

## Review: Nonlinear Techniques for Analysis of Heart Rate Variability

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**Abstract:** - Heart rate variability (HRV) is a measure of the balance between sympathetic mediators of heart rate that is the effect of epinephrine and norepinephrine released from sympathetic nerve fibres acting on the sino-atrial and atrio-ventricular nodes which increase the rate of cardiac contraction and facilitate conduction at the atrio-ventricular node and parasympathetic mediators of heart rate that is the influence of acetylcholine released by the parasympathetic nerve fibres acting on the sino-atrial and atrio-ventricular nodes leading to a decrease in the heart rate and a slowing of conduction at the atrio-ventricular node. Sympathetic mediators appear to exert their influence over longer time periods and are reflected in the low frequency power (LFP) of the HRV spectrum (between 0.04Hz and 0.15 Hz). Vagal mediators exert their influence more quickly on the heart and principally affect the high frequency power (HFP) of the HRV spectrum (between 0.15Hz and 0.4 Hz). Thus at any point in time the LFP:HFP ratio is a proxy for the sympatho- vagal balance. Thus HRV is a valuable tool to investigate the sympathetic and parasympathetic function of the autonomic nervous system. Study of HRV enhance our understanding of physiological phenomenon, the actions of medications and disease mechanisms but large scale prospective studies are needed to determine the sensitivity, specificity and predictive values of heart rate variability regarding death or morbidity in cardiac and non-cardiac patients. This paper presents the linear and nonlinear to analysis the HRV.

**Key- Words:** -Heart Rate Variability, Physiology of Heart Rate Variability, Nonlinear techniques.

### I. INTRODUCTION

Heart rate variability (HRV) is the temporal variation between sequences of consecutive heart beats. On a standard electrocardiogram (ECG), the maximum upwards deflection of a normal QRS complex is at the peak of the R-wave, and the duration between two adjacent R-wave peaks is termed as the R-R interval. The ECG signal requires editing before HRV analysis can be performed, a process requiring the removal of all non sinus-node originating beats. The resulting period between adjacent QRS complexes resulting from sinus node depolarizations is termed the N-N (normal-normal) interval. HRV is the measurement of the variability of the N-N intervals [1].

One example will be used throughout the following sections to explain morevisually, if possible, what the technique does and how it can be calculated onthetachogram. The chosen example is given in (Fig.1),

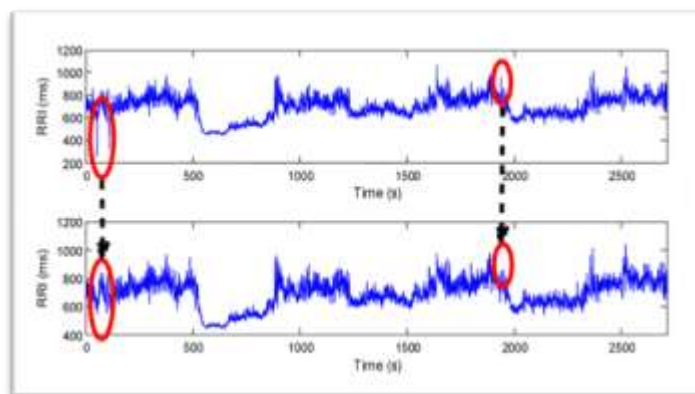
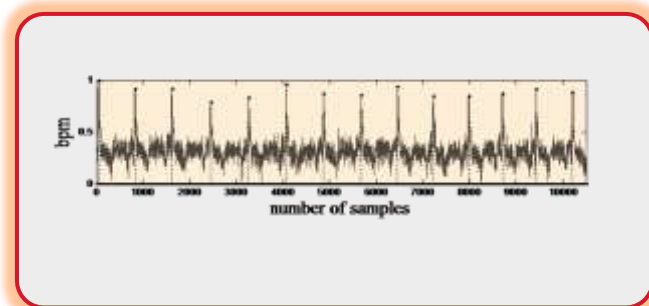


Figure 1 Thetachogram used as example [2].

being an RR intervaltime series extracted from an ECG signal monitored during a stress test. Thetachogram has a length of 2712 seconds (45 minutes) containing 3984 heart beats.. As indicated in the figure, some irregular or faulty RR intervalswere corrected this way, changing the shortest RR interval from 256 ms to 443ms. In other words, the impossible instantaneous heart rate of 234 bpm in suchcondition was corrected by the preprocessing algorithm to a maximal instantaneousheart rate of 135 bpm which was probably correct.The linear time and frequency domain techniques for HRV were standardized ina report of the Task Force of the European Society

of Cardiology and the North American Society of Pacing and Electrophysiology [2]. And another example is the normal case of HRV shown in **fig. 2**.



**Figure 2** Heart rate variation of a normal subject [3].

## II. Physiology of Heart Rate Variability

Heart rate variability, that is, the amount of heart rate fluctuations around the mean heart rate [4] is produced because of the continuous changes in the sympathetic-parasympathetic balance that in turn causes the sinus rhythm to exhibit fluctuations around the mean heart rate. Frequent small adjustments in heart rate are made by cardiovascular control mechanisms. This results in periodic fluctuations in heart rate. The main periodic fluctuations found are respiratory sinus arrhythmia and baroreflex-related and thermoregulation-related heart rate variability [5]. Due to inspiratory inhibition of the vagal tone, the heart rate shows fluctuations with a frequency equal to the respiratory rate [6]. The inspiratory inhibition is evoked primarily by central irradiation of impulses from the medullary respiratory to the cardiovascular center. In addition, peripheral reflexes due to hemodynamic changes and thoracic stretch receptors contribute to respiratory sinus arrhythmia. This is parasympathetically mediated [7]. Therefore, HRV is a measure of the balance between sympathetic mediators of the heart rate (HR) i.e. the effect of epinephrine and norepinephrine released from sympathetic nerve fibres, acting on the sino-atrial and atrioventricular nodes, which increase the rate of cardiac contraction and facilitate conduction at the atrioventricular node and parasympathetic mediators of HR i.e. the influence of acetylcholine released by the parasympathetic nerve fibres, acting on the sino-atrial and atrioventricular nodes, leading to a decrease in the HR and a slowing of conduction at the atrioventricular node. Sympathetic mediators appear to exert their influence over longer time periods and are reflected in the low-frequency power (LFP) of the HRV spectrum [8]. Vagal mediators exert their influence more quickly on the heart and principally affect the high-frequency power (HFP) of the HRV spectrum. Thus, at any point in time, the LFP:HFP ratio is a proxy for the sympatho-vagal balance.

## III. Nonlinear techniques

The cardiac system is dynamic, nonlinear, and nonstationary, with performance continually fluctuating on a beat-to-beat basis as extrinsic and intrinsic factors simultaneously influence the state of the system [9, 10]. Due to the assumptions and conditioning requirements, linear analyses may not account for all aspects of cardiac performance, particularly the subtle interactions between the control mechanisms that regulate cardiac function [11]. Analysis techniques arising from nonlinear system dynamics theory were therefore developed to ascertain the multidimensional processes that control the cardiac system [12].

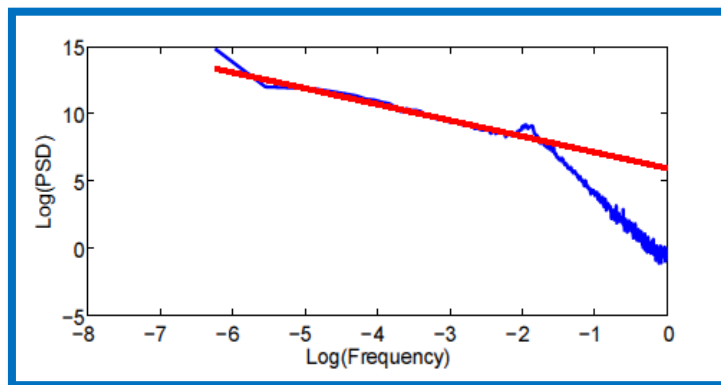
A nonlinear system is mathematically defined as a second- or higher-order power system, meaning that the independent variable in the mathematical equation contains an exponent. For example, the equation for a parabola,  $y = x^2$ , describes a simple nonlinear system. Whereas in a linear system the variables produce an output response, in a nonlinear system the variables contribute to the output response. Although a linear system can be decomposed into its component parts, in a nonlinear system, the parts interfere, cooperate, or compete with each other. A small change dramatically alters the nonlinear system because the initial condition of all variables along with the input stimulus influences the output response. Nonlinear system dynamics theory allows for the mathematical reconstruction of an entire system from one known variable since the reconstructed dynamics are geometrically similar to the original dynamics [13]. Chaos theory, which was popularized by Gleick's best-selling book [14], is a specialized subtheory of nonlinear system dynamics that describes systems that are low-dimensional (3 to 5 variables), have defined boundaries, and exhibit sensitive dependence on initial conditions. This theory alerted scientists to the value of mathematical error and physiological noise when describing a system's behavior [15]. Small differences in initial conditions (such as those due to rounding errors in numerical computation) yield widely diverging outcomes for chaotic systems, rendering long-term prediction impossible in general. This happens even though these systems are deterministic, meaning that their future

behavior is fully determined by their initial conditions, with no random elements involved. In other words, the deterministic nature of these systems does not make them predictable. This behavior is known as deterministic chaos, or simply chaos. Also, with sinus rhythm, deterministic behavior is exhibited during a cardiac cycle and stochastic behavior between cardiac cycles [15]. Consequently, analysis techniques based on the broader nonlinear system dynamics theory have been used to explain and account for the nonlinearity of the high-dimensional cardiac system. Numerous nonlinear analysis techniques exist.

Several commonly used nonlinear techniques will be explained now. Some recent review papers discussing nonlinear HRV are Acharya et al [16] and Voss et al [17].

### 3.1 $\frac{1}{f}$ slope

Kobayashi and Musha [18] first reported the frequency dependence of the power spectrum of RR interval fluctuations. The plots had an uneven density that might overweight for data in the higher-frequency range. Therefore, a logarithmic interpolation is used, resulting in a balanced number of points for linear interpolation. The slope of the regression line of the  $\log(\text{power})$  versus  $\log(\text{frequency})$  relation ( $1/f$ ), usually calculated in the  $10^{-4}$ – $10^{-2}$  Hz frequency range, corresponds to the negative scaling exponent  $\beta$  and provides an index for long-term scaling characteristics [19]. **Fig.3** indicates the  $(1/f)^\beta$  relation between PSD and frequency, reflected on a log–log scale approximately as a line. The figure is the result for the example used throughout this chapter, leading to a  $1/f$  slope of  $-1.34$ .



**Figure 3** *Log(power) versus log(frequency) plot of the tachogram example given in (Fig.1). The thick line indicates the  $1/f$  slope or scaling exponent  $\beta$  and is derived as the regression line calculated in the  $10^{-4}$ – $10^{-2}$  Hz frequency range.*

This broadband spectrum, characterizing mainly slow HR fluctuations indicates a fractal-like process with a long-term dependence [20]. Saul et al [19] found that  $\beta$  is similar to  $-1$  in healthy young men. This linearity of the regression line and the slope of  $-1$  in healthy persons mean that the plots of RR-interval versus time over 2 minutes ( $10^{-2}$  Hz), 20 minutes ( $10^{-3}$  Hz) and 3 hours ( $10^{-4}$  Hz) may appear similar. This is called scale-invariance or self-similarity in fractal theory. It has been suggested that the scale invariance may be a common feature of normal physiological function. The breakdown of normal physiological functioning could lead to either random or periodic behavior, indicated by steeper  $1/f$  slopes, which could lead to a more vulnerable state of homeostasis. Bigger et al [21] reported an altered regression line ( $\beta \approx -1.15$ ) in patients after MI. A disadvantage of this measure is the need for large datasets. Moreover, stationarity is not guaranteed in long datasets and artefacts and patient movement influence spectral components.

### 3.2 Fractal dimension

The term 'fractal' was first introduced by Mandelbrot [22]. A fractal is a set of points that when looked at smaller scales, resembles the whole set. An essential characteristic of a fractal is self-similarity. This means that its details at a certain scale are similar, but not necessarily identical, to those of the structure seen at larger or smaller scales. A simple mathematical example illustrating the self-similarity property is the Koch curve (**Fig.4**).

The concept of fractal dimension (FD) that refers to a non-integer or fractional dimension originates from fractal geometry. The FD emerges to provide a measure of how much space an object occupies between Euclidean dimensions. The FD of a waveform represents a powerful tool for transient detection. This feature has been used in the analysis of ECG and EEG to identify and distinguish specific states of physiological function. Several algorithms are available to determine the FD of the waveform, amongst others the algorithms proposed by Higuchi and Katz. From a practical point of view, one often estimates the FD via the box-counting method. The higher the FD, the more irregular the signal.

### 3.2.1 Algorithm of Katz

According to the method of Katz [23] the FD of a curve can be defined as

$$D^{Katz} = \frac{\log(L)}{\log(d)} \quad (1)$$

where L is the total length of the curve or sum of distances between successive points, and d is the diameter estimated as the distance between the first point of the sequence and the most distal point of the sequence. Mathematically, d can be expressed as:

$$d = \max(\|x(1) - x(i)\|) \forall i \quad (2)$$

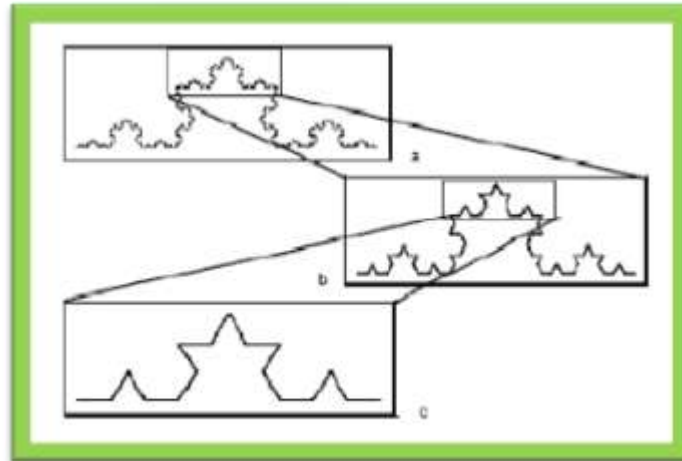


Figure 4 An illustration of how fractals look like with the feature of scale independence and self-similarity: (a) the Koch curve and (b and c) details of the top of the curve.

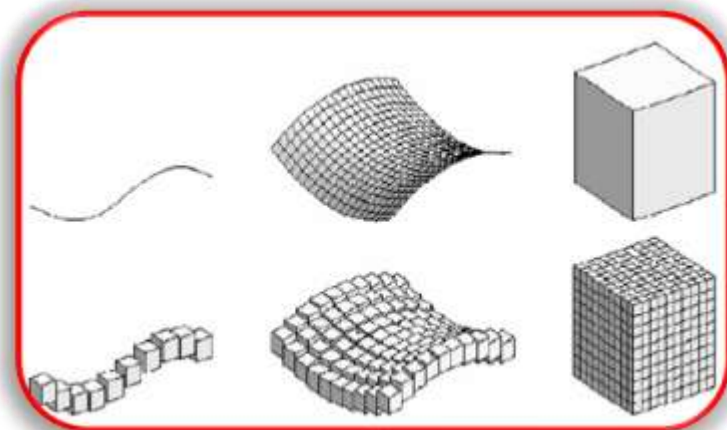
Considering the distance between each point of the sequence and the first, point  $i$  is the one that maximizes the distance with respect to the first point. The FD compares the actual number of units that compose a curve with the minimum number of units required to reproduce a pattern of the same spatial extent. FDs computed in this fashion depend upon the measurement units used. If the units are different, then so are the FDs. Katz approach solves this problem by creating a general unit or yardstick: the average step or average distance between successive points,  $a$ . Normalizing the distances,  $D^{katz}$  is then given by

$$FD = \frac{\log(\frac{L}{a})}{\log(\frac{d}{a})} \quad (3)$$

### 3.2.2 Box-counting method

What is the relationship between an object's length (or area or volume) and its diameter? The answer to this question leads to another way to think about dimension. Let us consider a few examples (Fig.5). If one tries to cover the unit square with little squares of side length  $\epsilon$ , one will need  $1/\epsilon^2$  boxes. To cover a segment of length 1, you only need  $1/\epsilon$  little squares. If the little cubes are used to cover a  $1 \times 1 \times 1$  cube,  $1/\epsilon^3$  is needed. Note that the exponent here is the same as the dimension. This is no coincidence, but the general rule is:

$$N_\epsilon(S) \sim \frac{1}{\epsilon^d} \text{ as } \epsilon \rightarrow 0 \quad (4)$$

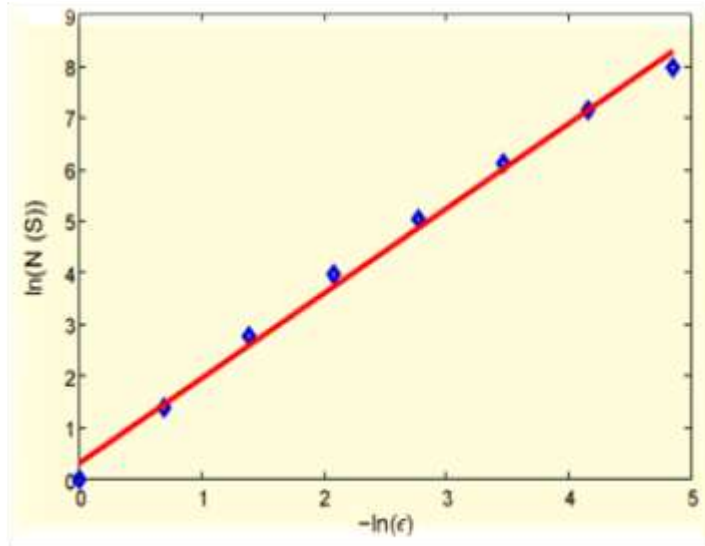


**Figure 5 Principle of box-counting algorithm [25].**

where  $\epsilon$  is the length of a box or square,  $S$  the full dataset and  $N_\epsilon(S)$  the minimum number of  $n$ -dimensional boxes needed to cover  $S$  fully.  $d$  is the dimension of  $S$ . This way, the FD can be estimated via a box-counting algorithm as proposed by Barabasi and Stanley [24] as follows:

$$FD = \lim_{\epsilon \rightarrow 0} \frac{\ln N_\epsilon(S)}{\ln \epsilon} \quad (5)$$

One also refers to the fractal dimension as the box-counting dimension or shortly box dimension. Given the standard RR interval time series as example (Fig. 1), the relation between the number of boxes and the box size is shown in (Fig. 6), resulting in a FD equal to 1.6443.



**Figure 6** Illustration of the box-counting method applied on the tachogram example given in (Fig.1). First a 2D plane is built based on the dataset  $S$ , here consisting of both the RR intervals and corresponding time points. The number of boxes in that plane containing points of the dataset is counted and given by  $N_\epsilon(S)$ . This depends on the size of the boxes, namely  $\epsilon$ . This relation is represented in a  $\ln - \ln$  scale by the rhombuses. The line is the best fit through these points and the slope of the line reflects the fractal dimension.

### 3.3 Detrended fluctuation analysis

Detrended fluctuation analysis (DFA) is used to quantify the fractal scaling properties of short interval signals. This technique is a modification of root-mean-square analysis of random walks applied to nonstationary signals [26]. The root-mean-square fluctuation of an integrated and detrended time series is measured at different observation windows and plotted against the size of the observation window on a log-log scale. First, the RR interval time series  $x$  (of total length  $N$ ) is integrated as follows:

$$y(k) = \sum_{i=1}^k |x(i) - x_{average}| \quad (6)$$

where  $y(k)$  is the  $k^{\text{th}}$  value of the integrated series,  $x(i)$  is the  $i^{\text{th}}$  RR interval and  $x_{average}$  is the mean of the RR intervals over the entire series. Then, the integrated time series is divided into windows of equal length  $n$ . In each window of length  $n$ , a least-squares line is fitted to the data, representing the trend in that window as shown in (Fig.7(a)). The y-coordinate of the straight line segments are denoted by  $y_n(k)$ . Next, the integrated time series is detrended,  $y_n(k)$ , in each window. The root-mean-square fluctuation of this integrated and detrended series is calculated using the equation:

$$F(n) = \sqrt{\frac{1}{N} \sum_{k=1}^N [y(k) - y_n(k)]^2} \quad (7)$$

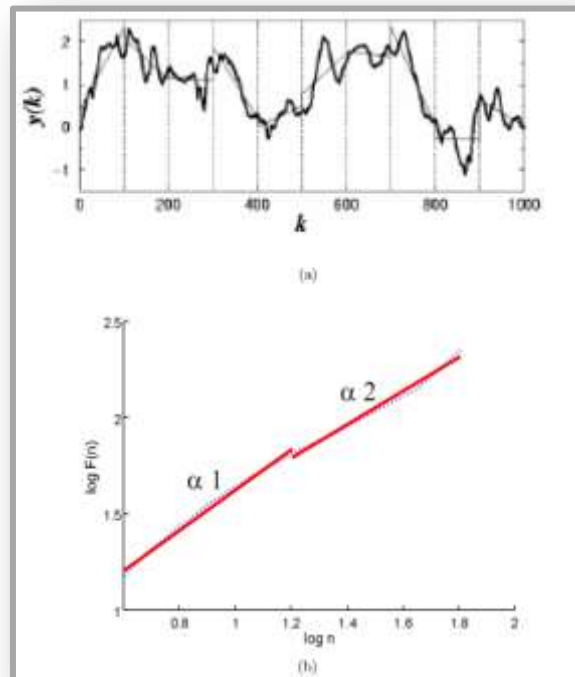


Figure 7 The principle of detrended fluctuation analysis (DFA).

This computation is repeated over all time scales (window sizes) to obtain the relationship between  $F(n)$  and the window size  $n$  (the number of points, here RR intervals, in the window of observation). Typically,  $F(n)$  will increase with window size. The scaling exponent DFA  $\alpha$  indicates the slope of this line, which relates  $\log(\text{fluctuation})$  to  $\log(\text{window size})$  as visualized in (Fig.7(b)). This method, based on a modified random walk analysis, was introduced and applied to physiological time series data. DFA usually involves the estimation of a short-term fractal scaling exponent  $\alpha_1$  over the range of  $4 \leq n \leq 16$  heart beats and a long-term scaling exponent  $\alpha_2$  over the range of  $16 \leq n \leq 64$  heart beats. Figure 7(b) shows the DFA plot for the HR example, where DFA  $\alpha_1$  is 1.0461 and DFA  $\alpha_2$  is 0.8418.

Healthy subjects revealed a scaling exponent of approximately 1, indicating fractal-like behavior. Patients with cardiovascular disease showed reduced scaling exponents, suggesting a loss of fractal-like HR dynamics ( $\alpha_1 < 0.85$  [28];  $\alpha_1 < 0.75$  [26]). From many studies on test signals, one had the following ranges:

- $0 < \alpha < 0.5$ : power-law anti-correlations are present such that large values are more likely to be followed by small values and vice versa.
- $\alpha = 0.5$ : indicates white noise.
- $0.5 < \alpha < 1$ : power-law correlations are present such that large values are more likely to be followed by large values and vice versa. The correlation is exponential.
- $\alpha = 1$ : special case corresponding to  $1/f$  noise.
- $\alpha > 1$ : correlations exist, but cease to be of a power-law form.
- $\alpha = 1.5$ : indicates Brownian noise.

The  $\alpha$  exponent can also be viewed as an indicator of the 'roughness' of the original time series: the larger the value of  $\alpha$ , the smoother the time series. In this context,  $1/f$  noise can be interpreted as a compromise or 'tradeoff' between the complete unpredictability of white noise (very rough 'landscape') and the much smoother landscape of Brownian noise.

It is important to note that DFA can only be applied reliably on time series of at least 2000 data points. DFA as such is a mono-fractal method, but also multi-fractal analysis exists [29]. This multifractal analysis describes signals that are more complex than those fully characterized by a mono-fractal model, but it requires many local and theoretically infinite exponents to fully characterize their scaling properties.

### 3.4 Approximate entropy and sample entropy

Entropy refers to system randomness, regularity, and predictability and allows systems to be quantified by rate of information loss or generation. Approximate Entropy (ApEn) quantifies the entropy of the system. More

specifically, it measures the likelihood that runs of patterns that are close will remain close for subsequent incremental comparisons. An intuitive presentation is shown in (Fig. 8). It was calculated according to the formula of Pincus [30]:

$$ApEn(m, r, N) = \frac{1}{N-m+1} \sum_{i=1}^{N-m+1} \log C_i^m(r) - \frac{1}{N-m} \sum_{i=1}^{N-m} \log C_i^m(r) \quad (8)$$

where

$$C_i^m(r) = \frac{1}{N-m+1} \sum_{j=1}^{N-m+1} \theta(r - \|x_i - x_j\|) \quad (9)$$

is the correlation integral with  $\theta$  the Heavyside step function.  $x_i$  and  $x_j$  are respectively the  $i^{\text{th}}$  and  $j^{\text{th}}$  RR interval from the tachogram of length  $N$ . The values of the input variables are chosen fixed, namely  $m = 2$  and  $r = 0.2$  as suggested by Goldberger et al [31] ( $m$  being the length of compared runs and  $r$  the tolerance level). High values of ApEn indicate high irregularity and complexity in time-series data.

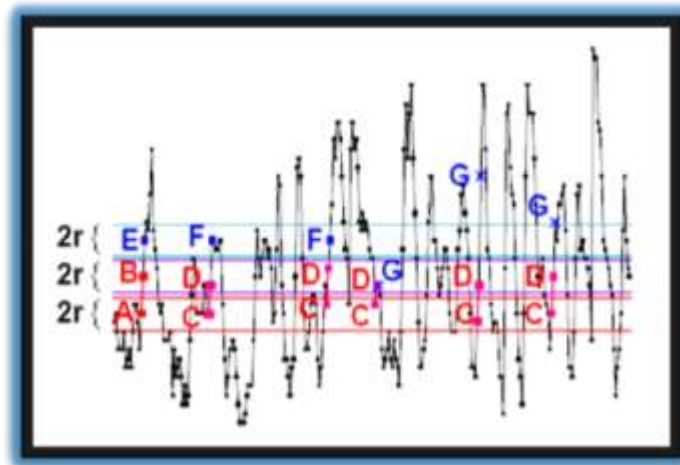
Sample Entropy (SampEn) was developed by Richman and Moorman [32] and is very similar to the ApEn, but there is a small computational difference. In ApEn, the comparison between the template vector and the rest of the vectors also includes comparison with itself. This guarantees that probabilities  $C_i^m(r)$  are never zero. Consequently, it is always possible to take a logarithm of probabilities. Because template comparisons with itself lower ApEn values, the signals are interpreted to be more regular than they actually are. These self-matches are not included in SampEn leading to probabilities  $C_i^m(r)$ :

$$C_i^m(r) = \frac{1}{N-m+1} \sum_{j=1}^{N-m+1} \theta(r - \|x_i - x_j\|) \quad j \neq i \quad (10)$$

Finally, sample entropy is defined as:

$$SampEn(m, r, N) = -\ln \left[ \frac{\varphi^m(r)}{\varphi^{m+1}(r)} \right] \quad (11)$$

SampEn measures the complexity of the signal in the same manner as ApEn. However, the dependence on the parameters  $N$  (number of points) and  $r$  is different. SampEn decreases monotonically when  $r$  increases. In theory, SampEn does not depend on  $N$  where ApEn does. In analyzing time series including  $<200$  data points, however, the confidence interval of the results is unacceptably large. For entropy measures, stationarity is required. In addition, outliers such as missed beats and artefacts may affect the entropy values. The sample entropy of the tachogram example given in (Fig.1) is 4.4837.



**Figure 8. Intuitive presentation of the principle of Approximate Entropy (ApEn) and Sample Entropy (SampEn).** For a two dimensional vector  $AB$ , the tolerance level  $r$  can be represented by horizontal red and violet lines around point  $A$  and  $B$  respectively, with width of  $2r \cdot SD$ . Then all vectors, say  $CD$ , whose first and second points (respectively  $C$  and  $D$ ) are within the tolerance ranges of  $A$  and  $B$  ( $\pm r \cdot SD$ ), are counted to measure within a tolerance level  $r$  the regularity, or frequency, of patterns similarly to a given pattern of  $AB$ . In the figure, five  $CD$  vectors are close to vector  $AB$ . When increasing vector dimension from 2 to 3 ( $ABE$ ), two vectors, namely  $CDF$ , remain close while the other three vectors,  $CDG$ , show emerging patterns. Thus the likelihood of remaining close is about  $2/5$ . It is clear that such likelihood tends to 1 for regular series, and produces  $ApEn = 0$  when taking the logarithm, while it tends to 0 for white noise and results in infinite  $ApEn$  theoretically. From [33].

### 3.5 Correlation dimension

To describe the complexity of a system, often a transition is needed from the time domain to the so called phase space. In mathematics and physics, a phase space is a space in which all possible states of a system are represented, with each possible state of the system corresponding to one unique point in the phase space. In a phase space, every degree of freedom or parameter of the system is represented as an axis of a multidimensional

space. For every possible state of the system, or allowed combination of values of the system's parameters, a point is plotted in the multidimensional space. Often this succession of plotted points is analogous to the system's state evolving over time. In the end, the phase space represents all that the system can be, and its shape can easily elucidate qualities of the system that might not be obvious otherwise. A phase space may contain many dimensions. The correlation dimension (CD) can be considered as a measure for the number of independent variables needed to define the total system, here the cardiovascular system generating the RR interval time series, in phase space [34].

Before explaining how CD is calculated from a tachogram, the terms attractor, trajectory and attractor reconstruction has to be clarified. An attractor is a set towards which a dynamical system evolves over time. That is, points that get close enough to the attractor remain close even if slightly disturbed. Geometrically, an attractor can be a point, a curve, a surface (called a manifold), or even a complicated set with a fractal structure known as a strange attractor. Describing the attractors of chaotic dynamical systems has been one of the achievements of chaos theory. A trajectory of the dynamical system in the attractor does not have to satisfy any special constraints except for remaining on the attractor. The trajectory may be periodic or chaotic or of any other type. For experimental and naturally occurring chaotic dynamical systems as the cardiovascular system is, the phase space and a mathematical description of the system are often unknown. Attractor reconstruction methods have been developed as a means to reconstruct the phase space and develop new predictive models. One or more signals from the system, here the RR interval time series reflecting heart rate, must be observed as a function of time. The time series are then used to build an approach of the observed states.

Correlation dimension analysis of HRV signals is based on the method of Grassberger and Procaccia [35]. As always, we start with a tachogram or RR interval time series  $x(t)$  of data points  $x_i = x(t_i)$  and  $i = 1 \dots N$  (the number of heart beats in the signal) (**Fig.1**). Next, an attractor reconstruction takes place. The reconstructed trajectory,  $X$ , can be expressed as a matrix where each row is a phase space vector,  $X = (x_1 \ x_2 \ \dots \ x_M)^T$ . For a time series of length  $N$ ,  $\{x_1, x_2, \dots, x_N\}$ , each  $x_i$  is given by  $x_i = (x_i, x_{i+\tau}, x_{i+2\tau}, \dots, x_{i+(m-1)\tau})$ .

The parameters  $m$  and  $\tau$  are respectively called the embedding dimension and the time delay. The time delay for the CD is the value of the first zero crossing of the normalized (mean = 0 and standard deviation = 1) autocorrelation function of the time series and the time axis. The embedding dimension is usually varied increasingly between the values 2 and 30. The distances between the reconstructed trajectories  $x_i$  and  $x_j$  ( $i, j = 1 \dots N$  and  $i < j$ ) are calculated and the total range of these distances is divided into discrete intervals, presented by  $r$ . Based on these distances, the correlation integral  $C^m(r)$ , as already defined in equation (9), is calculated as a function of  $r$  and this for successive values of  $m$ . As for a chaotic signal the relation  $C^m(r) \sim r^{CD}$  holds, CD can be derived by plotting  $C^m(r)$  versus  $r$  in a  $\ln - \ln$  scale. This is visualized in (**Fig.9(a)**) for different values of the embedding dimension  $m$ . Next, calculating the slope of such a curve results theoretically in the CD, but as can be seen in the figure, this slope depends on the choice of  $m$ . In fact, the slope becomes steeper as  $m$  increases but will saturate at a certain level of the embedding dimension. Therefore, the slope can be plotted as a function of this embedding dimension  $m$  which makes it possible to see from which  $m$  on the slope is saturated. As shown in (**Fig.9(b)**), the point on the  $y$  and  $x$  axis where this curve (slope versus  $m$ ) saturates is called respectively the correlation dimension CD and the embedding dimension of the time series.

Although the algorithm of Grassberger and Procaccia [35] is often used, it has several limitations such as the sensitivity to the length of the data, the unclear range of embedding dimensions to consider and the lack of having a confidence interval. To solve these problems, Judd [36] developed another algorithm to estimate the CD in a more robust way, which was used in this thesis. The CD for the (**fig. 2**) is 3.61 and for the tachogram example given in (**Fig.1**) is 3.7025.

When a finite value is found for the CD of a time series, correlations are present in the signal. To conclude whether these correlations are linear or nonlinear, a surrogate time series needs to be calculated. A significant difference between the CD of the surrogate and the original time series indicates that there are nonlinear correlations present in the signal. The significance level is calculated as:  $S = [CD_{surr} - CD_{data}] / SD_{surr}$ . A value of  $S > 2$  indicates that the measure reflects nonlinear correlations within the time series. In case of  $S > 2$  the signal can be chaotic, but this is not absolutely sure unless other nonlinear parameters like e.g. Lyapunov exponents are available and positive values found. With  $S < 2$  no significant difference is found between the two time series, the signal is not chaotic.

### 3.6 Lyapunov exponent

Lyapunov exponent ( $\Lambda$ ) is a quantitative measure of the sensitive dependence (SED) on the initial conditions. It defines the average rate of divergence of two neighboring trajectories. An exponential divergence of initially nearby trajectories in phase space coupled with folding of trajectories, ensure that the solutions will remain finite, is the general mechanism for generating deterministic randomness and unpredictability. Therefore, the existence of a positive  $\Lambda$  for almost all initial conditions in a bounded dynamical system is widely used. To discriminate between chaotic dynamics and periodic signals Lyapunov exponent ( $\Lambda$ ) are often used. It is a measure of the rate at which the trajectories separate one from other. The trajectories of chaotic signals in phase



space follow typical patterns. Closely spaced trajectories converge and diverge exponentially, relative to each other. For dynamical systems, sensitivity to initial conditions is quantified by the Lyapunov exponent ( $\Lambda$ ). They characterize the average rate of divergence of these neighboring trajectories. A negative exponent implies that the orbits approach a common fixed point. A zero exponent means the orbits maintain their relative positions; they are on a stable attractor. Finally, a positive exponent implies the orbits are on a chaotic attractor [37].

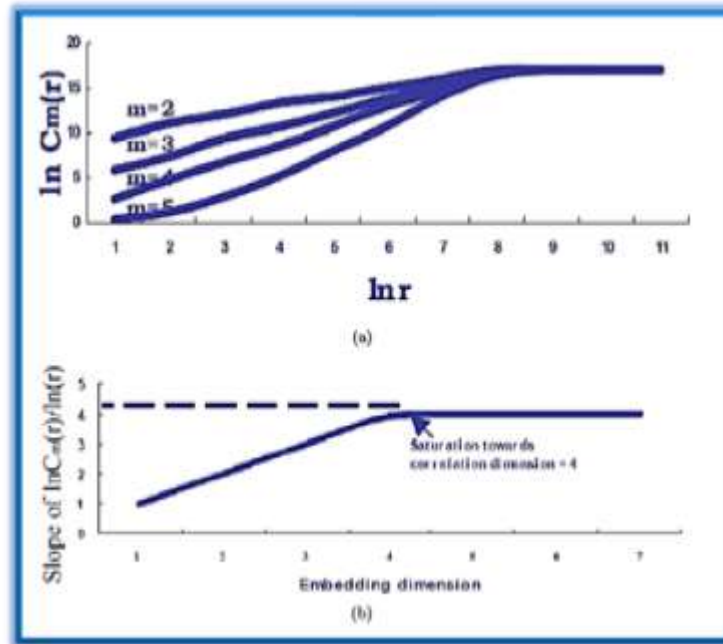


Figure 9. Example of how to calculate the correlation dimension (CD). (a) Correlation integral  $C^m(r)$  as function of the tolerance level  $r$  for different choices of the embedding dimension  $m$ . As  $C^m(r) \sim r^{CD}$ , the slope of such curve in a  $\ln - \ln$  scales results theoretically in the correlation dimension CD, but depends on  $m$ . (b) Plot of the slopes of  $\ln C^m(r)/\ln(r)$  as function of  $m$ .

### 3.6.1 Wolf's Algorithm

Wolf's algorithm is straightforward and uses the formulas defining the system. It calculates two trajectories in the system, each initially separated by a very small interval  $R_0$ . The first trajectory is taken as a reference, or 'fiducial' trajectory, while the second is considered 'perturbed'. Both are iterated together until their separation  $\text{abs}(R_1 - R_0)$  is large enough, at which point an estimate of the Largest Lyapunov Exponent LLE can be calculated as  $\Lambda_L = \frac{1}{\Delta t} \log_2 \text{abs} \left( \frac{R_1}{R_0} \right)$ . The perturbed trajectory is then moved back to a separation of  $\text{sign}(R_1)R_0$  towards the fiducial, and the process repeated. Over time, a running average of  $\Lambda_L$  will converge towards the actual LLE [38]. The normal HR signal shown in (Fig. 2) has LLE equal 0.505Hz.

### 3.6.2 Rosenstein algorithm

The first step of this approach involves reconstructing the attractor dynamics from the RR interval time series. The method of delays is used which is already described in detail when explaining the correlation dimension. After reconstructing the dynamics, the algorithm locates the nearest neighbor of each point on the trajectory. The nearest neighbor,  $x'_j$ , is found by searching for the point that minimizes the distance to the particular reference point,  $x_j$ . This is expressed as:

$$d_j(0) = \min_{j'} \|x_j - x_{j'}\| \quad \forall x_{j'} \quad (12)$$

where  $d_j(0)$  is the initial distance from the  $j^{\text{th}}$  point to its nearest neighbor and  $\| \dots \|$  denotes the Euclidean norm. An additional constraint is imposed, namely that nearest neighbors have a temporal separation greater than the mean period of the RR interval time series. Therefore, one can consider each pair of neighbors as the nearby SD initial conditions for different trajectories. The LLE is then estimated as the mean rate of the SD separation of the nearest neighbors. More concrete, it is assumed that the  $j^{\text{th}}$  pair of nearest neighbors diverge approximately at a rate given by the LLE  $\Lambda_L$ :

$$d_j(j) \approx d_j(0) e^{\Lambda_L(i \Delta t)} \quad (13)$$

By taking the  $\ln$  of both sides of this equation:

$$\ln d_j(j) \approx \ln d_j(0) + \Lambda_L(i \Delta t) \quad (14)$$

which represents a set of approximately parallel lines (for  $j = 1, 2, \dots, J$ ), each with a slope roughly proportional to the  $\Lambda_L$ .

The natural logarithm of the divergence of the nearest neighbor to the  $j^{\text{th}}$  point in the phase space is presented as a function of time. The LLE is then calculated as the slope of the least squares fit to the 'average' line defined by:

$$\Lambda_L(t) = \frac{1}{\Delta t} \langle \ln d_j(t) \rangle \quad (15)$$

where  $\langle \ln d_j(t) \rangle$  represents the mean logarithmic divergence over all values of  $j$  for all pairs of nearest neighbors over time. This process of averaging is the key to calculating accurate values for the LLE using smaller and noisy data sets compared to other algorithms [39]. The LLE computed using the Rosenstein algorithm is 0.7586 Hz for the HR signal shown in (Fig. 2).

### 3.6.3. The Mazhar-Eslam Algorithm

The Mazhar-Eslam [3, 40] algorithm uses Discrete Wavelet Transform (DWT) considering the merits of DWT over that of FFT. Although the FFT has been studied extensively, there are still some desired properties that are not provided by FFT. There are some points that lead to choose DWT instead of FFT. The first point is hardness of FFT algorithm pruning. When the number of input points or output points are small comparing to the length of the DWT, a special technique called pruning is often used [41]. However, it is often required that those non-zero input data are grouped together. FFT pruning algorithms does not work well when the few non-zero inputs are randomly located. In other words, sparse signal does not give rise to faster algorithm.

The other disadvantages of FFT are its speed and accuracy. All parts of FFT structure are one unit and they are in an equal importance. Thus, it is hard to decide which part of the FFT structure to omit when error occurring and the speed is crucial. In other words, the FFT is a single speed and single accuracy algorithm, which is not suitable for SED cases.

The other reason for not selecting FFT is that there is no built-in noise reduction capacity. Therefore, it is not useful to be used. According to the previous, the DWT is better than FFT especially in the SED calculations used in HRV, because each small variant in HRV indicates the important data and information. Thus, all variants in HRV should be calculated.

The Mazhar-Eslam algorithm depends to some extent on Rosenstein algorithm's strategies to estimate lag and mean period, and uses the Wolf algorithm for calculating the MVF ( $\Omega_M$ ) except the first two steps, whereas the final steps are taken from Rosenstein's method. Since the MVF ( $\Omega_M$ ) measures the degree of the SED separation between infinitesimally close trajectories in phase space, as discussed before, the MVF ( $\Omega_M$ ) allows determining additional invariants. Consequently, the Mazhar-Eslam algorithm allows to calculate a mean value for the MVF ( $\Omega_M$ ), that is given by

$$\overline{\Omega_M} = \sum_{i=1}^j \frac{\Omega_{M_i}}{j} \quad (16)$$

Note that the  $\Omega_{M_i}$ s contain the largest  $\Omega_{ML}$  and variants  $\Omega_M$ s that indicate to the helpful and important data. Therefore, the Mazhar-Eslam algorithm is a more SED prediction quantitative measure. Therefore, it is robust quantitative predictor for real time, in addition to its sensitivity for all time whatever the period.

Apply the Mazhar-Eslam algorithm to the HRV of the normal case given in (Fig. 2), it is found that the mean MVF ( $\overline{\Omega_M}$ ) as 0.4986 Hz, which is more accurate than Wolf (0.505 Hz) and Rosenstein (0.7586 Hz). Figure 10 shows the flowchart for calculating the Mazhar-Eslam MVF algorithm.

Figure 10 shows the flowchart steps for calculating the Mazhar-Eslam MVF<sub>M</sub> algorithm. First Start to select an initial condition. An embedded point in the attractor was randomly selected, which was a delay vector with  $d_E$  elements. A delay vector generates the reference trajectory (nearest neighbor vector). Then another trajectory is selected by searching for the point that minimizes the distance to the particular reference point. After that the divergence between the two vectors is computed. A new neighbour vector was considered as the evolution time was higher than three sample intervals. The new vector was selected to minimize the length and angular separation with the evolved vector on the reference trajectory. The steps are repeated until the reference trajectory has gone over the entire data sample. The divergence and  $\Omega_{L_i}$ s are calculated. Consequently, the  $\Omega_M$  is calculated by using equation (16).

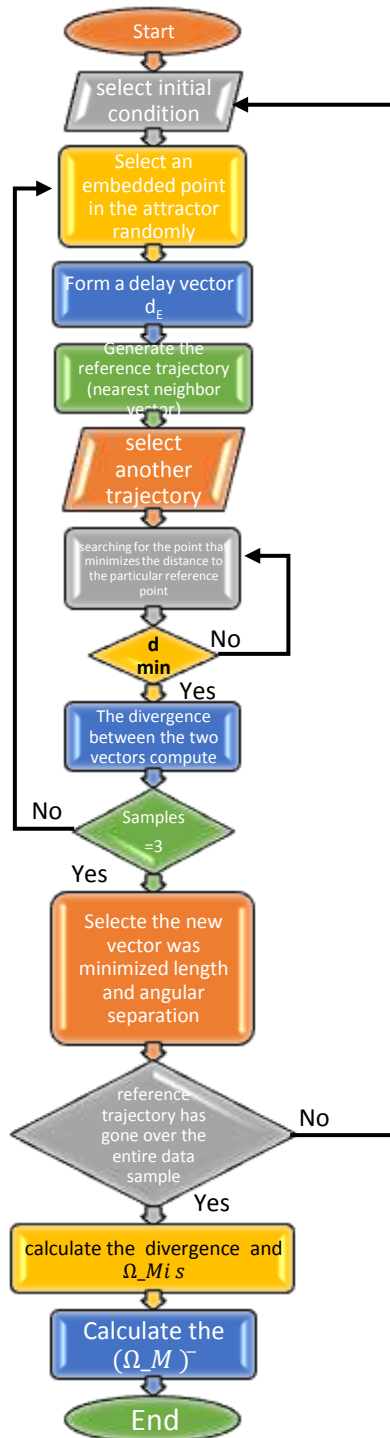


Figure 10 The flowchart of the Mazhar-Eslam algorithm.

Table (1) shows the different results of the normal case among Mazhar-Eslam, Wolf, and Rosenstein algorithms. From this table it is seen that, the Rosenstein algorithm has the lowest SED because of its quite high error ( $D = 51.72\%$ ) comparing to the optimum, while the Wolf algorithm takes a computational place for SED ( $D = 1\%$ ). However, the Mazhar-Eslam algorithm shows more sensitivity ( $D = 0.28\%$ ) than Wolf algorithm as shown in (Fig. 11). The patient case deviation  $D$  for normal HRV case is calculated as:

$$Deviation(D) = |\Omega_{Mnormal} - \Omega_{Mcase}| \quad (17)$$

the cases percentage deviation is to be calculated as:

$$D\% = \frac{D}{normal} \times 100\% \quad (18)$$

and, the variance for algorithms should be calculated as

$$var = (\Omega_{M_{normal}} - D)^2 \quad (19)$$

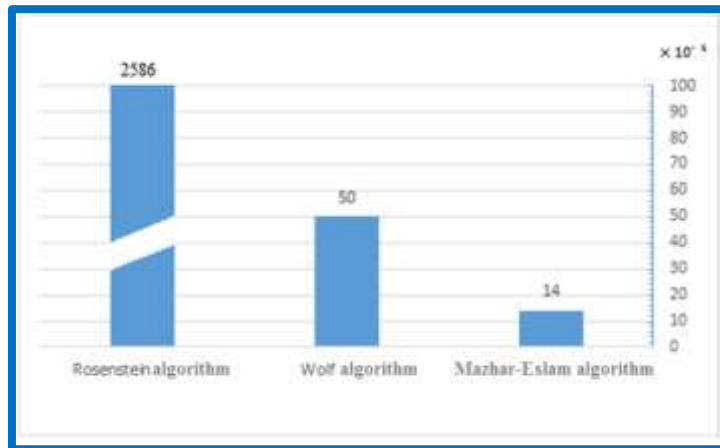


Figure 11 The three algorithms deviation for the normal case in (Fig.2).

The bar diagram in (Fig. 12) shows the percentage deviation of the three algorithms. From this figure it is seen that the Mazhar-Eslam algorithm gives the best result as it has the lowest percentage deviation (D = 14). At the same time, when calculating the variance to determine the accurate and best method, Mazhar-Eslam algorithm gives the best value. Figure 13 shows the bar diagram of the variance for normal control case using the HRV for Wolf, and Mazhar-Eslam algorithms. It is clear that the Mazhar-Eslam algorithm is more powerful and accurate than Wolf, because its variance is better than Wolf by 0.0036. This result comes because the Mazhar-Eslam considers all the variability mean frequencies  $\overline{\Omega_M}$ s unlike the Wolf method as it takes only the largest. Each interval of the HRV needs to be well monitored and taken into account because the variant in HRV is indication of cases.

Table 1 The results of the three algorithms for the normal case shown in (Fig. 2)

Method parameter	Optim	Rosenstein	Wolf	Mazhar-Eslam
$\Omega_M$	0.500000	0.758600	0.505000	0.498600
D	0.000000	0.258600	0.005000	0.001400
D%	0.000000	51.720000	1.000000	0.280000
Var	0.250000	0.058274	0.245025	0.248602

From the bar diagram in (Fig. 13) it is seen that the Mazhar-Eslam algorithm is most useful and sensitive comparing to Wolf and Rosenstein algorithms.

### 3.7 Hurst exponent (H)

The Hurst exponent is a measure that has been widely used to evaluate the self-similarity and correlation properties of fractional Brownian noise, the time series produced by a fractional (fractal) Gaussian process. Hurst exponent is used to evaluate the presence or absence of long-range dependence and its degree in a time series. However, local trends (nonstationarities) are often present in physiological data and may compromise the ability of some methods to measure self-similarity. Hurst exponent is the measure of the smoothness of a fractal time series based on the asymptotic behavior of the rescaled range of the process. The Hurst exponent H is defined as:

$$H = \log\left(\frac{R}{S}\right) / \log(T) \quad (20)$$

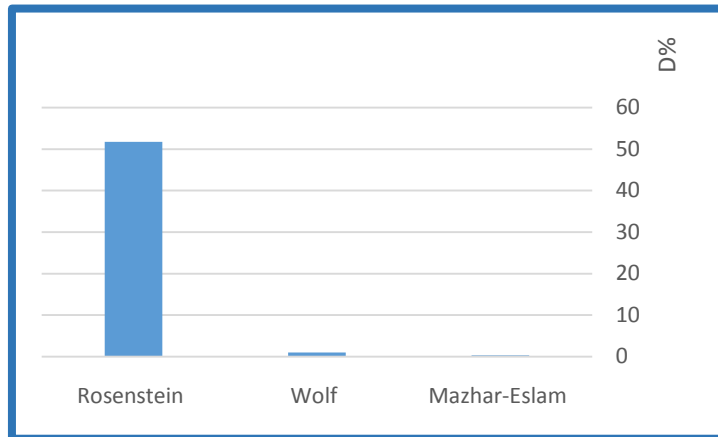


Figure 12 The three algorithms Percentage deviation (D%) for the normal case (Fig. 2).

where T is the duration of the sample of data and R/S the corresponding value of rescaled range. The above expression is obtained from the Hurst's generalized equation of time series that is also valid for Brownian motion. If  $H = 0.5$ , the behavior of the time series is similar to a random walk. If  $H < 0.5$ , the time series covers less "distance" than a random walk. But if  $H > 0.5$ , the time-series covers more "distance" than a random walk. H is related to the dimension CD given by:

$$H = E + 1 - CD \quad (21)$$

where E is the Euclidean dimension.

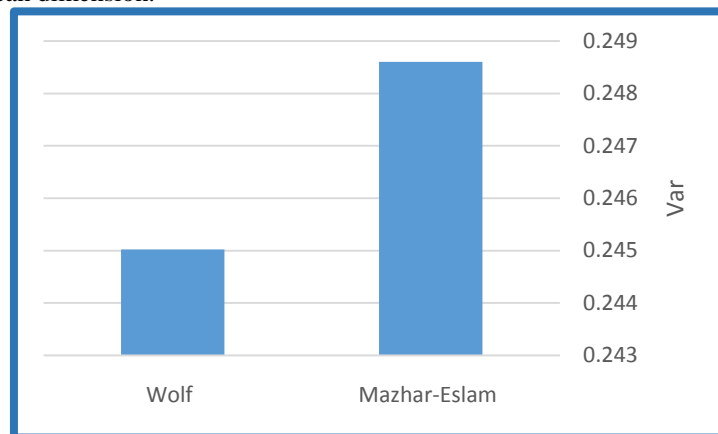


Figure 13 The Variance of Wolf and Mazhar-Eslam algorithm for normal case (Fig.2).

For normal subjects, the FD is high due to the variation being chaotic. And for Complete Heart Block (CHB) and Ischemic/dilated cardiomyopathy, this FD decreases because the RR variation is low. And for AF and SSS, this FD value falls further, because the RR variation becomes erratic or periodic respectively [42]. The H is 0.611 for the HR signal shown in (Fig. 2).

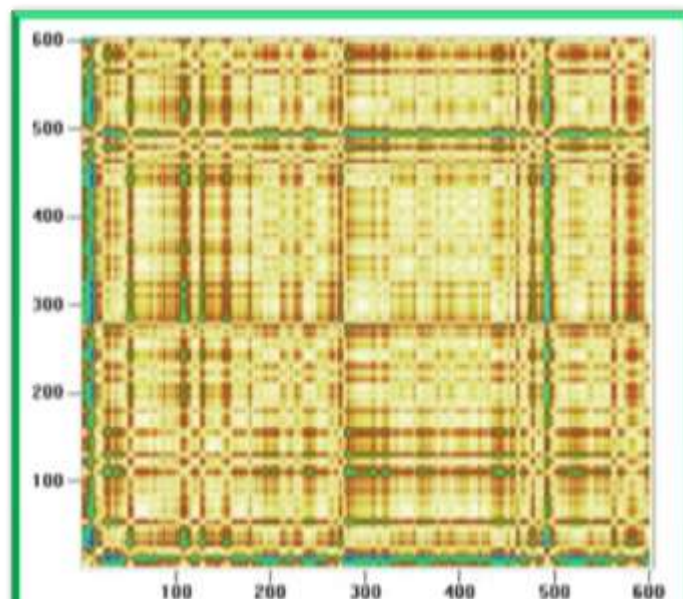


Figure 14 Recurrence plot of normal heart rate (shown in Fig. 2)

### 3.8 Recurrence plots

In time-series analysis, the dynamic properties of the data under consideration are relevant and valid only, if the data is stationary. Recurrence plots (RP) are used to reveal nonstationarity of the series. These plots were first proposed by Eckmann et al. [43] as graphical tool for the diagnosis of drift and hidden periodicities in the time evolution, which are unnoticeable otherwise. A brief description on the construction of recurrence plots is described below.

Let  $x_i$  be the  $i^{\text{th}}$  point on the orbit in an  $m$ -dimensional space. The recurrence plot is an array of dots in an  $N \times N$  square, where a dot is placed at  $(i, j)$  whenever  $x_j$  is sufficiently close to  $x_i$ . To obtain the recurrence plot, an  $m$ -dimensional orbit of  $x_i$  is constructed. A radius  $r$  such that the ball of radius  $r$  centered at  $x_i$  in  $\mathcal{R}^m$  contains a reasonable number of other points  $x_j$  of the orbit. Finally, a dot is plotted for each point  $(i, j)$  for which  $x_j$  is in the ball of radius  $r$  centered at  $x_i$ . The plot thus obtained is the recurrence plot. The plots will be symmetric along the diagonal  $i = j$ , because if  $x_i$  is close to  $x_j$ , then  $x_j$  is close to  $x_i$ . The recurrence plot of normal HR (shown in Fig. 2) is given in (Fig. 14). For normal cases, the RP has diagonal line and less squares indicating more variation indicating high variation in the HR. Abnormalities like CHB and in Ischemic/dilated cardiomyopathy cases, show more squares in the plot indicating the inherent periodicity and the lower HR variation [44].

## IV. Conclusion

This review introduces the mathematics and techniques, necessary for a good understanding of the methodology used in HRV analysis. After the peak detection algorithm and the preprocessing methods, the linear methods in time domain, frequency domain and the time-frequency representations were represented. Also an overview of some nonlinear techniques assessing scaling behavior, complexity and chaotic behavior were given.

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