its binary entries like a black dot at the point (i, j) if $\mathbf{R}(i, j) \equiv 1$ and a white dot if $\mathbf{R}(i, j) \equiv 0$ results in a recurrence plot. Recurrence plots exhibit characteristics large scale and small scale patterns referred to as typology and texture respectively [21]. Patterns exhibited by recurrence plots can be inspected visually to determine whether a series is stationary or nonstationary. For instance, homogenous recurrence plots are an indication of stationary and autonomous systems. Observation of white bands in recurrence plots may indicate nonstationarities.

An appropriate norm has to be chosen when constructing recurrence plots. Commonly used norms are the L_1 -norm, L_2 -norm and L_∞ -norm. For a fixed ϵ , the L_1 -norm, L_2 -norm and L_∞ -norm finds the least, intermediate and most neighbours respectively [58]. The L_1 -norm and L_2 -norm depend on the phase space dimension while the L_∞ -norm is independent of the phase space dimension when used in computing recurrence plots [56, 58]. This means when one wants to compare recurrence plots computed from different embeddings, the L_∞ -norm can be used directly without any rescaling required while the other norms would need rescaling [56, 58]. Furthermore, the L_∞ -norm is computationally faster than the other norms [58]. The L_∞ -norm is therefore used in this work because of the advantages it has over other norms when used to compute recurrence plots.

Another critical parameter in the construction of recurrence plots is the recurrence threshold ϵ . To appreciate the significance of this parameter, one has to note that two points in a phase space are considered recurrent if the distance between them is less than ϵ . This means there may be almost no recurrence points if ϵ is chosen too small thus resulting in nothing being learnt about the recurrence structure of the system under study [58]. A too large ϵ on the other hand gives rise to almost every point in the phase space being a neighbour of every other point thus leading to a lot of artefacts [58]. The selection of the recurrence threshold has received a lot of attention in the literature [57, 59], however, the question of choosing an appropriate ϵ is still yet to be answered satisfactorily [57]. Nevertheless, choosing a appropriate ϵ involves striking a balance between having a very small threshold and sufficient number of recurrences [57, 59].

The choice of ϵ is somehow dependent on the value range of the series or the diameter of the phase space [58]. This has served as a basis for a number of approaches proposed in the literature regarding the selection of ϵ . Some of the approaches suggested in the literature include, selecting ϵ such that it does not exceed 10% of the maximum phase space diameter [58, 91] and choosing ϵ such that the recurrence point density

is approximately 1% [58, 91]. The approaches suggested in the literature are rather rules of thumb than actual guidelines [57], so an optimal selection of ϵ is challenging and depends on a particular problem and question [57]. In this work, the recurrence threshold is chosen such that it does not exceed 10% of the maximum phase space diameter. This approach is used because it has been found useful for a variety of dynamical systems [57, 58].

3.2 Surrogate data analysis

The technique of surrogate data analysis was first introduced in nonlinear time series analysis by Theiler *et al* [77]. As introduced earlier, the main idea of the method is to construct a number of surrogate series similar to the original series $\{x_i\}$ but consistent with a specified null hypothesis and the computation of a discriminating statistic. In the literature, two approaches are often employed to construct the surrogate series [71, 78]. The first approach involves fitting a best model to $\{x_i\}$ and then generating surrogates series that are typical realisations of that model [39, 71, 78]. This approach is often called the typical realisations approach [39, 71, 77]. The second approach does not do any model fitting. It attempts to constrain the surrogates series so that they are similar to $\{x_i\}$ for a specified set of sample statistics [78]. The approach is commonly referred to as the constrained realisations approach [71]. Theiler and Prichard [78] pointed out that a comparative performance of hypothesis testing schemes based on these approaches depend on whether the discriminating statistic is pivotal or not. A statistic is said to be pivotal if it has the same distribution for all processes consistent with the null hypothesis [78]. The first approach requires the statistic to be pivotal while the second approach does not [78]. The second approach is therefore adopted in the present work because of its flexibility in the choice of a discriminating statistic.

Now that an approach for constructing the surrogates series have been identified, the null hypothesis that we want to test against has to be specified. Null hypotheses which are commonly employed in the literature are :

- The series $\{x_i\}$ is generated by an independent and identically distributed process [44, 71].
- The series $\{x_i\}$ is generated by a stationary Gaussian linear stochastic process

$$u_i = \sum_{j=1}^{M_0} a_j u_{i-j} + \sum_{k=0}^{M_1} b_k \eta_{i-k}, \quad (3.2)$$

where a_j and b_k are referred to as nuisance parameters and $\{\eta_i\}$ are Gaussian uncorrelated random increments [44, 71].

- The series $\{x_i\}$ is generated by a Gaussian linear stochastic process which may be distorted by a static (instantaneous) function h , that is

$$x_i = h(u_i), \quad u_i = \sum_{j=1}^{M_0} a_j u_{i-j} + \sum_{k=0}^{M_1} b_k \eta_{i-k}. \quad (3.3)$$

The function h may be linear or nonlinear and monotonic or non monotonic [44, 71].

The last null hypothesis is more general than the first two hypotheses. It is in fact among the most general null hypotheses of the technique of surrogate data analysis [44]. This null hypothesis (H_0) is therefore adopted in the current work.

As per the requirements of the surrogate data analysis technique, it is important that the surrogates series constructed in the current work are similar to the heart beat series used and consistent with H_0 . In order for the surrogate series $\{z_i\}$ constructed from the heart beat series $\{x_i\}$ to be consistent with H_0 it must satisfy the following two conditions:

- $\{z_i\}$ should preserve the marginal distribution of $\{x_i\}$, that is,

$$f_x(x_i) = f_z(z_i) \quad (3.4)$$

where $f_x(x_i)$ and $f_z(z_i)$ are the marginal probability density functions of $\{x_i\}$ and $\{z_i\}$ respectively [44, 71].

- $\{z_i\}$ should preserve the linear correlations of $\{x_i\}$, that is,

$$R_x(\tau) = R_z(\tau), \quad \tau = 1, \dots, \tau^* \quad (3.5)$$

where $R_x(\tau)$ and $R_z(\tau)$ represent the autocorrelations of $\{x_i\}$ and $\{z_i\}$ respectively and τ^* a sufficiently large lag time [44, 71].

Once the proper surrogates have been constructed, discriminating statistics are computed for both $\{x_i\}$ and $\{z_i\}$ in order to test H_0 . Rejection of H_0 is established by using either a parametric or nonparametric approach. Specifically, suppose q_0 is the discriminating statistic for the original series $\{x_i\}$ and $q_1, \dots, q_M$ are discriminating statistics for M surrogate series $\{z_i\}$. In the parametric approach, the measures $q_1, \dots, q_M$ are assumed to be fairly normally distributed. A significance S defined by

$$S = \frac{|q_0 - \langle q \rangle|}{\sigma_q}, \quad (3.6)$$

is then calculated, where $\langle q \rangle$ is the average and σ_q the standard deviation of $q_1, \dots, q_M$. The null hypothesis is rejected at the 95% level of confidence when $S \geq 2$ and M is roughly greater than 30 [43]. The nonparametric approach does not make any assumptions on the distributions of the measures $q_1, \dots, q_M$. Rather, it orders the measures $q_0, q_1, \dots, q_M$ according to their ranks. The significance level is then determined for instance as the 95% percentile of the rank ordered measures [44, 77]. The nonparametric approach is adopted in this work because it does not make any assumption on the distributions of the discriminating statistics.

Some of the algorithms that are commonly used in practice to generate the surrogate series are detailed next. Since the constrained realisation approach is adopted in this work, we restrict our discussion only to schemes that follow this approach. For the interested reader, a detailed review of various algorithms used to construct surrogate series can be found in [53].

3.2.1 Algorithms used to generate surrogate series

Numerous algorithms that follow the constrained realisation approach to construct the surrogate series exist in the literature [24, 44, 71]. Here we restrict ourselves to algorithms which attempt to construct surrogate series $\{z_j\}$ that match the linear correlations and marginal distribution of the original series $\{x_j\}$. Some of the commonly used schemes which meet this include the amplitude adjusted Fourier transform (*AAFT*) [77] and the iterative amplitude adjusted Fourier transform (*IAAFT*) [71]. The *AAFT* and *IAAFT* schemes employ the Fourier phase randomisation procedure to produce the surrogate series [44, 71]. The procedure involves transforming $\{x_i\}$ from time into frequency domain using Fourier transform. It then randomises Fourier phases across $\{x_i\}$ and converts the series of randomised Fourier phases back to the time domain.

It is difficult in practice to construct the surrogate series $\{z_i\}$ perfectly matching the linear correlations and marginal distribution of the original series $\{x_i\}$. If one condition is matched, there is a possibility of a deviation in the other [44]. The *AAFT* and *IAAFT* schemes construct the $\{z_i\}$ with the exact marginal distribution and approximate linear correlations of $\{x_i\}$. However, the surrogate series generated by the *AAFT* algorithm often fail to match well the linear correlations compared to those constructed by the *IAAFT* algorithm [43, 44]. The main reason why the *AAFT* constructs the surrogates that fail to match well the linear correlations is due to that it assumes the static transform in H_0 is monotonic which in practice is not always the case [43, 44]. On the other hand, the *IAAFT* scheme does not make any assumptions on the static transform in H_0 hence why it generates surrogates which approximate the linear correlations well [44, 71].

As demonstrated by Kugiumtzis [44], bias in the linear correlations can arise when $\{x_i\}$ is consistent with H_0 (but the static transform is not monotonic) or when $\{x_i\}$ is not consistent with H_0 (but contains nonlinear dynamics). In both cases, rejection of H_0 is favoured when a nonlinear discriminating statistic sensitive to linear correlations is employed [44]. Since it is crucial to minimise the possibility of falsely rejecting H_0 when testing for nonlinearity, the *IAAFT* algorithm is adopted in the present work because it approximate the linear correlations well. The next discussion concerns discriminating statistics employed in this work.

3.2.2 Discriminating Statistics

The literature contains a number of measures that can be employed to discriminate the observed series $\{x_i\}$ from its surrogates $\{z_i\}$ when testing for the presence of nonlinearities in $\{x_i\}$. Some of the measures which can be used include mutual information, false nearest neighbours, nonlinear prediction error and correlation dimension estimates [44, 46]. However, linear statistics such as the mean and variance which can be obtained directly from histogram of the series or from the autocorrelation function (or equivalently, the power spectrum) cannot be used as discriminating statistics [40]. This is because by construction $\{z_i\}$ have the same linear properties as $\{x_i\}$ so these measures cannot discriminate $\{x_i\}$ from $\{z_i\}$ [39, 40]. A discussion of measures that are employed as discriminating statistics in this work follows.

Consider an observed series $\{x_i\}$. The series $\{x_i\}$ is said to be time reversible or time symmetric if

$$P(x_i, x_{i+1}, \dots, x_{i+k}) = P(x_{i+k}, x_{i+k-1}, \dots, x_i), \forall i, k \in \mathbb{Z}, \quad (3.7)$$

where $P(\cdot)$ denotes the joint probability function [19]. It has been demonstrated that deviations from time reversibility are a strong indication of nonlinearity [11, 19, 39]. In fact, for nonlinear processes, time reversibility often do not hold [19, 39]. It has also been shown that Gaussian linear stochastic processes (which may have been distorted by static functions) are time reversible [46]. It is therefore possible to use a quantity that measures time irreversibility to test H_0 . A useful quantity that is frequently used to detect deviations from time reversibility and is employed in the present work as a discriminating statistic is the third-order correlation function [19] given by

$$\phi^{rev}(\tau) = \frac{\sum_{i=\tau+1}^n |x_i - x_{i-\tau}|^3}{\left(\sum_{i=\tau+1}^n |x_i - x_{i-\tau}|^2 \right)^{\frac{3}{2}}}, \quad (3.8)$$

where n is the length of the series $\{x_i\}$.

The mutual information is another measure employed in this work as a discriminating statistic. It is defined for two continuous random variables A and B as the amount of information that is known for one variable given the other [46]. Mathematically, it is written as

$$I(A, B) = \int_A \int_B f_{AB}(a, b) \log \frac{f_{AB}(a, b)}{f_A(a)f_B(b)} da db, \quad (3.9)$$

where $f_{AB}(a, b)$ is the joint probability density function of A and B , $f_A(a)$ and $f_B(b)$ are the marginal probability density functions of A and B respectively [46, 62]. If a partition is assumed over the domain of A and B , the double integral from Equation (3.9) becomes a sum over the cells of a two dimensional partition, that is

$$\begin{aligned} I(A, B) &= \sum_{i,j} P_{AB}(a_i, b_j) \log \frac{P_{AB}(a_i, b_j)}{P_A(a_i)P_B(b_j)} \\ &= \sum_{i,j} P_{AB}(a_i, b_j) \log P_{AB}(a_i, b_j) - \sum_i P_{AB}(a_i, b_j) \log P_A(a_i)P_B(b_j) \\ &= \sum_{i,j} P_{AB}(a_i, b_j) \log P_{AB}(a_i, b_j) - \sum_i P_A(a_i) \log P_A(a_i) - \sum_j P_B(b_j) \log P_B(b_j) \end{aligned} \quad (3.10)$$

where $P_A(a_i)$, $P_B(b_j)$ and $P_{AB}(a_i, b_j)$ are the marginal and joint probability mass functions over the elements of the one and two dimensional partition [46, 62]. For a series $\{x_i\}$, mutual information is defined as a function of the delay τ assuming the two variables $A = x_i$ and $B = x_{i+\tau}$. Hence for a series $\{x_i\}$, Equation (3.10) simplifies to

$$I(\tau) = \sum_{ij} P_{ij}(\tau) \log P_{ij}(\tau) - 2 \sum_{i=1} P_i(\tau) \log P_i(\tau) \quad [39]. \quad (3.11)$$

Since $I(\tau)$ can be considered as a correlation measure for time series that quantifies the linear and nonlinear correlations, it is used in this work to test H_0 . When computing the $I(\tau)$, the commonly used histogram based technique was employed to estimate the probabilities P_{ij} .

We also employ a measure derived from a correlation sum as a discriminating statistic in this work. The correlation sum $C_m(\epsilon, N)$ for a set of points $\mathbf{x}_i \in \mathbb{R}^m$, $i, m \in \mathbb{Z} > 0$ is the fraction of all possible pairs of points which are separated by a distance less than a given radius ϵ in a particular norm [24, 39]. Mathematically, $C_m(\epsilon, N)$ is written as

$$C_m(\epsilon, N) = \frac{2}{N(N-1)} \sum_{1 \leq i < j \leq N} \Theta(\epsilon - \|\mathbf{x}_i - \mathbf{x}_j\|), \quad (3.12)$$

where $N = n - m + 1$, n is the length of the series, m is an embedding dimension,

$\Theta(\cdot)$ a Heaviside function, $\|\cdot\|$ a norm and ϵ a given radius. The quantity given by Equation (3.12) involve phase space vectors as the locations of points on an attractor thus for a series $\{x_i\}$, phase space reconstruction has to be performed first. Since $C_m(\epsilon, N)$ is capable of detecting both the linear and nonlinear correlations it can be used as a discriminating statistic [46]. It follows that measures derived from $C_m(\epsilon, N)$ can also be employed as discriminating statistics [46]. In the current work, the radius ϵ of a specified correlation sum is used to test H_0 .

3.3 Correlation dimension

Suppose $U \in \mathbb{R}^m$ is a chaotic attractor due to a dynamical system $\mathbf{x}'(t) = \mathbf{F}(\mathbf{x}(t)) \in \mathbb{R}^m$. Let $\mathbf{x} \in U$ and denote an m -dimensional hypercube centered at $\mathbf{x}$ by $B_{\mathbf{x}}$. Furthermore, suppose ρ is a probability measure. The probability measure $\rho(B_{\mathbf{x}})$ is defined by Ding *et al* [20] as the fraction of time spent by a typical orbit in the cube. Since $\rho(B_{\mathbf{x}})$ is induced by the dynamics, it is also called a natural measure [20]. In order to characterise $\rho(B_{\mathbf{x}})$, the generalised dimensions D_q are often employed. If U is covered with a uniform grid of mesh size ϵ and the natural measure in the i^{th} cube is denoted by P_i , the generalised dimensions D_q are given by

$$D_q = \lim_{\epsilon \rightarrow 0} \frac{1}{q-1} \frac{\log \sum_{i=1}^K P_i^q}{\log \epsilon}, q \in \mathbb{R}, \quad (3.13)$$

where $K = K(\epsilon)$ is the total number of cubes with $P_i > 0$ [20]. The case $q = 2$ gives the correlation dimension. From Equation (3.13), the correlation dimension D_2 is defined as

$$D_2 = \lim_{\epsilon \rightarrow 0} \frac{\log \sum_{i=1}^K P_i^2}{\log \epsilon}. \quad (3.14)$$

The correlation dimension quantifies the number of degrees of freedom that govern the observed dynamics of a dynamical systems. It is adopted in the present work to determine the deterministic nature of HRV because it is easier to estimate compared to other dimensions such as the box-counting dimension D_0 and information dimension D_1 [20]. To illustrate this, an alternative definition of D_2 based on a correlation integral $C(\epsilon)$ is provided. A correlation integral $C(\epsilon)$ is defined as the probability that a pair of points chosen randomly with respect to the measure ρ is separated by a distance less than ϵ on U [20]. The correlation dimension D_2 is then defined as [20, 39]

$$D_2 = \lim_{\epsilon \rightarrow 0} \frac{\log C(\epsilon)}{\log \epsilon}. \quad (3.15)$$

The definition of D_2 given by Equation (3.15) requires an infinite set of points, however since only a finite set of points are available in practice, D_2 is often estimated

numerically. This is done by using the correlation sum $C(\epsilon, N)$ which approximates the correlation integral $C(\epsilon)$ [20, 39]. In order to estimate D_2 of an observed series $\{x_i\}$, one starts by transforming the observations x_i 's into state vectors through phase space reconstruction. Once the state vectors $\mathbf{x}_i$ are reconstructed the estimation of D_2 is done in two steps. The first step involves computing $C(\epsilon, N)$ for various embedding dimensions m and threshold distance ϵ . The correlation sum $C(\epsilon, N)$ is then inspected for signatures of self-similarity [39]. If these signatures are convincing enough, a value of D_2 can then be computed. The algorithm by Grassberger and Procaccia [31] is often used in the literature to estimate D_2 . It is therefore adopted in the present work to estimate D_2 of heart beat series.

3.4 Maximal Lyapunov exponent

Consider a dynamical system $\mathbf{x}'(t) = \mathbf{F}(\mathbf{x}(t)) \in \mathbb{R}^m$. Assume the existence of an infinitesimal ball of radius $\delta\mathbf{x}(t_0)$ at initial time t_0 . Suppose the long term evolution of this ball is monitored. As the ball evolves, it will become an ellipsoid due to the locally deforming nature of the flow [25, 88]. Furthermore, due to its infinitesimal size, the deformation will only be determined by the linear part of the flow [25, 88]. Let $\delta\mathbf{x}_i(t)$ be the i^{th} principal axis of the ellipsoid at time t . The i^{th} Lyapunov exponent (LE) is then defined as [25, 81].

$$\lambda_i = \lim_{\delta\mathbf{x}(t_0) \rightarrow 0} \lim_{t \rightarrow \infty} \frac{1}{t} \frac{\delta\mathbf{x}_i(t)}{\delta\mathbf{x}(t_0)}, \quad i = 1, \dots, m. \quad (3.16)$$

Lyapunov exponents quantify the average rate of divergence or convergence of two trajectories that are initially close to each other [52]. A negative LE indicates a rate of convergence while a positive one indicates a rate of divergence [45]. Only the largest LE λ_1 is considered in this work. From Equation (3.16), λ_1 is formally defined as

$$\lambda_1 = \lim_{\delta\mathbf{x}(t_0) \rightarrow 0} \lim_{t \rightarrow \infty} \frac{1}{t} \frac{\delta\mathbf{x}_1(t)}{\delta\mathbf{x}(t_0)}. \quad (3.17)$$

A positive λ_1 is a strong signature of chaotic dynamics which is why it is employed in the present work to establish the presence of chaos in heart rate variability. The definition of λ_1 given by Equation (3.17) requires an infinite sets of observations. However, since only a finite set of observations are available in practice, λ_1 is often estimated numerically [24, 39]. In order to estimate λ_1 of an observed series $\{x_i\}$, one starts by transforming the observations x_i 's into state vectors through phase space reconstruction. Denote by δ_0 the distance between state vectors $\mathbf{x}_i$ and $\mathbf{x}_j$, that is $\|\mathbf{x}_i - \mathbf{x}_j\| = \delta_0$. Furthermore, denote by $\delta_{\Delta n} \ll 1$ the distance some time $\Delta n \gg 1$ ahead between the trajectories emerging from state vectors $\mathbf{x}_i$ and $\mathbf{x}_j$, that is $\|\mathbf{x}_{i+\Delta n} -$

$\|\mathbf{x}_{j+\Delta n}\| = \delta_{\Delta n}$. The maximal LE λ_1 can then be determined by [39]

$$\delta_{\Delta n} \approx \delta_0 e^{\lambda_1 \Delta n}. \quad (3.18)$$

A number of algorithms that use Equation (3.18) to compute λ_1 exist in the literature. In the current work, the algorithm by Rosenstein *et al* [69] is used to estimate λ_1 of heart beat series. This is mainly because the algorithm has been demonstrated to be suitable for estimating λ_1 from short time series such as the heart beat series used in this study [69].

Chapter 4

Application of Nonlinear Time Series Analysis Techniques and Measures to Heart Rate Variability

Nonlinear time series analysis techniques and measures detailed in earlier are employed in this chapter to characterise the dynamics of HRV using heart beat series provided by PhysioNet [8] to the journal of Chaos. Specifically, the chapter starts by introducing heart beat series to be used in this study. The possibility of reconstructing an attractor from these heart beat series is then considered. Nonlinear time series analysis methods and measures discussed Chapter 3 are then employed to establish if the dynamics of HRV are stationary, nonlinear and/or chaotic using these heart beat series.

4.1 The heart beat series

The heart beat series employed in our study were used as a challenge for analysis methods for the 2008 special issue of the journal of Chaos which dealt with dynamical characterisation of the human heart rate variability [28]. A set of 15 data sets of which 5 were normal, 5 had heart failure and 5 atrial fibrillation were provided. Each set comprised approximately 24 hours long filtered heart beat series and its unfiltered version. In order to be able to compare our results to those of others, we chose to use the filtered heart beat series as suggested by PhysioNet [8]. All the series were derived from continuous ambulatory ECGs. Continuous ambulatory ECGs record the electrical activity of individuals while they are carrying out their normal day to day activities. Ambulatory means an individual is able to walk during the recording. The series belonging to the normal and congestive heart failure are all in sinus rhythm while for the atrial fibrillation ones the rhythm is atrial fibrillation. Table 4.1 presents the filtered versions of data sets provided by PhysioNet to the journal of Chaos.

Table 4.1: Details of filtered versions of data sets provided by PhysioNet to the journal of Chaos

Subjects	Data sets	Length
NH	n1nn	99767
NH	n2nn	86925
NH	n3nn	101145
NH	n4nn	86822
NH	n5nn	81280
AF	a1nn	101145
AF	a2nn	114322
AF	a3nn	85304
AF	a4nn	135431
AF	a5nn	138850
CHF	c1nn	74496
CHF	c2nn	76949
CHF	c3nn	88501
CHF	c4nn	88499
CHF	c5nn	115062

Prior to analysis, each of the data sets in Table (4.1) were first partitioned into nonoverlapping segments of length 16834. These segments are presented in Tables (4.2) - (4.4). Each segment is denoted by using the name of the series and the position of the segment. For instance, the first segment of the n1nn series is denoted n1nn1, the second segment n1nn2 etc. Ranges from which the segments were extracted from are also indicated in Tables (4.2) - (4.4). Stationary epochs employed in the present study were extracted from the segments presented in Tables (4.2) - (4.4).

Table 4.2: Partioned segments extracted from data sets of healthy subjects

Partioned segments	Extracted from	Extracted range
n1nn1	n1nn	1 - 16384
n1nn2	n1nn	16385 - 32768
n1nn3	n1nn	32769 - 49152
n1nn4	n1nn	49153 - 65536
n1nn5	n1nn	65537 - 81920
n1nn6	n1nn	81921 - 98304
n2nn1	n2nn	1 - 16384
n2nn2	n2nn	16385 - 32768
n2nn3	n2nn	32769 - 49152
n2nn4	n2nn	49153 - 65536
n2nn5	n2nn	65537 - 81920
n3nn1	n3nn	1 - 16384
n3nn2	n3nn	16385 - 32768
n3nn3	n3nn	32769 - 49152
n3nn4	n3nn	49153 - 65536
n3nn5	n3nn	65537 - 81920
n3nn6	n3nn	81921 - 98304
n4nn1	n4nn	1 - 16384
n4nn2	n4nn	16385 - 32768
n4nn3	n4nn	32769 - 49152
n4nn4	n4nn	49153 - 65536
n4nn5	n4nn	65537 - 81920
n5nn1	n5nn	1 - 16384
n5nn2	n5nn	16385 - 32768
n5nn3	n5nn	32769 - 49152
n5nn4	n5nn	49153 - 65536

Table 4.3: Partioned segments extracted from data sets of heart failure subjects

Partioned segments	Extracted from	Extracted range
c1nn1	c1nn	1 - 16384
c1nn2	c1nn	16385 - 32768
c1nn3	c1nn	32769 - 49152
c1nn4	c1nn	49153 - 65536
c2nn1	c2nn	1 - 16384
c2nn2	c2nn	16385 - 32768
c2nn3	c2nn	32769 - 49152
c2nn4	c2nn	49153 - 65536
c3nn1	c3nn	1 - 16384
c3nn2	c3nn	16385 - 32768
c3nn3	c3nn	32769 - 49152
c3nn4	c3nn	49153 - 65536
c3nn5	c3nn	65537 - 81920
c4nn1	c4nn	1 - 16384
c4nn2	c4nn	16385 - 32768
c4nn3	c4nn	32769 - 49152
c4nn4	c4nn	49153 - 65536
c4nn5	c4nn	65537 - 81920
c5nn1	c5nn	1 - 16384
c5nn2	c5nn	16385 - 32768
c5nn3	c5nn	32769 - 49152
c5nn4	c5nn	49153 - 65536
c5nn5	c5nn	65537 - 81920
c5nn6	c5nn	81921 - 98304
c5nn7	c5nn	98305 - 14688

Table 4.4: Partioned segments extracted from data sets of atrial fibrillation subjects

Partioned data sets	Extracted from	Extracted range
a1nn1	a1nn	1 - 16384
a1nn2	a1nn	16385 - 32768
a1nn3	a1nn	32769 - 49152
a1nn4	a1nn	49153 - 65536
a1nn5	a1nn	65537 - 81920
a1nn6	a1nn	81921 - 98304
a2nn1	a2nn	1 - 16384
a2nn2	a2nn	16385 - 32768
a2nn3	a2nn	32769 - 49152
a2nn3	a2nn	49153 - 65536
a2nn4	a2nn	65537 - 81920
a2nn5	a2nn	81921 - 98304
a2nn6	a2nn	98305 - 114688
a3nn1	a3nn	1 - 16384
a3nn2	a3nn	16385 - 32768
a3nn3	a3nn	32769 - 49152
a3nn4	a3nn	49153 - 65536
a3nn5	a3nn	65537 - 81920
a4nn1	a4nn	1 - 16384
a4nn2	a4nn	16385 - 32768
a4nn3	a4nn	32769 - 49152
a4nn4	a4nn	49153 - 65536
a4nn5	a4nn	65537 - 81920
a4nn6	a4nn	81921 - 98304
a4nn7	a4nn	98305 - 114688
a4nn8	a4nn	114689 - 131072
a5nn1	a5nn	1 - 16384
a5nn2	a5nn	16385 - 32768
a5nn3	a5nn	32769 - 49152
a5nn4	a5nn	49153 - 65536
a5nn5	a5nn	65537 - 81920
a5nn6	a5nn	81921 - 98304
a5nn7	a5nn	98305 - 114688
a5nn8	a5nn	114689 - 131072

4.2 Attractor reconstruction from heart beat series

HRV can also be defined as the time interval between successive R -peaks of an ECG. This definition of HRV is used here to construct an argument concerning the possibility of reconstructing an attractor from heart beat series. The heart beat series is defined in the current work as a sequence of consecutive R -peaks of an ECG. We now pose the question: Can the time intervals between two successive R -peaks be considered as phase space observable and therefore embedding theorems for the reconstruction of a phase space from scalar time series become valid? Before providing an answer to this question, note that time series generated from dynamical systems can be transformed into sequences of time intervals between relevant events [39]. In this study, it is assumed that the ECG signal is a series obtained from a dynamical system while relevant events are the R -peaks of the ECG signal. It can then be argued using theoretical results by Hegger and Kantz [32] that these time intervals are phase space observables and therefore embedding theorems are applicable. The ideas from [65] can then be employed to argue that it is possible to reconstruct an attractor from heart beat series. The next discussion concerns this.

Suppose there exist a dynamical system $\mathbf{x}' = \mathbf{F}(\mathbf{x}(t))$ such that the observed signal $x_i = x(t_i), i \in \mathbb{Z}^+$ is a function of the system's state $x_i = x(t_i) = h(\mathbf{x}(t))$. Embedding theorems by Takens [75] and Sauer *et al* [79] guarantee that delay vectors $\mathbf{z}(t) = \{x(t), x(t + \tau), \dots, x(t + (m - 1)\tau)\} = \boldsymbol{\eta}(\mathbf{x}(t))$ can be constructed. They also state that for a suitable m and τ on the system attractor, $\mathbf{z}$ will be a one-to-one function of the system state $\mathbf{x}(t)$ [79]. Specifically, knowing $\mathbf{z}$ one can in principle find $\mathbf{x}$. From this point of view, the heart beat series can be regarded as a particular observable resembling the Poincare section technique or an integrate and fire process [39]. The validity of this approach is the fundamental assumption that the duration on an interval is only a function of the state system at the beginning, that is $\Delta t = \phi(\mathbf{x}(t))$ [65]. It is then possible to construct a new dynamical system

$$\mathbf{x}_{l+1} = \mathbf{G}(\mathbf{x}_l), \quad (4.1)$$

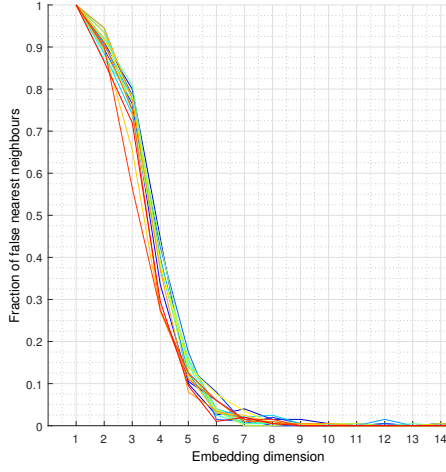
where $\mathbf{x}_l$ and $\mathbf{x}_{l+1}$ are the system phase vectors at the beginning and end of the heart beat series respectively. Under such assumptions for the newly constructed dynamical system described by Equation (4.1), Δt becomes the phase space observable [65]. Techniques from nonlinear dynamics and deterministic chaos can therefore be applied to provide information about the attractor of (4.1). Potapov [65] used the Lorenz model to demonstrate this. Castro and Sauer [14] also demonstrated that the approach works for neuron models such as the FitzHugh and Nagumo model.

4.3 Estimating embedding parameters

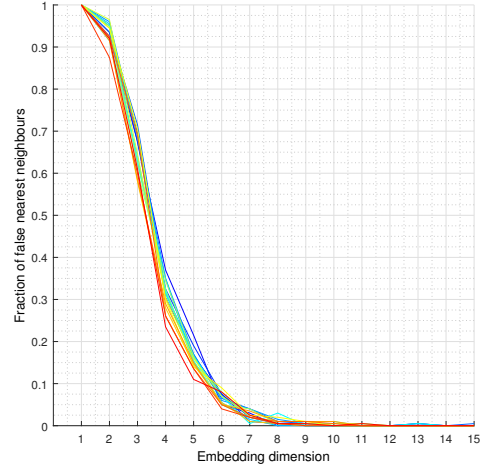
The claim made in the preceding subsection concerning the possibility of reconstructing an attractor from heart beat series is put in practice here. Since the heart beat series used in this study are a sequence of time intervals between successive R -peaks of an ECG, they can be categorised as interspike interval series [32, 39]. The interspike embedding theorem introduced previously then becomes applicable. The theorem basically ensures that attractors of time series which can be classified as interspike interval series such as the heart beat series can be reconstructed.

The embedding parameters required to reconstruct an attractor are the time delay τ and the minimum embedding dimension m . The time delay is used to compute the minimum embedding dimension and it is usually calculated first. According to the interspike interval embedding theorem [70] which our results are based on, $\tau = 1$ is enough as there is no explicit time delay involved in the case of interspike interval time series. This is true atleast in our study as different values of τ yielded the same embedding dimension as $\tau = 1$ (see Figures 4.1a , 4.2a and 4.3a when $\tau = 1$ and Figures 4.1b , 4.2b and 4.3b when $\tau = 9$). This study therefore adopts $\tau = 1$ as the time delay.

The technique of false nearest neighbours introduced previously was used to estimate the embedding dimension of the series provided by PhysioNet and the segments of length 16834 extracted from them. According to Kennel *et al* [42], any dimension that yields a fraction of false nearest neighbors below 0.01 is sufficient enough to be taken as the minimum embedding dimension. From Figures 4.1 and 4.3, when $m = 10$ the fraction of false nearest neighbours for the healthy and atrial fibrillation series together with segments extracted from them are atmost 0.01. From Figure 4.2, it can also be observed that when $m = 10$, the fraction of false nearest neighbors for almost all the heart failure series are 0.01. The embedding dimension of 10 was therefore selected as the required embedding dimension of all the heart beat series considered in this work.

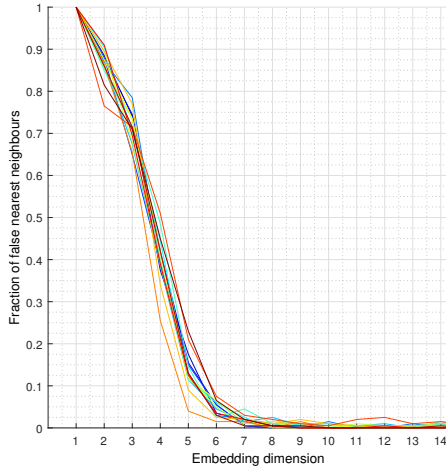


(a) $\tau = 1$

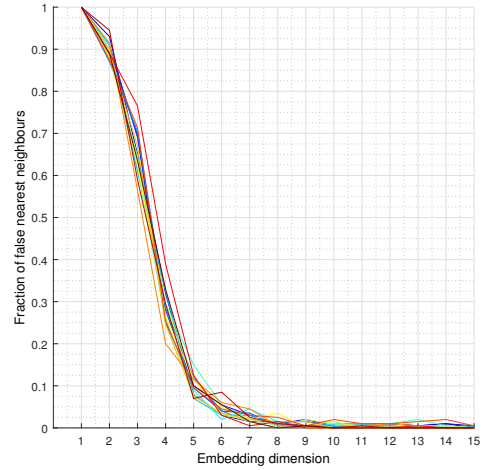


(b) $\tau = 9$

Figure 4.1: False nearest neighbour plots for heart beat series obtained from healthy individuals together with segments of length 16834 extracted from them $\tau = 1$ and $\tau = 9$. Notice that in both cases the fraction of false nearest neighbours for all the series is almost 0 when the embedding dimension is 10.



(a) $\tau = 1$



(b) $\tau = 9$

Figure 4.2: False nearest neighbour plots for heart beat series obtained from heart failure individuals together with segments of length 16834 extracted from them when $\tau = 1$ and $\tau = 9$. Observe that in both cases the fraction of false nearest neighbours for most of the series is almost 0 when the embedding dimension is 10.

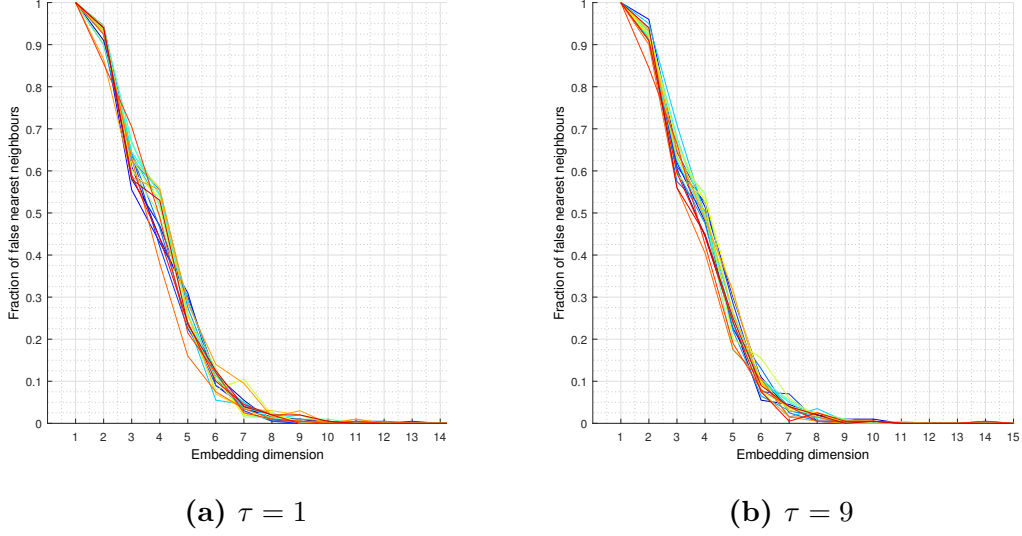


Figure 4.3: False nearest neighbour plots for heart beat series obtained from atrial fibrillation individuals together with segments of length 16834 extracted from them $\tau = 1$ and $\tau = 9$. It can be observed that in both cases the fraction of false nearest neighbours for all the series is almost 0 when the embedding dimension is 10.

4.4 Stationarity and Nonstationarity in Heart Rate Variability

The techniques and measures employed in this work to establish the presence of non-linear and/or chaotic dynamics in HRV require the series under investigation to be stationary in order to produce reliable results. It is therefore important to first search for stationary segments from the heart beat series used before any application of the methods and measures. The method of recurrence plots introduced previously is therefore applied to detect stationary epochs within the series documented in Tables (4.2) - (4.4). When producing recurrence plots, all the segments were embedded with the same embedding dimension and time delay. An embedding dimension of 10 and time delay of 1 are sufficient in this study (see Figures 4.1- 4.3). Furthermore, for each recurrence plot, a fixed recurrence threshold was used.

The ultimate goal in selecting recurrence threshold ϵ is having a balance between a very small threshold and a sufficient number of recurrences [57]. The threshold used is based on the rule of thumb that a recurrence threshold should be chosen such that it is less than 10% of the phase space diameter [59]. In our study, a recurrence threshold of 7.5% was used. For each considered segment, the phase space diameter was computed as the Euclidean distance of the difference between the maximum and minimum component of the segment's reconstructed attractor. A Theiler window w was also used in our

calculations to exclude temporarily correlated points when producing recurrence plots. A Theiler window refers to the minimum separation that nearest neighbours (points in the phase space) are supposed to have and it was chosen according to [26]. It is suggested in [26] that $w \geq (m - 1)\tau$ so in this work $w = 9$ is sufficient and is used.

4.4.1 Recurrence Plots of Healthy Subjects

Some of the recurrence plots produced from segments of heart beat series of healthy individuals are discussed in this subsection. Each recurrence plot is accompanied by a plot of the time series that it was produced from. A given time series is stationary if it has a homogenous recurrence plot. Furthermore, grey or black blocks along the line of identity in a recurrence plot indicate stationary epochs within the time series. In Figure 4.4(b) grey blocks can be observed along the line of identity. These blocks correspond to stationary epochs within the heart beat series. Large grey blocks are observed when the RR-interval number N is between 1 and 3000 and when it is between 8500 and 13500. It can be seen in the corresponding heart beat series in Figure 4.4(a) that these epochs are stationary.

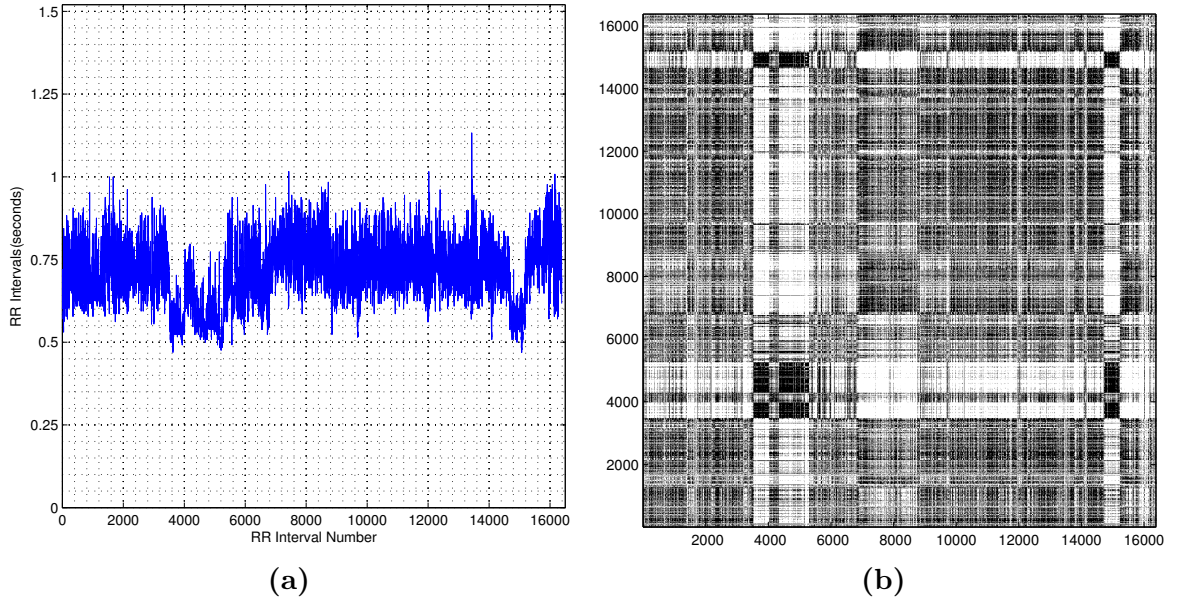


Figure 4.4: (a) A segment of length 16384 (n1nn3) obtained from RR-interval number 32769 – 49152 of the n1nn heart beat series. (b) The recurrence plot produced from the segment in (a) using $m = 10$, $\tau = 1$, $\epsilon = 0.0998$ and $w = 9$. The vertical and horizontal axes of the recurrence plot correspond to RR-interval numbers. Notice the grey blocks along the line of identity. These blocks are the stationary epochs in the corresponding segment. The largest of these blocks is observed when $8500 < N < 14500$.

Grey or black blocks of various sizes can also be observed in recurrence plots in Figures 4.5(b), 4.6(b), 4.7(b) and 4.8(b) (see Figures 4.5(a), 4.6(a), 4.7(a) and 4.8(a) for the corresponding heart beat series.). The largest of these blocks can be observed when N

is between 1 and 4200 in Figure 4.6(b). It worth mentioning that the epoch between 6000 and 16384 in Figure 4.6(b) is not stationary as a whole but contains subepochs which are stationary. One of these subepochs is between 12000 and 15000 (see Figure 4.4(a) for the corresponding heart rate series.). Disrupted recurrence plots can also be observed in Figures 4.5(b) and 4.7(b). These disruptions correspond to nonstationarities in the heart beat series as can be observed in Figures 4.5(a) and 4.7(a).

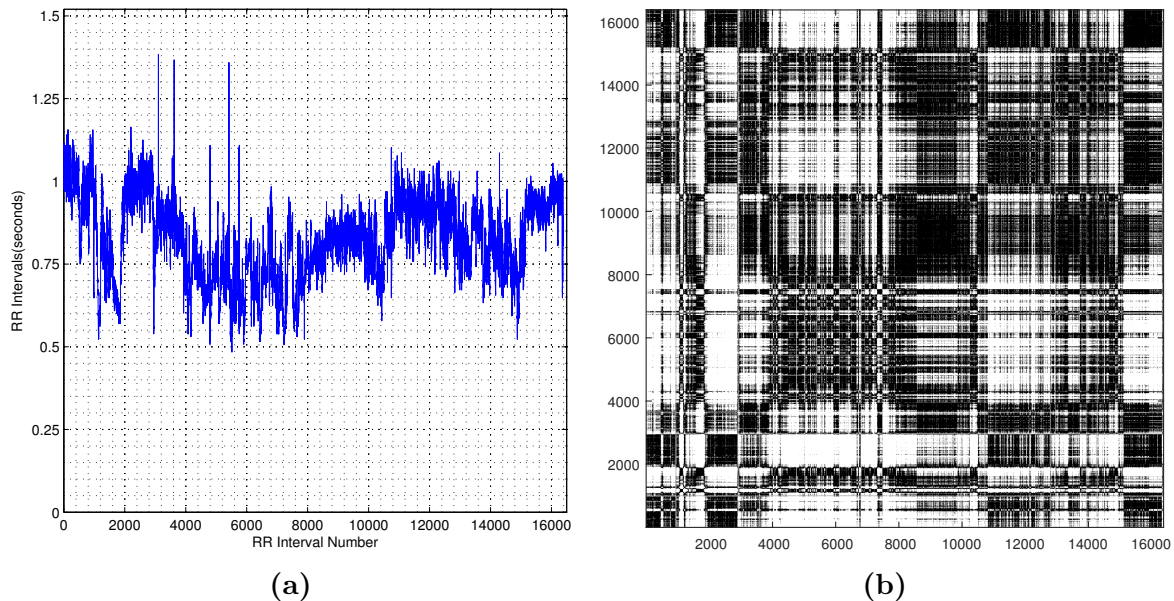


Figure 4.5: (a) A segment of length 16384 (n2nn2) obtained from RR-interval number 16385 – 32768 of the n2nn heart beat series. (b) The corresponding recurrence plot produced using $m = 10$, $\tau = 1$, $\epsilon = 0.1301$ and $w = 9$. The vertical and horizontal axes of the recurrence plot correspond to RR-interval numbers. The white bands in the recurrence plot correspond to transitions in the dynamics of heart rate variability. Small black blocks which corresponds to stationary epochs of small size can also be observed along the line of identity.

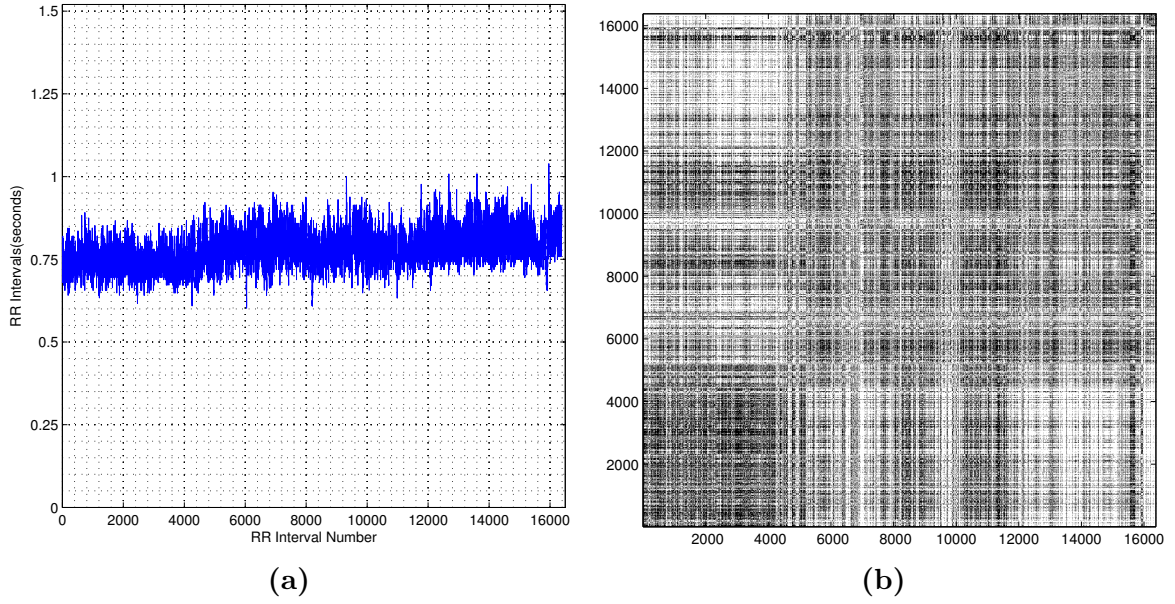


Figure 4.6: (a) A segment of length 16384 (n3nn3) obtained from RR-interval number 32769 – 49152 of the n3nn heart beat series. (b) The corresponding recurrence plot produced using $m = 10$, $\tau = 1$, $\epsilon = 0.0698$ and $w = 9$. The vertical and horizontal axes of the recurrence plot correspond to RR-interval numbers. A grey block can be observed when $1 \leq N \leq 4096$ indicating a stationary epoch in the corresponding segment. It has to be noted that the interval $4097 \leq N \leq 16384$ is not stationary as a whole but has some stationary subepochs. One of these subepochs is observed when $12000 < N < 15000$.

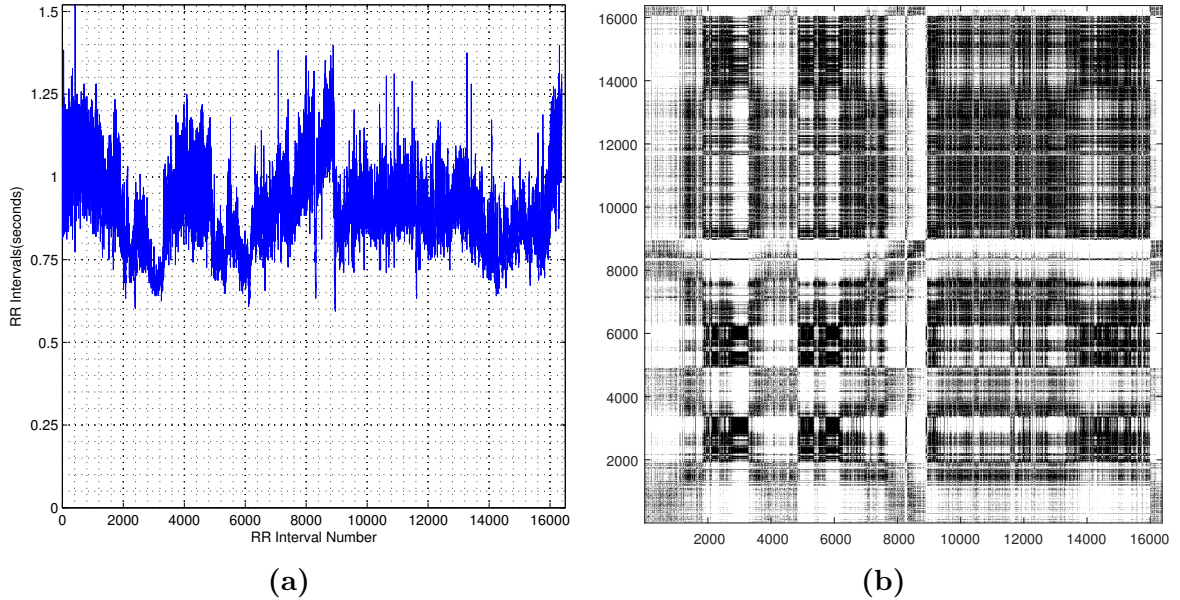


Figure 4.7: (a) A segment of length 16384 (n4nn4) obtained from RR-interval number 49153 – 65536 of the n4nn heart beat series. (b) The corresponding recurrence plot produced using $m = 10$, $\tau = 1$, $\epsilon = 0.1424$ and $w = 9$. The vertical and horizontal axes of the recurrence plot correspond to RR-interval numbers. White bands can be observed corresponding to transitions in the dynamics of heart rate variability.

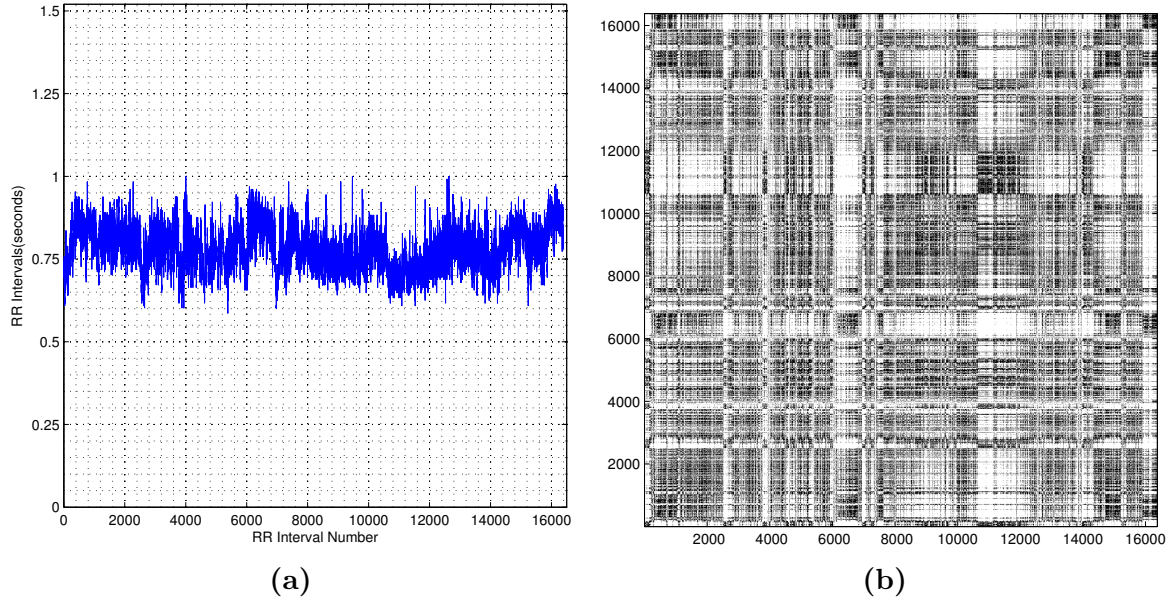


Figure 4.8: (a) A segment of length 16384 (n5nn2) obtained from RR-interval number 32769 – 49152 of the n5nn heart beat series. (b) The recurrence plot produced from the segment in (a) using $m = 10$, $\tau = 1$, $\epsilon = 0.0689$ and $w = 9$. The vertical and horizontal axes of the recurrence plot correspond to RR-interval numbers. Notice the small grey blocks along the line of identity. These blocks are stationary epochs of small size in the corresponding segment. The white bands corresponding to transitions in the dynamics of heart rate variability can be observed.

4.4.2 Recurrence Plots of Congestive Heart Failure Subjects

This subsection considers recurrence plots produced from heart beat series of congestive heart failure subjects. These recurrence plots are characterised by black blocks along the line of identity indicating stationary epochs (see Figures 4.9(b), 4.11(b), 4.12(b) and 4.13(b) for recurrence plots and 4.9(a), 4.11(a), 4.12(a) and 4.13(a) for the corresponding heart beat series.). Spikes in the heart beat series can be observed in the recurrence plots as white scratches. These spikes are an indication of nonstationarities in the time series. They also indicate sudden changes in the dynamics (see Figure 4.10 for the recurrence plot and its corresponding heart beat series.).

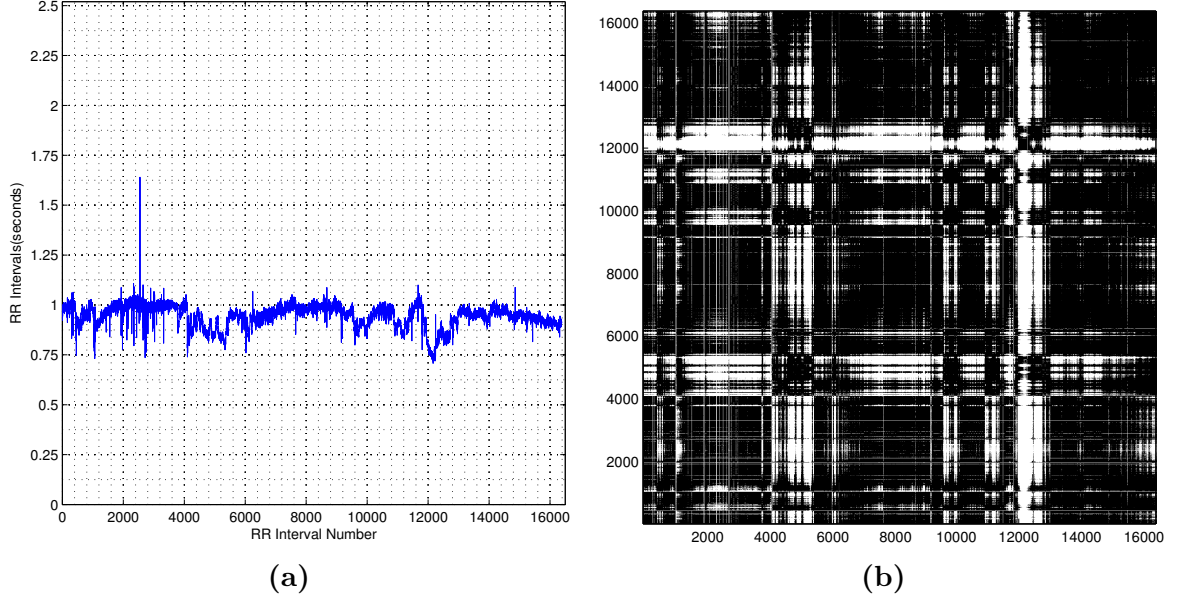


Figure 4.9: (a) A segment of length 16384 (c1nn2) obtained from RR-interval number 16385 – 32768 of the c1nn heart beat series. (b) The recurrence plot produced from the segment in (a) using $m = 10$, $\tau = 1$, $\epsilon = 0.0891$ and $w = 9$. The vertical and horizontal axes of the recurrence plot correspond to RR-interval numbers. Black blocks corresponding to stationary epochs can be observed along the line of identity. White bands which correspond to transitions in the dynamics of heart rate variability can also be observed.

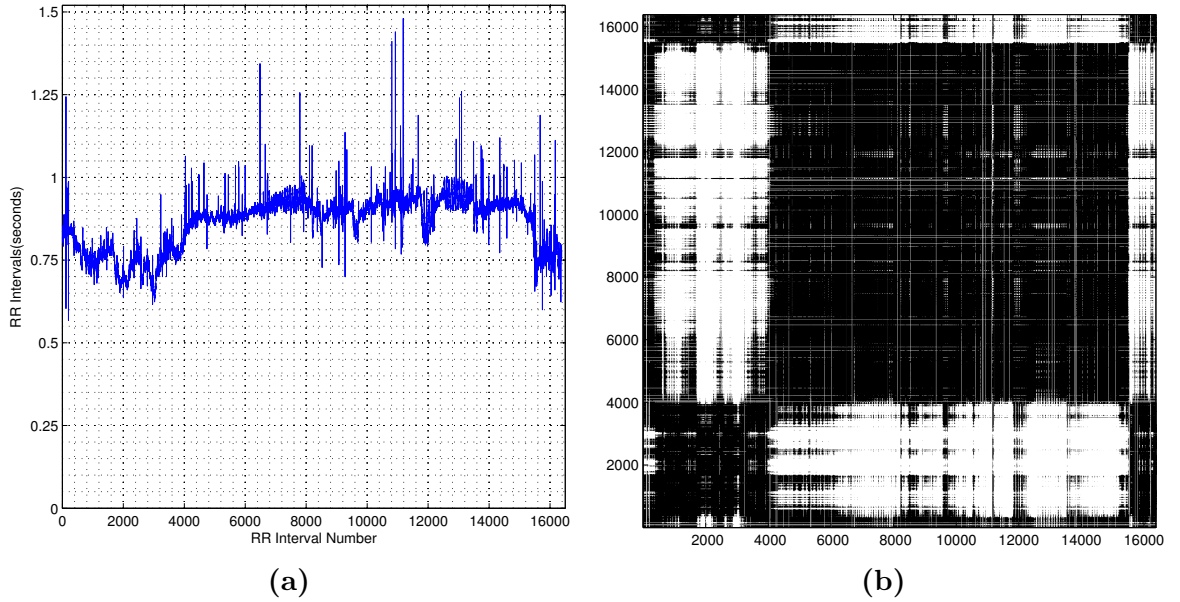


Figure 4.10: (a) A segment of length 16384 (c2nn3) obtained from RR-interval number 32769 – 49152 of the c2nn heart beat series. (b) The corresponding recurrence plot produced from using $m = 10$, $\tau = 1$, $\epsilon = 0.0979$ and $w = 9$. The vertical and horizontal axes of the recurrence plot correspond to RR-interval numbers. Spikes in the heart beat series are characterised by the thin white lines in the recurrence plot. The white lines indicate nonstationarities in the time series. Notice the white bands corresponding to transitions in the dynamics of heart rate variability.

The recurrence plot in Figure 4.11(b), is characterised by 4 blocks along the line of identity separated by horizontal and vertical white bands. The white bands correspond to sudden transitions in the dynamics of heart rate variability. The black blocks indicate stationary epochs in the heart beat series (see Figure 4.11(a) for the corresponding heart beat series.). The largest stationary epoch is between 3500 and 11500. In Figure 4.11(a) this epoch is well defined. Another large stationary epoch can be observed between 10200 and 15500 in Figure 4.12(b) (see Figure 4.12(a) for the corresponding heart beat series.). White horizontal and vertical bands can also be observed in Figure 4.12(b). They indicates sudden transtions in the dynamics of heart rate variability as mentioned before. The recurrence plot in Figure 4.13(b) can be described in a similar way to that in Figure 4.11(b) and 4.12(b).

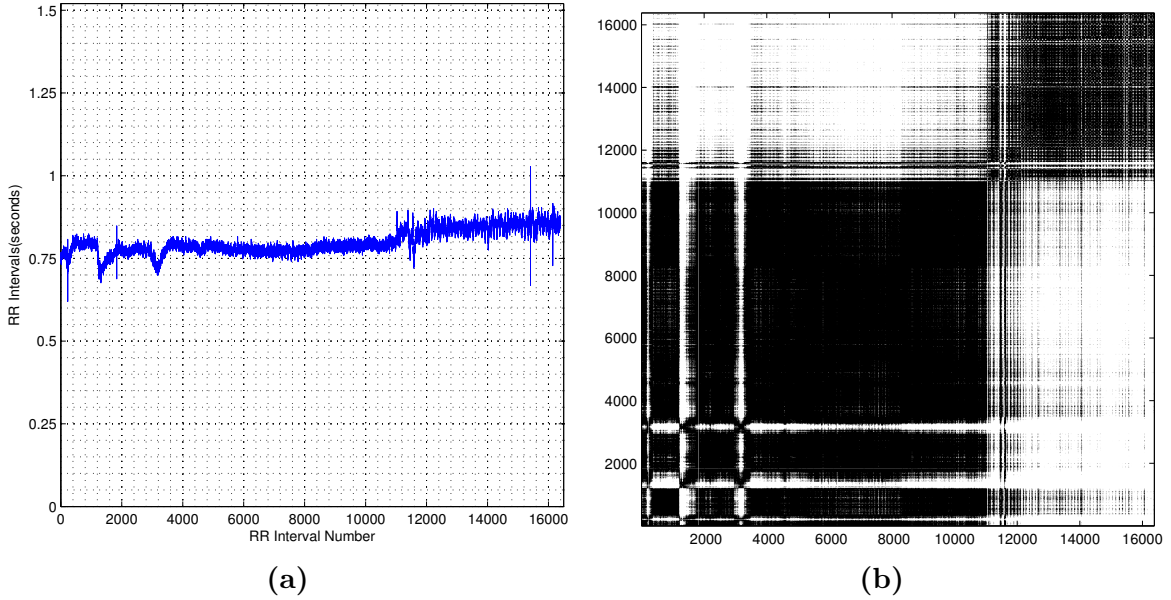


Figure 4.11: (a) A segment of length 16384 (c3nn4) obtained from RR-interval number 49153 – 65536 of the c3nn heart beat series. (b) The corresponding recurrence plot produced using $m = 10$, $\tau = 1$, $\epsilon = 0.0419$ and $w = 9$. The vertical and horizontal axes of the recurrence plot correspond to RR-interval numbers. Notice the black blocks along the line of identity separated by white bands. These blocks are the stationary epochs in the corresponding segment while the white bands indicate transitions in dynamics of heart rate variability. The largest of these blocks is observed when $3500 < N < 11000$.

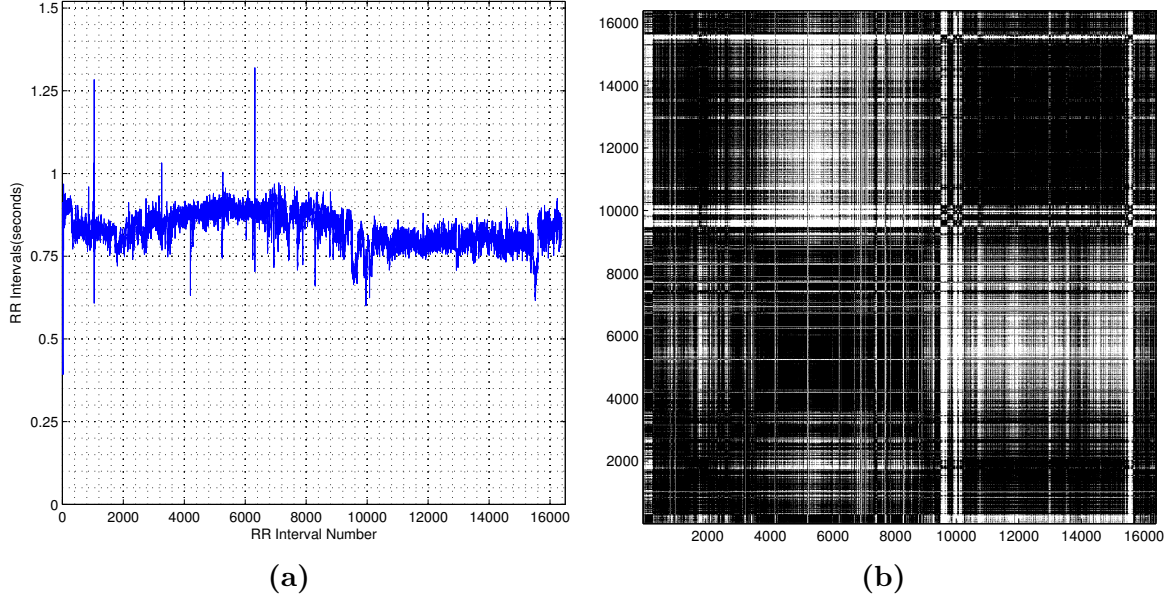


Figure 4.12: (a) A segment of length 16384 (c4nn1) obtained from RR-interval number 1–16384 of the c4nn heart beat series. (b) The corresponding recurrence plot produced using $m = 10$, $\tau = 1$, $\epsilon = 0.0806$ and $w = 9$. The vertical and horizontal axes of the recurrence plot correspond to RR-interval numbers. Thin white lines which indicate nonstationarities in the time series can be observed in the recurrence plot. A large black block can be noticed along the line of identity when $10000 < N < 15500$. This block corresponds to a stationary epoch in the segment.

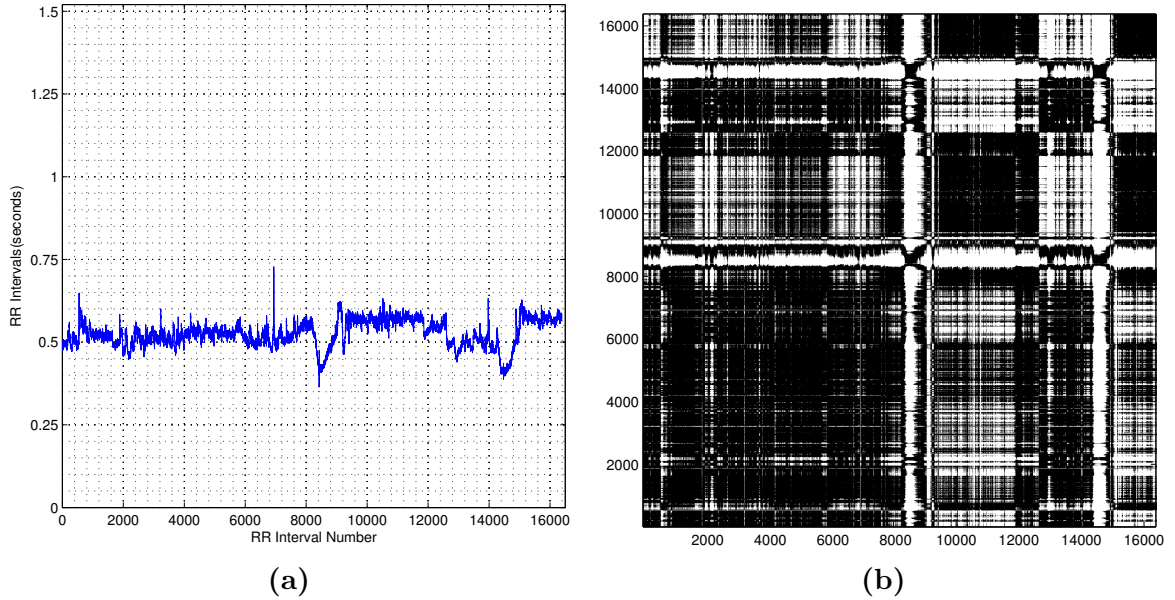


Figure 4.13: (a) A segment of length 16384 (c5nn4) obtained from RR-interval number 49153–65536 of the c5nn heart beat series. (b) The corresponding recurrence plot produced using $m = 10$, $\tau = 1$, $\epsilon = 0.0485$ and $w = 9$. The vertical and horizontal axes of the recurrence plot correspond to RR-interval numbers. Notice black blocks of varying sizes along the line of identity. These blocks are the stationary epochs in the corresponding segment. White bands which corresponds to transitions in dynamics of heart rate variability can also be observed.

4.4.3 Recurrence Plots of Atrial Fibrillation Subjects

In this subsection recurrence plots obtained from heart beat series of atrial fibrillation subjects are discussed. Almost all the recurrence plots in this subsection are homogenous. Homogenous recurrence plots indicate that the dynamics are stationary (see Figure 4.15(b), 4.17(b) and 4.18(b) for recurrence plots and Figure 4.15(a), 4.17(a) and 4.18(a) for the corresponding heart beat series.). In Figure 4.16(b) we notice 2 grey blocks along the line of identity which indicates stationary epochs. The largest of these epochs is between 1 and 8000 (see Figure 4.16(a) for the corresponding heart beat series.).

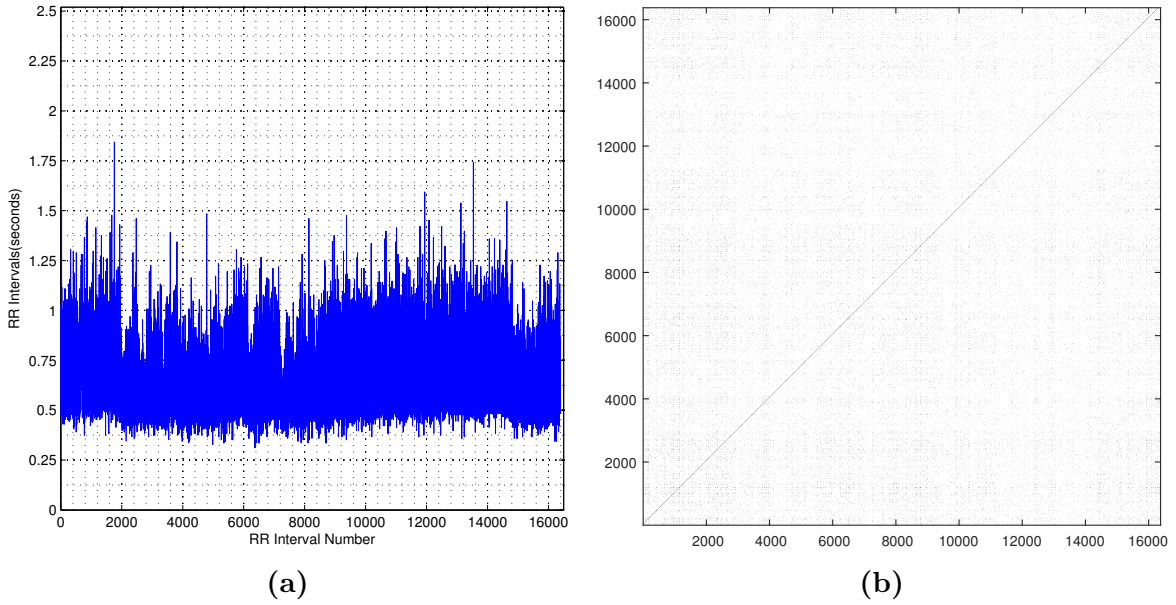


Figure 4.14: (a) A segment of length 16384(a1nn6) obtained from RR-interval number 81921 – 98304 of the a1nn heart beat series. (b) The recurrence plot produced from the segment in (a) using $m = 10$, $\tau = 1$, $\epsilon = 0.1502$ and $w = 9$. The vertical and horizontal axes of the recurrence plot correspond to RR-interval numbers. Notice how the points are uniformly distributed throughout the recurrence plot. This means the segment under consideration is stationary.

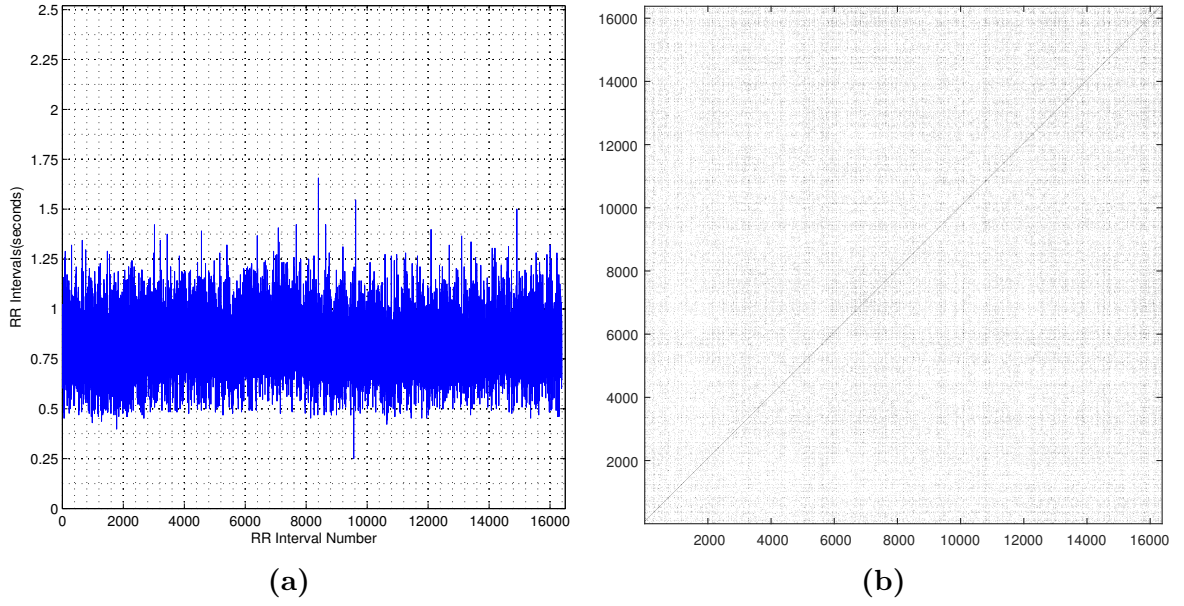


Figure 4.15: (a) A segment of length 16384(a2nn3) obtained from RR-interval number 32769 – 49152 of the a2nn heart beat series. (b) The corresponding recurrence plot produced using $m = 10$, $\tau = 1$, $\epsilon = 0.1200$ and $w = 9$. The vertical and horizontal axes of the recurrence plot correspond to RR-interval numbers. The recurrence plot is homogenous which means the corresponding heart beat series is stationary.

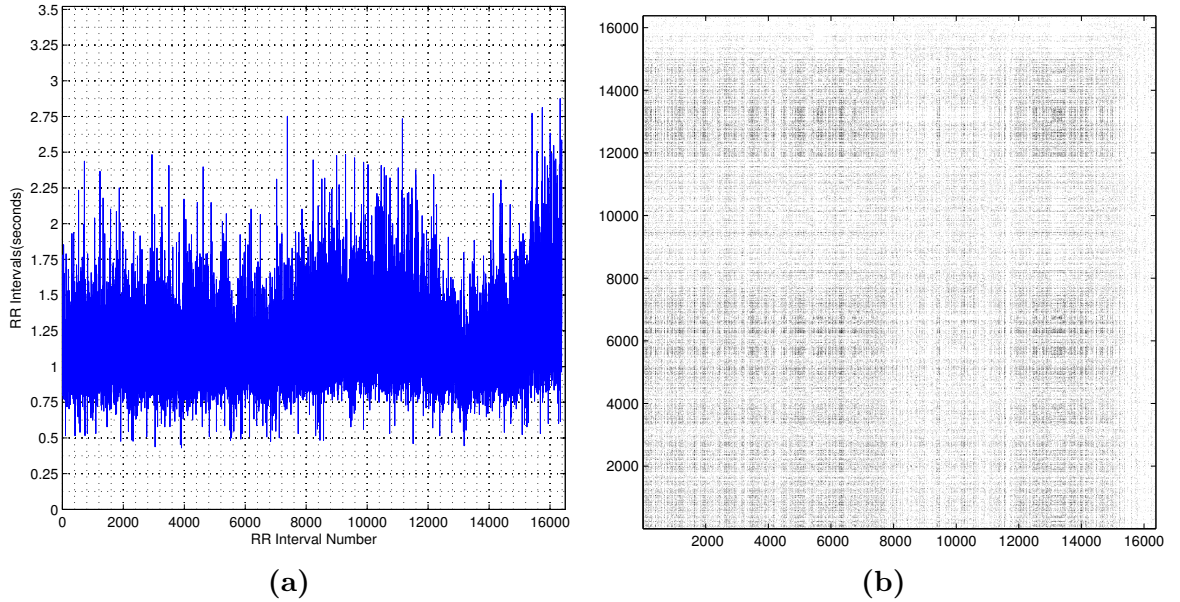


Figure 4.16: (a) A segment of length 16384(a3nn4) obtained from RR-interval number 49153 – 65536 of the a3nn heart beat series. (b) The recurrence plot produced from the segment in (a) using $m = 10$, $\tau = 1$, $\epsilon = 0.2423$ and $w = 9$. The vertical and horizontal axes of the recurrence plot correspond to RR-interval numbers. Notice blocks of varying greyness along the line of identity. These blocks indicate stationary epochs in the corresponding segment. The largest stationary epoch can be observed when $1 < N < 8000$.

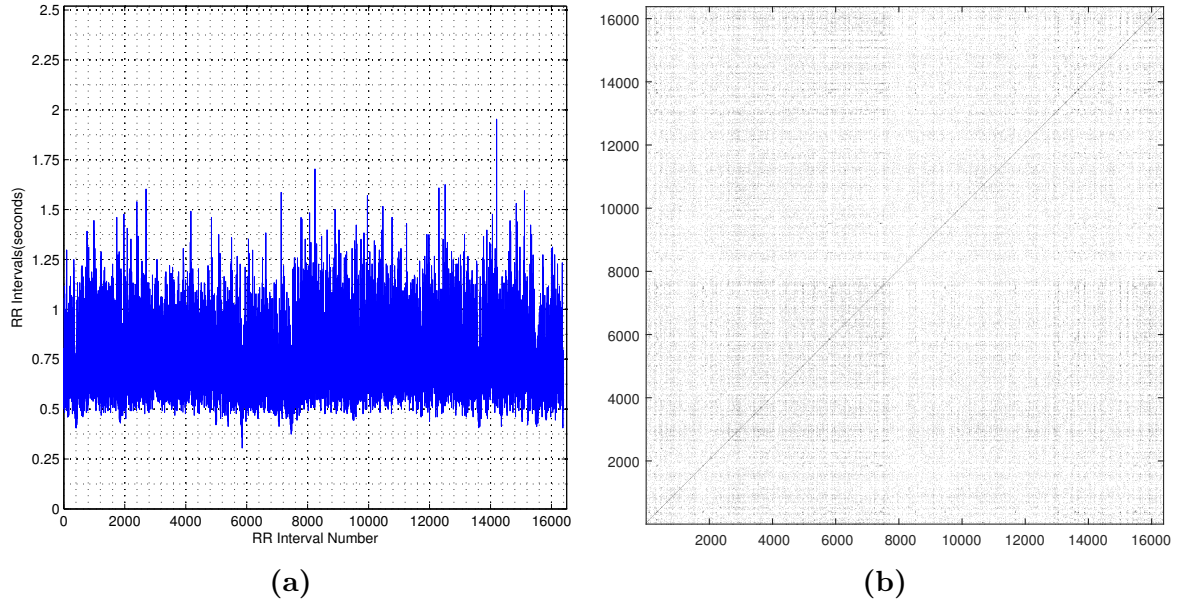


Figure 4.17: (a) A segment of length 16384(a4nn6) obtained from RR-interval number 81921 – 98304 of the a4nn heart beat series. (b) The corresponding recurrence plot produced using $m = 10$, $\tau = 1$, $\epsilon = 0.1442$ and $w = 9$. The vertical and horizontal axes of the recurrence plot correspond to RR-interval numbers. The points are uniformly distributed throughout the recurrence plot indicating that the segment under consideration is stationary.

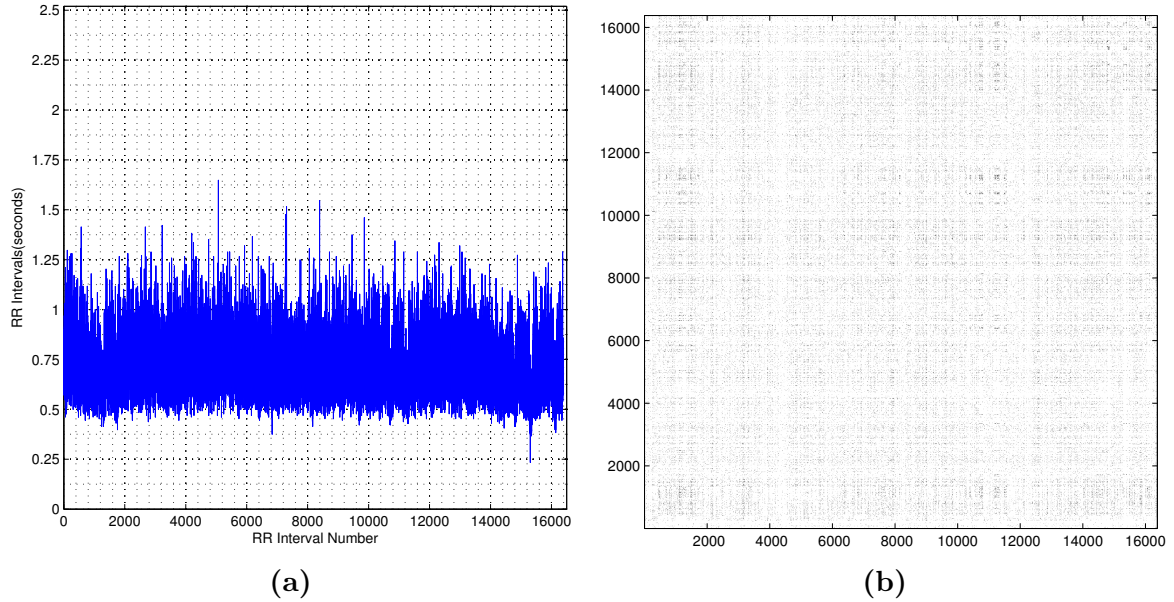


Figure 4.18: (a) A segment of length 16384(a5nn6) obtained from RR-interval number 81921 – 98304 of the a5nn heart beat series. (b) The corresponding recurrence plot produced using $m = 10$, $\tau = 1$, $\epsilon = 0.1229$ and $w = 9$. The vertical and horizontal axes of the recurrence plot correspond to RR-interval numbers. The recurrence plot is homogenous which means the corresponding heart beat series is stationary.

4.5 Linerity And Nonlinearity in Heart Rate Variability

This section aims to establish if the stationary epochs determined from Section 4.4 are nonlinear or not. Understanding if these epochs are nonlinear is crucial because nonlinearity is a requirement for chaos which we also aim to establish from the provided heart rate time series in Section 4.6. It is also important to detect whether the stationary epochs are nonlinear or not because it allows us to know when linear time series analysis techniques such as spectral analysis are capturing or failing to capture all the information in a time series [40]. The technique of surrogate data testing detailed in Chapter 3 is used in this section to determine whether the stationary epochs from Section 4.4 are nonlinear or not.

The surrogate data testing technique involves specifying a null hypothesis H_0 and generating surrogate time series similar to the original time series but consistent with H_0 . In the present work, the null hypothesis H_0 is such that a given stationary epoch is generated by a Gaussian linear stochastic process which may be distorted by a static (instantaneous) function h . The function h may be linear or nonlinear and monotonic or non monotonic [44]. The presence of linear dynamics in the stationary epoch is only accounted for by the Gaussian process while the function h accomodates deviations from the Gaussian marginal distribution [44].

We used the *IAAFT* algorithm [39] to generate 250 surrogates for each stationary epoch considered. The consistency of the surrogate time series to the null hypothesis is determined by the preservation of the marginal probability distribution and linear correlations of the original time series [44]. By construction, the marginal probability distribution of the surrogates is the same as that of the original time series. The algorithm used approximated the linear correlations well (see Figures (4.19) - (4.21)). False rejection of the null hypothesis when discriminating statistics sensitive to linear correlations are used is therefore not expected.

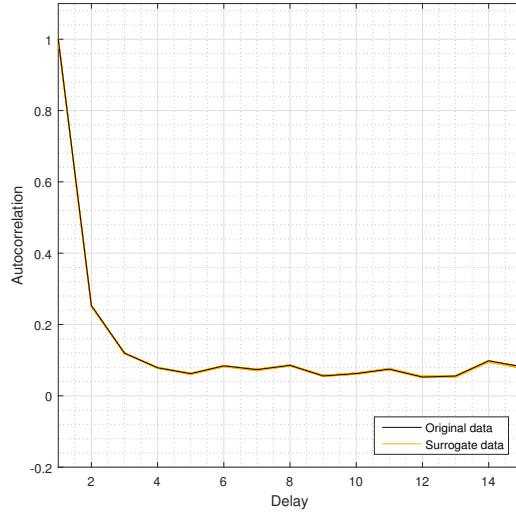


Figure 4.19: Autocorrelation against time delay τ for the stationary epoch obtained from the RR-interval number 2001 – 7000 of the a1nn1a (black line) segment and its surrogates (orange portion). Observe how the autorrelation of the surrogates match those of the original stationary epoch. We do not expect false rejections of the null hypothesis when discriminating statistics sensitive to linear correlations such as mutual information are used.

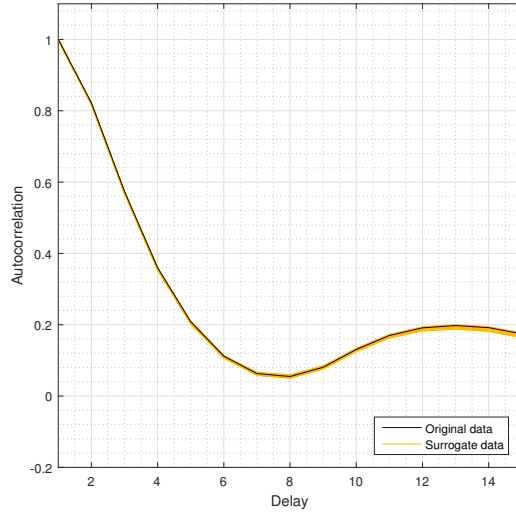


Figure 4.20: Autocorrelation against time delay τ for the stationary epoch obtained from the RR-interval number 8801 – 13500 of the n1nn3b (black line) segment and its surrogates (orange portion). Observe how the autorrelation of the surrogates match those of the original stationary epoch. We do not expect false rejections of the null hypothesis when discriminating statistics sensitive to linear correlations such as mutual information are used.

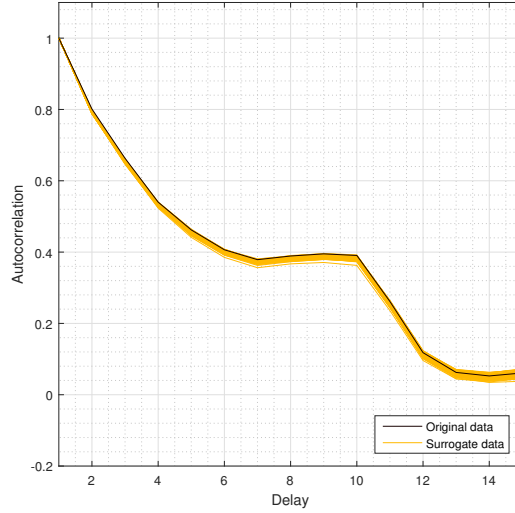


Figure 4.21: Autocorrelation against time delay τ for the stationary epoch obtained from the RR-interval number 2001 – 4000 of the c4nn5a (black line) segment and its surrogates (orange portion). Observe how the autorrelation of the surrogates match those of the original stationary epoch. We do not expect false rejections of the null hypothesis when discriminating statistics sensitive to linear correlations such as mutual information are used.

The mutual information I , the value of a radius ϵ_0 that corresponds to a given correlation sum $C(\epsilon_0)$ and a third order autocorrelation function ϕ^{rev} are used as discriminating statistics. The mutual information measures both the linear and nonlinear correlation in a time series. The third order autocorrelation function detects any deviations from time reversibility for a given heart beat series. The correlation sum $C(\epsilon_0, N)$ was fixed to a value of 0.5 in all our computations.

In order to reject or accept H_0 , a discriminating statistic is computed for each stationary epoch and the surrogate time series generated from it. Suppose a_0 is the statistic computed from the original stationary epoch and $a_1, \dots, a_M$ are the statistics computed from M generated surrogates consistent with H_0 . Using a two sided test based on a distribution free approach, the null hypothesis H_0 is rejected if a_0 is less than the $\frac{\alpha}{2}$ quantile or greater than the $1 - \frac{\alpha}{2}$ quantile of the set $\{a_0, \dots, a_M\}$ for a given significance level α . We used a two sided test, $M = 250$ and $\alpha = 0.05$ in our computations. The null hypothesis was rejected if a_0 was in the first or last 6 positions of the rank ordered sequence $\{a_0, \dots, a_M\}$.

The results obtained for the stationary segments considered in the present work are in Tables (4.5) - (4.7). The $\checkmark$ means the null hypothesis has been rejected while $\times$ means it is not rejected. Notice that based on the criteria used in this work almost all the segments from healthy subjects considered in Table (4.5) are nonlinear. The opposite is observed in Table (4.7) where the null hypothesis was not rejected in most the segments from the atrial fibrillation subjects.

Table 4.5: Nonlinearity test for stationary segments extracted from data sets of healthy subjects

Stationary segments	Length	ϕ^{rev}	ϵ_0	I
n1nn3a	3500	✓	✗	✓
n1nn3b	4700	✓	✓	✓
n2nn3a	2000	✓	✓	✓
n2nn3b	1634	✓	✓	✓
n3nn3a	4000	✓	✓	✓
n3nn3b	2500	✓	✓	✓
n3nn4a	2500	✓	✓	✓
n4nn2a	2500	✗	✓	✗
n4nn3a	1700	✗	✓	✓
n4nn5a	2884	✓	✓	✓
n5nn4a	2000	✓	✓	✗

Table 4.6: Nonlinearity test for stationary segments extracted from data sets of congestive heart failure subjects

Stationary segments	Length	ϕ^{rev}	ϵ_0	I
c3nn3a	1800	✓	✓	✗
c3nn3b	2000	✓	✓	✓
c3nn4a	4400	✓	✗	✗
c3nn4b	2000	✓	✗	✓
c4nn3a	1800	✓	✓	✓
c4nn5a	2000	✓	✗	✓
c5nn1a	2000	✓	✓	✓
c5nn2a	2000	✓	✓	✓
c5nn3a	2384	✗	✓	✗
c5nn5a	1600	✓	✗	✓

Table 4.7: Nonlinearity test for stationary segments extracted from data sets of atrial fibrillation subjects

Stationary segments	Length	ϕ^{rev}	ϵ_0	I
a1nn1a	5000	✓	✓	✓
a1nn3a	3500	✓	✗	✓
a1nn4a	4000	✓	✓	✓
a2nn1a	2000	✓	✗	✓
a2nn3a	3000	✗	✗	✓
a2nn6a	2500	✗	✗	✓
a3nn2a	2200	✗	✗	✓
a4nn1a	3000	✗	✗	✗
a4nn3a	3000	✗	✗	✗
a4nn6a	3000	✗	✗	✗
a5nn2a	2000	✗	✗	✗
a5nn4a	2000	✗	✓	✗

4.6 Chaos in Heart Rate Variability

This section attempts to answer the question of whether the human heart rate is chaotic or not. In particular, the heart rate time series which have been established to be stationary and nonlinear from Section 4.4 and 4.5 respectively are further tested for chaos. The maximal Lyapunov exponent and correlation dimension detailed in Chapter 3 are computed from each stationary and nonlinear epoch to determine the chaotic nature and dimensionality respectively.

The maximal Lyapunov exponent quantifies the average rate of divergence of two trajectories that are initially close to each other. Correlation dimension on the other hand quantifies the number of degrees of freedom that govern the observed dynamics of the system. If a given dynamical system is deterministic, we have $C(\epsilon, N) \approx \epsilon^{D_2}$ where D_2 is the correlation dimension [46]. In our computations, embedding dimensions varying from 5 to 16 and a time delay of 1 were used to produce different plots to estimate the maximal Lyapunov exponent and correlation dimension of each segment. A Theiler window w was also used in our calculations to exclude temporarily correlated points when estimating the correlation dimension and maximal Lyapunov exponent.

The results obtained for the nonlinear stationary segments determined in this work are shown in Table (4.8). When computing both correlation dimension and maximal Lyapunov exponent it was ensured that scaling region was over several scales. The measures of time series analysis (MATS) software by Kuguimtzis [46] and the algorithm by Rosenstein *et al* [69] which takes the scaling region into consideration when computing D_2 and λ_1 respectively were used. The scaling region refers to a portion

in which the logarithmic graph of $C(\epsilon, N)$ vs ϵ or $\log \Delta n$ vs time (steps) have almost parallel straight lines. The average of the gradients of the almost parallel straight lines gives an estimate of λ_1 for the graph $\log \Delta n$ vs time (steps) and D_2 for the logarithmic graph of $C(\epsilon, N)$ vs ϵ .

The criteria suggested by Eckmann and Ruelle [22] that $2 \log N \geq D_2$, where N is the length of the series, was employed in this work to check the validity of the correlation dimensions obtained. Notice from Table (4.8) that according to this criteria, the results obtained hold except for the c3nn3b segment. From the results obtained in Table (4.8), λ_1 seem to converge to positive values at higher dimensions for most of the segments from healthy and atrial fibrillation subjects. In case of segments from congestive heart failure subjects, the results point to low dimensional chaos in all but one segment. The criteria that $D_2 \geq 5$ implies higher dimensions and the condition that $D_2 < 5$ and $\lambda_1 \geq 0$ implies an operational definition of low dimensional chaos [10] were adopted when interpreting the results from Table (4.8).

Table 4.8: Correlation dimension (D_2) and maximal Lyapunov exponent (λ_1) for nonlinear stationary segments

Nonlinear stationary			
segments	Length	D_2	λ_1
n1nn3b	4700	6.350 ± 0.452	0.067 ± 0.001
n2nn3a	2000	6.334 ± 0.452	0.055 ± 0.001
n2nn3b	1634	1.080 ± 0.086	0.058 ± 0.001
n3nn3b	2500	6.128 ± 0.446	0.065 ± 0.001
n3nn4a	2500	5.789 ± 0.432	0.049 ± 0.001
n4nn5a	2884	6.369 ± 0.389	0.054 ± 0.001
c3nn3b	2000	7.608 ± 0.230	0.042 ± 0.001
c4nn3a	1800	2.017 ± 0.184	0.057 ± 0.001
c5nn1a	2000	1.529 ± 0.112	0.066 ± 0.001
c5nn2a	2000	2.029 ± 0.170	0.067 ± 0.001
a1nn1a	5000	6.026 ± 0.634	0.045 ± 0.001
a1nn4a	4000	6.305 ± 0.479	0.043 ± 0.001

Chapter 5

Conclusions and Further Work

We shall here draw the main conclusions from this thesis. Our main objective was to characterise the nature of the dynamics of the human heart rate variability from three different groups: normal, congestive heart failure and atrial fibrillation subjects. This was particularly done by using heart rate time series provided by PhysioNet, and nonlinear time series analysis techniques such as recurrence plots to answer the questions which were as follows: Are the dynamics of the human heart rate variability stationary or nonstationary? Are they linear or nonlinear? If they are nonlinear are they chaotic?

Recurrence plots were used to explore the stationarity of heart rate variability from the time series provided and break it down into epochs within which the dynamics are understood to be stationary. Using the technique of surrogate data testing, stationary epochs were checked to determine if they are nonlinear. The maximal Lyapunov exponent and correlation dimension were computed to determine the chaotic nature and dimensionality respectively. The results obtained indicate that the dynamics of heart rate variability are generally nonstationary. Nevertheless, stationary epochs corresponding to abrupt changes in the dynamics were found in some cases. The dynamics of healthy subjects were found to be nonlinear. Some of the dynamics of the atrial fibrillation and congestive heart failure subjects were found to be nonlinear while others could not be classified by the technique used. The maximal lyapunov exponents computed for various nonlinear stationary epochs seem to converge to positive values at higher dimensions. The correlation dimension estimates also point to both low and high dimensional systems.

Using recurrence plots, it was possible to distinguish healthy subjects from the atrial fibrillation and congestive heart failure subjects. Since only a small set of heart rate time series was considered, it would be interesting to see if recurrence plots can distinguish normal heart rates from abnormal ones if a large set of heart rate time series is considered. This can be significant as recurrence plots have a potential of discrimi-

nating patients with healthy hearts from those with unhealthy ones. It was also noted that correlation dimension and maximal Lyapunov estimates of healthy subjects were higher than those of congestive heart failure and atrial fibrillation subjects. However, a large set of heart rate time series is worth investigating further to see if correlation dimension and maximal Lyapunov estimates of healthy subjects can still be higher than those of congestive heart failure and atrial fibrillation subjects. Whether maximal Lyapunov exponent and correlation dimension estimates can have any potential clinical application is debatable because of the many factors that affect their computations. As future work, it would be interesting to establish if the dynamics of heart rate variability admits a chaotic model. Finally, since the technique of surrogate data testing failed to characterise the dynamics of some of the congestive heart failure and atrial fibrillation subjects, an alternative approach is worth applying to try and characterise these subjects.

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